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Original Article

Interaction between VA-ECMO and the right ventricle

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ABSTRACT

Background: The response of the right ventricle (RV) to the hemodynamic effects of veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is currently unpredictable. We hypothesized that the presence of uni- or bi-ventricular failure before implantation and the cannulation strategy may influence this interaction. We sought to assess the RV performance during VA-ECMO support and identify RV-related predictors of successful weaning.

Methods: Changes in RV size and function during VA-ECMO support by echocardiography were retrospectively analyzed in 87 consecutive adult patients between February 2008 and June 2017. Predictors of successful weaning due to myocardial recovery were evaluated by multivariable logistic regression.

Results: RV echocardiographic parameters did not vary significantly during VA-ECMO support and neither after stratification by the type of cannulation or the presence of isolated or biventricular failure. Successful weaning was conditioned by the absence of RV dysfunction before implantation (OR, 14.7; 95% CI, 13.3-140.3; $p = 0.025$) or in the last day of support (OR, 9.5; 95% CI, 1.6-54; $p = 0.011$) and was favored by a total or partial recovery of RV function during the assistance (OR, 6.2; 95%CI, 1.7-22.4; $p = 0.005$). RV improvement was more often observed in patients with acute RV failure and longer support, while VA-ECMO configuration, additional mechanical support, or pharmacological therapy had no effect.

Conclusions: Preservation or improvement of RV function during VA-ECMO is essential for successful weaning. RV echocardiographic performance does not change significantly during VA-ECMO support and is not influenced by cannulation type or the presence of uni- or bi-ventricular failure before implantation.

1. Introduction

Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is a short-term mechanical support connected to a gas exchange membrane that provides circulatory and respiratory assistance during refractory cardiogenic shock as a bridge to myocardial recovery, durable mechanical circulatory support, or heart transplant.

The hemodynamic effects of VA-ECMO depend, partially, on the cannulation strategy and the location of the cannulas.[1–4] Central access, through intrathoracic cannulation of the right atrium and the ascending aorta, remains the primary choice in postcardiotomy patients, whereas the peripheral approach is widely used in emergent situations of cardio-circulatory collapse,[5] where the

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drainage is inserted in a distal vein and the return cannula is commonly placed in the femoral artery. The interaction between VA-ECMO and the circulation is complex. Although used as a life-saving strategy in circulatory collapse, it may carry several detrimental hemodynamic effects.[6] With each increase in pumped flow, there is a progressive unloading of the right chambers with an increase in left ventricular (LV) afterload caused by retrograde arterial flow, resulting in increases in LV, left atrial, and pulmonary artery pressures, increase in LV volumes, and a potential decrease in LV stroke volume. These changes may lead to an increase in right ventricle (RV) afterload and a narrowing and right/upward shift of the LV pressure-volume loop.[2,6]

Although the influence of long-term LV assist devices (LVAD) has been extensively described,[7] there is a lack of data regarding the effect of VA-ECMO on short-term RV hemodynamics.[8] The adaptation of the RV to the hemodynamic stress imposed by VA-ECMO circulation, including a sustained reduction in RV preload and an increased RV afterload, cannot be predicted now. We hypothesize that this response is probably conditioned by the pre-existing RV compensatory reserve and by the LV function. We speculate that the type of cannulation of VA-ECMOs can modify the geometry and function of the RV, assuming that central devices allow for a better drainage of the right side of the heart with a lower impact on LV afterload since the return cannula, placed in aorta, minimizes the retrograde flow.

The objectives of our study are as follows: (1) to evaluate the RV performance by echocardiography during the different phases of VA-ECMO support, (2) to explore the influence of the type of cannulation and the degree of ventricular systolic dysfunction (univentricular −LV or RV− or biventricular), and (3) to identify RV-related predictors of successful weaning from VA-ECMO in the setting of myocardial recovery.

2. Methods

2.1. Patients and data

All the patients requiring VA-ECMO ≥18-year-old at the Royal Brompton Hospital from February 2008 to June 2017 were retrospectively studied. Demographic and clinical characteristics, VA-ECMO configuration, treatment, and outcomes were included in the analysis. Hemodynamic and analytical variables before insertion were assessed to filiate critical severity and organ failure. Data were obtained directly from clinical records. The study was conducted in accordance with the Declaration of Helsinki Ethical Principles and Good Clinical Practices.

2.2. Definitions

LV or RV systolic dysfunction was evaluated according to current echocardiographic and CMR criteria.[9–11] Acute RV failure before VA-ECMO insertion comprised the following:[1] the development of RV systolic dysfunction in previously healthy patients or in patients with heart disease but preserved RV function ("de novo") or[2] any additional deterioration in RV systolic function in patients with pre-existing reduced RV systolic function ("worsening"). The temporal evolution of RV systolic function after VA-ECMO insertion was classified as follows:[1] improvement (total or partial RV function recovery, implying at least one qualitative degree rise in the RV systolic function evaluated with echo),[2] worsening (any degree of deterioration in RV systolic function), and[3] stability (persistence of the RV systolic function present at the beginning during the time of assistance). Predominance of RV failure over LV failure involves that the RV systolic dysfunction overcomes at least one qualitative degree −mild, moderate, or severe− the severity of the LV dysfunction. Myocardial recovery was defined as VA-ECMO decannulation without the need of other heart replacement therapies. Severe respiratory failure was considered in patients with a $Pa0_2/FiO_2$ ratio <200.[12] Chronic kidney disease was designated as eGFR <60 ml/min/1,73 m^2. Severe acute renal failure was defined according to KDIGO definition as a 3-fold baseline value or increase in serum creatinine to >4 mg/dl (≥353.6 μmol/l), initiation of renal replacement therapy, urine output of <0.3 ml/kg/h for ≥24 h, or anuria for ≥12 h.[13] Acute elevations of ALT >10 times the upper limit level were arbitrarily considered as severe acute liver injury.[14] "Primary" cardiac arrest was defined as an event occurring in the absence of heart disease and no obvious cause of the arrest.

2.3. Echocardiographic measures

Echocardiographic parameters were obtained as follows:[1] pre-ECMO implantation (immediately before ECMO cannulation),[2] on-ECMO (within first 24 h after implantation), and[3] last-day ECMO (the last day on ECMO provided that the length of stay was >24 h). LV and RV dimension and volume parameters were acquired according to guidelines.[10,15,16] LV velocity time integral (LVVTI) was obtained in the apical 5-chamber view sampling the flow at the level of the LV outflow tract with pulse wave Doppler.[17] RV dilation was defined as RV basal diameter >42 mm. RV systolic dysfunction was graded as mild, moderate, or severe by integrating the TAPSE value and the visual assessment of the contractility of the RV outflow tract, RV apex, and interventricular septum. Systolic pulmonary artery pressure was estimated using the simplified Bernoulli's equation.[9]

The weaning protocol consisted of reduction in ECMO pump flow in steps of 0.5 L down to 1.0 L/min. After 30 min at minimal flow, if cardiac output did not decrease, filling pressures remained low, and signs of peripheral perfusion (lactate, SvO_2, end-tidal carbon dioxide if available) and echocardiographic findings of ventricular insufficiency were absent, the mechanical support was removed.

2.4. Statistical analysis

Continuous variables were assessed for normal distribution using the 1-sample Kolmogorov-Smirnov test and expressed as means ± standard deviations or median and 25th-75th percentile range if they did not fulfill this condition. Categorical variables were expressed as frequencies and percentages. Hemodynamic data were not included in the analysis if VA-ECMO was implanted during cardiac arrest. Differences among categorical variables and medians in all the three phases of ECMO assistance were assessed with the Friedman test. Mean differences were evaluated with ANOVA test for unpaired groups or ANOVA test for paired data. A two-tailed probability value of <0.05 was considered statistically significant. Multivariable logistic regression was used to analyze the relationship between potential predictors of successful weaning and RV function improvement over VA-ECMO support. Statistical analyses were performed with SPSS software version 21.

3. Results

3.1. Baseline characteristics, clinical situation, and indication

A total of 87 patients were included in the study. Baseline characteristics and comorbidity are shown in Supplementary Table 1. Mean age was 48.5 ± 16.4 years, 64.4% were males (n = 56), and 64.4% had any type of prior cardiac comorbidity, being the valvular disease (25.3%) and the coronary artery disease (12.6%) the most common. Medical history of LV and RV systolic

dysfunction was present in 26 (29.9%) and 16 patients (18.4%), respectively. The main indication for VA-ECMO implantation was refractory cardiogenic shock (n = 76; 87.4%), followed by primary cardiac arrest (n = 9; 10.3%). Causes of cardiogenic shock are described in Supplementary Table 2. The main hemodynamic and indirect organ-failure parameters before cannulation are summarized in Table 1. Half of the patients were INTERMACS 1, and the other half of the patients were INTERMACS 2.

3.2. Technical characteristics, settings of VA-ECMO, and additional support

Central cannulation was performed in 33 patients (37.9%), whereas the pump was inserted peripherally in 54 patients (62.1%), of whom 20.4% required an additional femoral cannula to prevent ischemia. Five patients with peripheral VA-ECMO (5.7%) were upgraded to VVA-ECMO to improve venous drainage because of insufficient unloading flow. Conversion to central cannulation due to ineffective offloading and severe LV dilation was required in 6 patients (11.1%). The device was placed during cardiac arrest in 21 patients (24.1%).

The mean maximal blood flow was 4.8 ± 0.8 lpm (index 2.6 ± 0.4 lpm·m-2) without significant differences in relation to the presence of isolated RV/LV systolic dysfunction or biventricular failure (p = 0.832). Additional support with intra-aortic balloon pump was required in 36 patients (41.4%), 22 of whom were assisting patients with peripheral VA-ECMO (40.7% of peripheral ECMO). All patients were supported by vasoactive drugs: 18 patients (20.7%) with vasopressor drugs, 2 patients with inotropic drugs (2.3%), and 67 patients (77%) with both vasopressor and inotropic drugs. Thirty-nine patients (44.8%) had a vasoactive-inotropic score >85%.

Table 1
Hemodynamic characteristics and multiorgan failure before VA-ECMO implantation

Hemodynamic characteristics	*N* = 43
Heart rate, bpm (mean ± SD)	104.2 ± 18.5
SBP, mmHg (mean ± SD)	77.6 ± 18.9
DBP, mmHg (mean ± SD)	54 ± 18
MAP, mmHg (mean ± SD)	60.6 ± 17.2
Pulse pressure, mmHg (mean ± SD)	23.5 ± 14.5
CVP, mmHg (mean ± SD)	13.9 ± 5.6
Cardiac Index, lpm/m2 (mean ± SD)	1.8 ± 0.5
Stroke volume index, ml (mean ± SD)	19.2 ± 6.2
Pulmonary artery mean pressure, mmHg (mean ± SD)	27.8 ± 5.5
SVR index, dynes·s·cm^{-5}· m^2 (mean ± SD)	1299 ± 522
PVR index, dynes·s·cm^{-5} ·m^2 (mean ± SD)	204 ± 50
RV stroke work index, Gm·m/m^2 (mean ± SD)	13.2 ± 2.9
Tissue perfusion	*N* = 56
Lactate, mmol/l (median, IQ)	5 (2.7-12.8)
Organ function	N = 87
Respiratory function	
Severe respiratory failure (PaO_2/FiO_2 <200) (n, %)	13 (14.9)
Mechanical ventilation (n,%)	52 (59.8)
Oxygen index (mean ± SD)	3.6 ± 4.3
Renal function	
Creatinine, μmol/l (mean ± SD)	119.6 ± 52.8
Urea, mmol/l (mean ± SD)	7.7 ± 3.7
Severe acute kidney injury (n, %)	53 (60.9)
Renal-replacement therapy (n, %)	35 (40.2)
Hepatic function	
AST, IU/l (mean ± SD)	197.5 ± 171.8
ALT, IU/l (mean ± SD)	347.4 ± 82.5
ALP, IU/l (mean ± SD)	57.7 ± 19.9
Bilirubine, μmol/l (mean ± SD)	36.2 ± 26.1
Severe acute liver injury (n, %)	10 (11.5)

3.3. Assessment of right ventricular function

Echocardiographic assessment before VA-ECMO insertion and within the first day of mechanical circulatory support was available in 68 patients (78%), but only 63 patients had sufficient information recorded in the last VA-ECMO day available for analysis.

During echocardiographic evaluation in the first 24 h of mechanical support, 65 patients (95.6%) were on the maximal blood flow, 35 patients (51.5%) required predominantly inotropic drugs (milrinone (n = 29; 42.6%) or dobutamine (n = 6; 8.8%)), 26 patients (38.2%) needed pulmonary vasodilators (nitric oxide (n = 18; 26.4%), sildenafil (n = 6; 8.8%), and epoprostenol (n = 2; 2.9%), and 1 patient required an additional extra right mechanical support with Impella. In the last echocardiographic evaluation (>24 h of assistance), only 37 patients (58.7%) were on the maximal pump flow, none of them required Impella RP®, and no significant differences were found in RV inotropic drugs and pulmonary vasodilators when compared to the first 24 h (p = 0.784 and p = 0.842, respectively).

No significant differences in the dimensions and functional parameters of both ventricles and in valve functional measures were found over the three evaluated phases (Table 2). No relevant differences in the main echocardiographic parameters, including RV dimensions and functional parameters, were found within the first 24 h and on the last day of mechanical circulatory support when the type of cannulation (Table 3) and when the presence of prior isolated RV, isolated LV, or biventricular systolic dysfunction were considered (Supplementary Table 3).

Acute RV systolic failure before VA-ECMO implantation occurred in 58 patients (85.3%), 50 of whom developed “de novo” deterioration, and 8 worsening of pre-existing RV systolic impairment. In most cases (n = 46, 58%), RV dysfunction was severe before cannulation. RV systolic function remained stable in all patients within the first 24 h. However, RV systolic function in the last ECMO day significantly improved in 20 patients (31.8%), worsened in 11 patients (17.4%), and remained stable in 32 patients (50.8%). At that moment, only 14 patients showed normal RV function (22%).

3.4. Clinical Outcomes

The median length of the mechanical circulatory support was 7 days (interquartile range, 2-14). Mortality on VA-ECMO occurred in 49 patients (56.3%), 19 (38.7%) within the first 48 h. The causes of mortality on ECMO were as follows: multiorgan failure in 38 patients (77.6%); fatal bleeding in 5 patients (10.2%); irreversible brain damage in 3 patients (6.1%), and the limitation of therapeutic effort in 3 patients (6.1%). Twenty-one patients (24%) were successfully weaned off mechanical support due to myocardial recovery; 15 patients (17.2%) were converted to a ventricular assist device (7 patients to LVAD, 7 patients to BiVAD, and 1 to artificial heart), and 2 patients (0.2%) underwent heart transplantation, one of them after LVAD implantation. Overall, 8 patients needed specific long-term RV support. ICU mortality was 69% (n = 60), and in-hospital mortality was 72.4% (n = 63), as other lethal complications emerged after the removal of ECMO in 14 patients. The median length in ICU was 26.5 days (17.8-37.3). Finally, only 24 patients (27.6%) were discharged from hospital, and the 30-day survival was the same, with a follow-up available in the 100% of the discharged patients.

3.5. RV parameters predicting successful weaning

We identified the following RV-related predictive factors of successful weaning from VA-ECMO in patients showing myocardial recovery: normal RV function before VA-ECMO insertion (OR, 14.7;

Table 2
Echocardiographic parameters evolution during VA-ECMO support.

	Pre-ECMO	<24h on ECMO	>24h on ECMO	*p*
N	n = 68	n = 68	n = 63	
LV diastolic diameter, mm (mean ± SD)	53.34 ± 15.59	54.86 ± 13.89	56.18 ± 14.62	0.317
Men	56.04 ± 15.68	58.01 ± 13.63	59.96 ± 13.84	0.429
Women	48.44 ± 14.51	47.22 ± 11.73	45.61 ± 11.64	0.656
LV dilation according to Dd, n (%)	57 (83.8)	24 (35.3)	18 (28.6)	0.358
Severe	53 (77.9)	9 (13.2)	12(19)	0.092
LV systolic diameter, mm	45.28 ± 11.67	45.17 ± 14.58	46.07 ± 15.59	0.963
LVEF, n (%)	20 (10-38.75)	17.5 (10-30)	25 (10-40)	0.102
LVOT VTI, cm	8.92 ± 4.74	8.84 ± .5.88	10,17 ± 6,19	0.691
RV basal diameter, mm (mean ± SD)	41.05 ± 9.79	38.92 ± 9.17	40.05 ± 9.56	0.484
RV mid diameter, mm (mean ± SD)	34.67 ± 8.96	-	35.45 ± 10.6	0.781
RV longitudinal diameter, mm (mean ± SD)	71.16 ± 13.88	-	71.77 ± 12.13	0.732
RVOT distal diameter, mm (mean ± SD)	20.97 ± 0.69	-	21.08 ± 4.38	0.617
RV end-diastolic area, cm^2 (mean ± SD)	20.25 ± 7.84	-	20.68 ± 8.85	0.693
RV EDA indexed to BSA (cm^2/m^2)				
Men	10.44 ± 4.03	-	10.47 ± 4.44	0.951
Women	10.95 ± 2.94	-	11.31 ± 4.01	0.605
RV dilation n (%)				
According to EDAi	18 (26.5)	-	19 (30.1)	0.385
According to Dd	32 (47)	22 (33.3)	25 (39.7)	0.097
RV systolic dysfunction, n (%)	65 (95.6)	65 (95.5)	43 (68.2)	0.073
Severe	53 (77.9)	55 (78.6)	27 (42.8)	0.846
TAPSE, mm	10.47 ± 0.55	9.25 ± 5.9	9.34 ± 4.53	0.775
RVOT VTI, cm	9.01 ± 4.63	7,35 ± 4,27	8.32 ± 5.73	0.159
Tricuspid regurgitation, n (%)	50 (73.4)	37 (54.3)	49 (77.8)	0.146
Severe	8 (11.7)	4 (5.8)	5(8)	0.276
Pulmonary systolic pressure, mmHg (mean ± SD)	41.54 ± 24.13	39.09 ± 20.24	45.29 ± 25.73	0.783
Aortic regurgitation, n (%)	47 (69.1)	39 (57.4)	35 (55.5)	0.775
Severe	3 (4.4)	1 (1.5)	2 (3.2)	0.638
Mitral regurgitation, n (%)	64 (94.1)	48 (70.5)	44 (69.8)	0.591
Severe	14 (20.6)	9 (13.2)	8 (12.7)	0.136

Dd: diastolic diameter; EDAi: end-diastolic area index; EF: ejection fraction; LV: left ventricle; LVOT: left ventricle outflow tract; RV: right ventricle; RVOT: right ventricle outflow tract; VTI: velocity time integral.

Table 3
Echocardiographic parameters stratified by the technique of cannulation

	<24h on ECMO			>24h on ECMO		
	Central	Peripheral	*p*	Central	Peripheral	*p*
N	n = 25	n = 43		n = 22	n = 41	
LV diastolic diameter, mm (mean ± SD)	56.6 ± 15.8	53.8 ± 12.7	0.502	55.4 ± 18	56.6 ± 12.6	0.806
LV dilation according to Dd n (%)	10 (40)	14 (32.5)	0.428	6 (27.3)	12 (29.3)	0.385
LV systolic diameter, mm (mean ± SD)	47.5 ± 16	43.6 ± 13.6	0.376	46.3 ± 16.3	45.9 ± 15.5	0.943
LVEF n (%)	17 (10-24)	17 (10-31)	0.778	25 (15-40)	22 (13-41)	0.923
LV systolic dysfunction, n (%)	19 (76)	32 (74.4)	0.432	19 (27.3)	36 (87.8)	0.951
Severe	17 (68)	24 (55.8)	0.736	12 (54.5)	24 (58.5)	0.873
LVOT VTI, cm (mean ± SD)	10.2 ± 7.9	7.6 ± 4.1	0.186	11.3 ± 6.4	8.4 ± 5.2	0.159
RV basal diameter, mm (mean ± SD)	38.9 ± 5.4	40.3 ± 8	0.517	38.8 ± 9.4	40.7 ± 9.6	0.406
RV mid diameter, mm (mean ± SD)	-	-	-	32.4 ± 8.7	37.1 ± 11.2	0.097
RV longitudinal diameter, mm (mean ± SD)	-	-	-	68.7 ± 9.6	73.3 ± 13	0.162
RVOT diameter, mm (mean ± SD)	-	-	-	22.7 ± 2.5	20.7 ± 4.7	0.380
RV dilation according to Dd, n (%)	7 (28)	15 (34.9)	0.828	7 (31.8)	18 (43.9)	0.667
RV systolic dysfunction, n (%)	25 (100)	40 (93)	0.418	17 (77.2)	26 (63.4)	0.543
Severe	23 (92)	32 (74.4)	0.743	11 (50)	16 (39)	0.438
TAPSE, mm (mean ± SD)	8.1 ± 5.9	9.9 ± 5.9	0.382	8.7 ± 4	9.9 ± 4.7	0.434
RVOT VTI, cm (mean ± SD)	7.2 ± 5.5	6.93 ± 3	0.857	10.9 ± 4.2	8.34 ± 3.4	0.089
Tricuspid regurgitation, n (%)	15 (60)	22 (51.2)	0.806	22 (100)	27 (65.8)	0.438
Severe	1(4)	3(7)	0.532	0 (0)	2 (4.9)	0.154
Pulmonary systolic pressure, mmHg (mean ± SD)	31.6 ± 10.4	41.8 ± 22.8	0.486	34.2 ± 11.3	60 ± 35	0.216
Aortic regurgitation, n (%)	14 (56)	25 (58.1)	0.543	13 (59.1)	22 (53.6)	0.179
Moderate-severe	4 (16)	4 (9.3)	0.927	0 (0)	1 (2.4)	0.675
Mitral regurgitation, n (%)	16 (64)	32 (74.4)	0.602	16 (72.7)	28 (68.3)	0.728
Severe	3 (12)	6 (13.9)	0.189	1 (4.5)	4 (9.7)	0.823

Dd: diastolic diameter; EF: ejection fraction; LV: left ventricle; LVOT: left ventricle outflow tract; RV: right ventricle; RVOT: right ventricle outflow tract; VTI: velocity time integral.

95%CI, 13.3-140.3; p = 0.025), normal RV function on the last day of VA-ECMO (OR 9.5; 95%CI 1.6-54; p = 0.011), and improvement of RV systolic function >24 h after VA-ECMO support initiation (OR 6.2; 95%CI, 1.7-22.4; p = 0.005). On the other hand, the predominance of RV systolic dysfunction over LV systolic dysfunction before ECMO implantation was associated with a lower success for weaning (OR, 0.2; 95%CI, 0.1-0.9; p = 0.043). RV dilation (before or on the last day of VA-ECMO), past history of RV systolic

dysfunction or pulmonary hypertension, acute RV failure or isolated RV systolic dysfunction were not associated with a successful weaning (Fig. 1).

Given that the improvement in RV systolic function on the last ECMO day, implying >24 h after the initiation of ECMO support, was one of the predictors of successful weaning without the need of further assistance, we analyzed the factors associated with early RV function recovery (Fig. 2). These were the acute development of RV failure before VA-ECMO (OR, 12.8; 95%CI 1.6-101; p = 0.016) and a length of ECMO support >7 days (OR 3.3; 95%CI 1.2-10.7; p = 0.026). On the contrary, the settings of VA-ECMO (maximal flow, maximal flow index, and the type of cannulation), therapeutic strategies (use of more than two vasoactive drugs, use of specific drugs for RV, and use of intra-aortic balloon pump or pulmonary vasodilators), clinical condition during VA-ECMO implantation (cardiac arrest, postcardiotomy), RV preconditioning (prior history of RV dysfunction, RV dilation before ECMO insertion, or pulmonary hypertension), and the location of injury (isolated RV dysfunction, or predominance of LV dysfunction over RV systolic dysfunction) were not associated with the improvement of RV failure after VA-ECMO. Among patients with RV improvement on ECMO support, those who presented "de novo" RV dysfunction (OR 5.5; 95%CI 1.5-20; p = 0,011) showed an association with successful weaning while those deteriorating from a prior RV dysfunction did not (OR 1.1; 95%CI 0.2-1.31; p = 0.89).

4. Discussion

Our study, one of the largest series assessing RV performance in patients under VA-ECMO support by echocardiography, shows that the size of the RV does not significantly change along the duration of mechanical support. Neither RV diameters nor the proportion of patients with RV dilation changed significantly during the assistance. Although these findings are counterintuitive as there is a theorical RV preload reduction induced by the device,[18] they may be explained at least in part by the lack of simultaneous correlated hemodynamic invasive monitoring, proving the occurrence of a real RV unloading, and the technical difficulty of 2D echocardiography to obtain accurate RV volume measures. The functional analysis shows that, globally, the proportion of patients with some degree of RV systolic dysfunction or with severely reduced function did not vary throughout the three analyzed phases. However, in the subgroup of patients who had developed acute RV failure before the insertion of the device, RV systolic function did not vary in the first 24 h of VA-ECMO support, but a majority of these patients significantly improved after >24 h of VA-ECMO assistance.

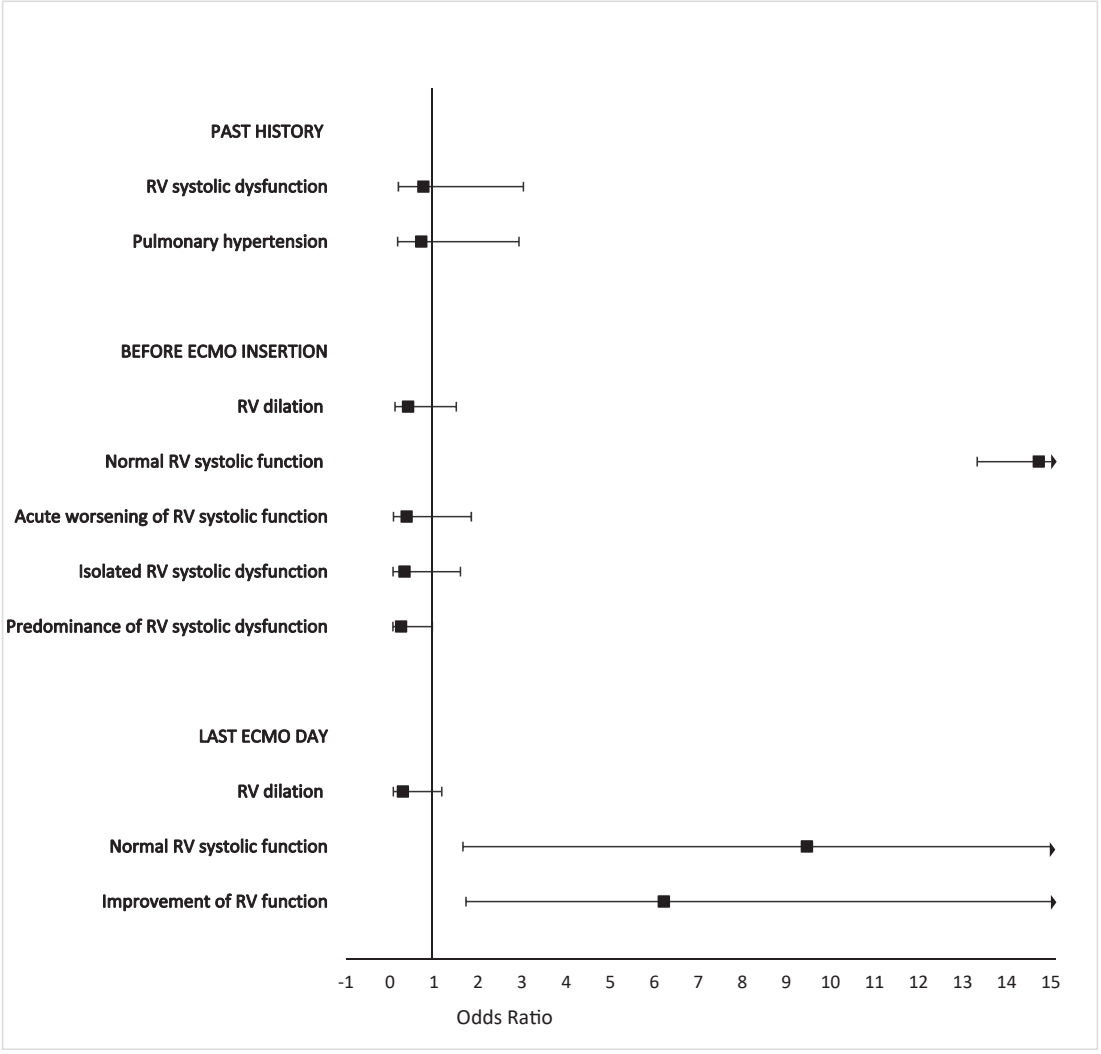

Figure 1. RV-related predictors of successful VA-ECMO weaning in patients evolving with myocardial recovery. Abbreviations: RV, right ventricle.

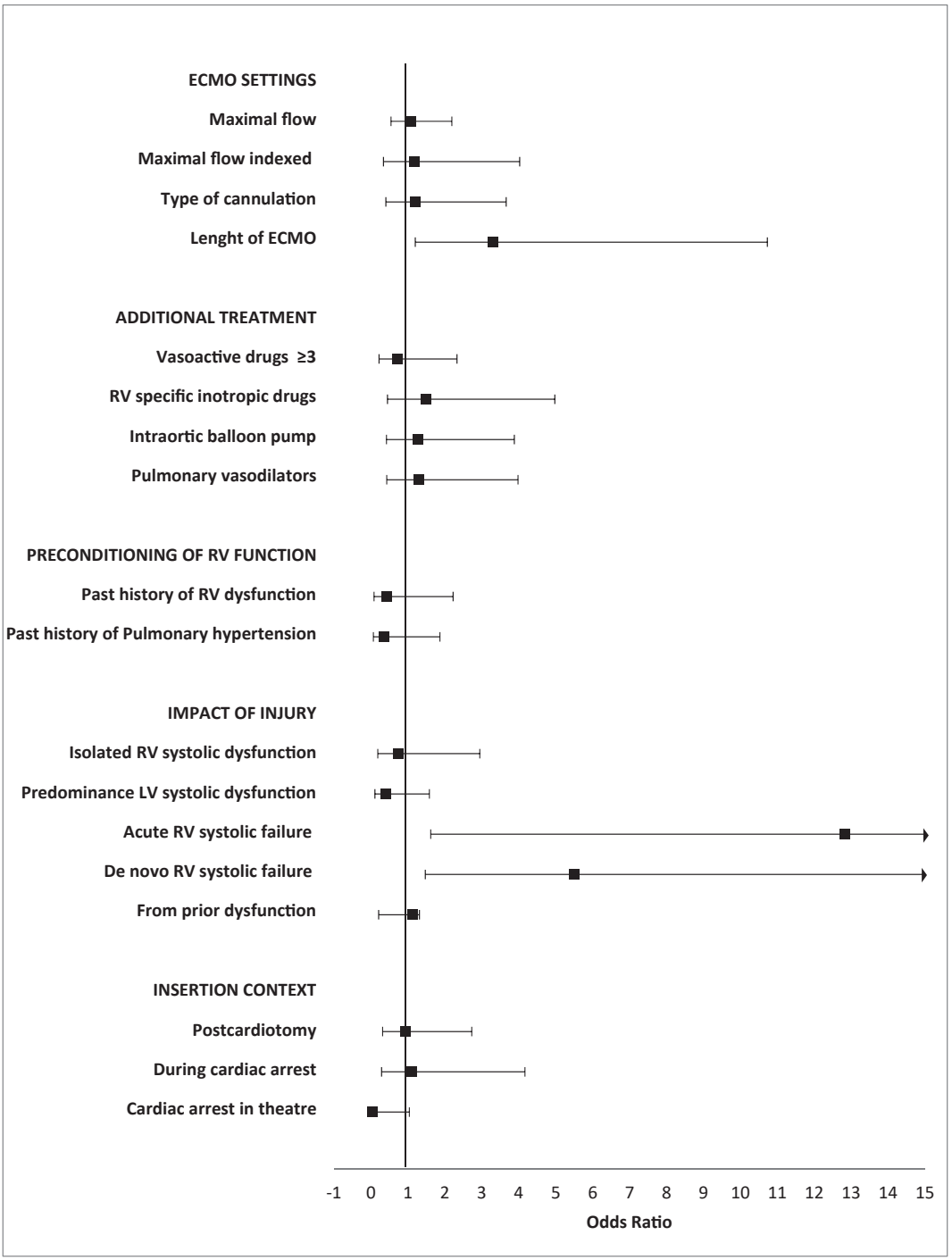

Figure 2. Predictors of improvement in RV systolic function during VA-ECMO support. Abbreviations: RV, right ventricle.

According to our results, the type of cannulation does not affect significantly neither RV size nor RV systolic function. Hypothetically, as central devices achieve greater RV unloading and generate less RV afterload compared with peripheral support devices,[19] we expected them to be associated with smaller RV diameters and probably a lower proportion of patients with RV systolic dysfunction after the therapy. In parallel, RV diameters did not change significantly when the presence of uni- and bi-ventricular systolic dysfunction was considered. Perhaps, the prevention and early management of RV dysfunction may have masked the presence of real differences.

We found three RV-related predictors probably associated with a successful weaning off VA-ECMO in patients with myocardial recovery: normal RV function before ECMO, normal RV function on the last day of support, or partial recovery of the RV function during the support. We observed that the preservation of a normal RV function (both, before insertion and on the last day of support) is crucial, as previously reported.[20] We assume that the adaptability to the hemodynamic stress associated with VA-ECMO is higher in these cases. A novel finding is that the improvement in RV function during short-term mechanical circulatory support, even partially, also favors weaning. Moreover, when RV systolic dysfunction

predominates over LV systolic dysfunction, the disconnection is hindered, reinforcing the concept of a key role of RV systolic function in allowing successful weaning. The study design does not allow understanding the real role that VA-ECMO, other therapies, or myocardial functional restoration plays in this improvement. However, based on this data, strategies for monitoring and targeting simultaneously LV and RV functional restoration may be designed to facilitate safer and more successful VA-ECMO weaning in the future.

Two factors associated with RV functional improvement during VA-ECMO support have been identified, the development of acute RV failure, mainly as "de novo" presentation, and a longer duration of mechanical support. It may be hypothesized that, given the particular pathophysiology of the RV.[21] there may be a significant component of stunned myocardium in the cases of acute RV failure, while in cases of deterioration of chronic RV dysfunction, the absence of compensatory reserve precludes the RV from overcoming the detrimental hemodynamic effects of VA-ECMO. More research is needed to understand the mechanisms of RV dysfunction and its improvement, and to find effective approaches to preserve or improve RV performance.

It is also possible that a longer ECMO support may buy more time for the RV to recover, particularly after an acute insult. However, it is important to remark that the longer the mechanical support is used, the higher the possibility of developing complications such as bleeding, leg ischemia, or infections. Therefore, finding the optimal time frame to allow recovery without increasing risks is essential for VA-ECMO.[22,23] The lack of influence of other factors in predicting RV functional improvement may be due to the small sample size, the highly heterogeneous group with multiple causes of cardiogenic shock, the different degrees of prior RV systolic function, often with severe dysfunction prior to insertion, or the classification of pulmonary hypertension as a dichotomic variable, missing potentially valuable information if analyzed as a continuous variable.

Interestingly, we observed no improvement in cases presenting with isolated RV failure. This was unexpected as we had speculated that with preserved LV systolic function, the RV would work under more favorable conditions, and this should facilitate functional recovery. Special circumstances such as cardiogenic shock after cardiac surgery or cardiac arrest, or specific interventions in the ECMO configuration, additional mechanical support or pharmacological therapies targeted to optimize RV function, did not make a difference as well.

A number of limitations deserve consideration in this study. Its retrospective design inherently implies the presence of bias and missing data. The global severity of the disease before the implantation of mechanical support was not measured by a validated score, but the separate analysis of the hemodynamic severity and the different organ failures gave us a vision of the complexity and seriousness of the study group, comparable to patients from other series, with predominantly hemodynamic deterioration over respiratory failure. The complex RV geometry and critical clinical situation of these patients (supine position, poor acoustic windows, limited time to perform the study, etc.) make the assessment of RV function particularly challenging by echocardiography. These conditions led us to evaluate the RV function mainly subjectively, missing many objective parameters (S′, fractional area change, right ventricular index of myocardial performance, dp/dt), and preventing us to use advanced new techniques, such as longitudinal strain measured by speckle tracking. Unfortunately, simultaneous invasive hemodynamic data were not collected and, therefore, the interpretation of isolated echocardiographic data is incomplete. The dose, time of onset, and duration of RV inotropic drugs and pulmonary vasodilators was not available as well. Finally, the factors related with successful weaning should be interpreted cautiously because our sample is slightly small to assert absolute association (only 32% of events)".

5. Conclusions

Although RV systolic function seems to be important for successful VA-ECMO weaning, we found no major differences in RV systolic performance assessed by echocardiography during VA-ECMO support in a heterogenous group of patients with cardiogenic shock. The type of cannulation used or the presence of uni- or bi-ventricular failure before ECMO implantation had no influence on RV functional evolution. Improvements in RV systolic function during mechanical support were, however, observed among patients with acute RV failure but not in those with deterioration of prior RV dysfunction. Preservation or improvement of RV function during mechanical support should be considered a priority since they are associated with successful weaning.

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Conflict of interest

Dr. Bueno received research funding from the Instituto de Salud Carlos III, Spain (PIE16/00021 & PI17/01799), AstraZeneca, BMS, and Novartis; has received consulting fees from AstraZeneca, Bayer, BMS-Pfizer, Novartis; and speaking fees or support for attending scientific meetings from Amgen, AstraZeneca, Bayer, BMS-Pfizer, Novartis, and Medscape-the heart.org. All other authors declare no conflicts of interest.

Appendix A. Supplementary data

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