

Supplemental Content

Preload responsiveness in patients with acute respiratory distress syndrome managed with extracorporeal membrane oxygenation

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Institutional management strategy for patients on **VV ECMO** support

*Indications for **veno-venous extracorporeal membrane oxygenation***

In agreement with the guidelines established by the Extracorporeal Life Support Organization ¹ and the EOLIA (ECMO to rescue lung injury in severe ARDS) trial ², veno-venous extracorporeal membrane oxygenation (**VV ECMO**) is initiated in fully sedated patients (Richmond Agitation-Sedation Scale -5) with

- arterial partial pressure of oxygen/fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) < 50 mmHg for longer than 3 h or
- $\text{PaO}_2/\text{FiO}_2$ < 80 mmHg for longer than 6 h or persistent acidosis (arterial pH < 7.25 and arterial partial pressure of carbon dioxide (PaCO_2) > 60 mmHg for longer than 6 h)

despite protective mechanical ventilation (tidal volume of 6 mL/kg, a positive end-expiratory pressure adjustment according to the ARDSNetwork table ³ and a driving pressure < 15 cmH₂O) and prone positioning ^{2,4-7}. Prone positioning and neuromuscular blocking agents are prescribed according to the attending physician.

Furthermore, **VV ECMO** is considered in severe acute respiratory distress syndrome (ARDS) without clinical improvement despite protective mechanical ventilation and at least two cycles of prone positioning ^{2,8}. We do not initiate **VV ECMO** support in patients who prefer palliative support, in patients with known end-stage chronic cardiopulmonary failure, and in patients with an expected survival of less than 24 h determined by the attending physician. In patients with therapy refractory hemodynamic instability (mean arterial pressure < 65 mmHg, heart rate > 130

beats/min, or cardiac index < 2.2 L/min/m²) without any relevant end-stage disease, we prefer to initiate veno-veno-arterial ECMO support ⁹.

Cannulation strategy

According to the standard operating procedure of our unit, a 29 French multi-stage drainage cannula (HLS Cannula, Maquet, Rastatt, Germany) and a 23 French venous return cannula (HLS Cannula, Maquet, Rastatt, Germany) are inserted through the right femoral and jugular veins, respectively. The **VV ECMO** circuit is completed with a magnetically levitated rotor pump (Centrimag Circulatory Support System, Abbot, GmbH, Wiesbaden, Germany) and gas exchange membrane (PLS System, Maquet, Rastatt, Germany).

ECMO management

The **VV ECMO** blood and gas flow are adjusted to obtain an arterial PaO₂ between 65 and 90 mmHg and an arterial pH of 7.35–7.45 ². During ECMO support, the ventilator is set to volume-controlled mode with a tidal volume of 2 mL/kg of predicted bodyweight, a respiratory rate of 12/min and a fraction of inspired oxygen of 40%. Positive end-expiratory pressure is titrated according to the lowest elastance of the respiratory system as described previously ¹⁰. If the arterial lactate level start to increase (> 2 mmol/L) under **VV ECMO** support, a Passive Leg Raised Test in conjunction with echocardiographic assessment is performed to evaluate cardiac preload and fluid responsiveness. A lack of fluid responsiveness requires further echocardiographic assessment to rule out right or left ventricular failure. A positive fluid balance in patients with ARDS has been associated with increased mortality and longer duration of mechanical ventilation ¹¹⁻¹³. Thus, after an initial **VV ECMO**

stabilization period, we use diuretics or hemodialysis to facilitate a negative fluid balance. After this initial stabilization period and achieving a negative fluid balance, we promote spontaneous breathing by tapering the analgo-sedation. If clinically feasible, a **VV ECMO** weaning trial is performed by reducing the **VV ECMO** gas flow to 0 L/min for at least 24 h. **VV ECMO** support is discontinued if the PaO₂ is > 70 mmHg and the arterial pH is > 7.25 have been achieved with a fraction of inspired oxygen < 60% and an inspiratory plateau pressure < 30 cmH₂O^{2,10}.

Description of the echocardiographic parameters

Measurements of Δ SVC and Δ IVC

The superior vena cava was visualized in a cross-section of a mid-esophageal right pulmonary vein. Changes in the diameter of the superior vena cava (Δ SVC) during the respiratory cycle were quantified with M-Mode. The inferior vena cava was examined using a similar approach from a transgastric view or a transabdominal approach if transgastric views were impossible to obtain¹⁴. Changes in the diameter (Δ IVC) were also quantified with M-Mode.

Measurements of SVV_Echo and $V_{max}Ao$ measurements

The diameter of the left ventricular outflow tract (dLVOT) was measured in a mid-esophageal long axis view, and the cross-sectional area was calculated as $(dLVOT/2)^2 \times \pi$. Cardiac stroke volume was calculated as the cross-sectional area times the velocity time integral in the left ventricular outflow tract obtained from pulsed wave Doppler in transgastric long axis view or deep transgastric five-chamber view. SVV_Echo was calculated as the maximum percentage change in the cardiac stroke

volume over 3 respiratory cycles. $\Delta V_{\max Ao}$ was derived from the maximal Doppler velocity in the LVOT.

$V_{\max TP}$ and VTI_{TP} measurements

VTI_{TP} was obtained from the pulsed wave Doppler signal in the truncus pulmonalis from a mid-esophageal ascending aorta short axis view. ΔVTI_{TP} was calculated as the maximum percentage change in the pulsed wave Doppler volume-time integral in the truncus pulmonalis over 3 respiratory cycles. $\Delta V_{\max TP}$ was derived from the maximal Doppler velocity in the truncus pulmonalis.

Right and left ventricular morphology and function

The size of the left (LV) and right ventricle (RV) was quantified by transthoracic echocardiography in an apical 4 chamber view and normalized to the body surface area. Change in the right ventricular fractional area was calculated as the difference between right ventricular end-diastolic area and right ventricular end-systolic area divided by the right ventricular end-diastolic area $\times 100$. Tricuspid annular plane systolic excursion was also obtained from an apical 4 chamber view using M-Mode through the tricuspid lateral annulus for measurement of the distance of systolic annular RV excursion with transthoracic echocardiography.

Additional statistical analyses

The overall performance, discriminative ability, and calibration of the logistic model was assessed. First, the fit of the logistic model was further tested using the likelihood ratio test. Second, we dichotomized the parameters with cut-off values in the clinically relevant range as well as for clinically relevant points on the ROC curves represented

by 90% sensitivity or 90% specificity and calculated the corresponding sensitivity, specificity, positive predictive value, negative predictive value, diagnostic odds ratio (DOR), and the Youden Index. DOR was calculated as a single, prevalence-independent indicator of diagnostic performance. DOR values range from zero to infinity, with higher values indicating better discriminatory performance. As the sensitivity and specificity of the test becomes near perfect, the DOR increases steeply¹⁵. The Youden Index further describes the performance of a dichotomous diagnostic test and is calculated as sensitivity + specificity - 100¹⁶. The best compromise between sensitivity and specificity for each parameter, as defined by the Youden Index, was derived from the ROC and used to dichotomize the continuous variables¹⁶. For specificity, sensitivity, positive predictive value, and negative predictive value, confidence intervals (CI) were calculated using the Wilson-Brown method. The CIs for the likelihood ratio and DOR were determined using the method proposed by Altman et al.¹⁷ and $\log(\text{DOR})$ with back-transformation¹⁵, respectively. Agreement between the predicted probability of the model and the observed probability was assessed graphically on a calibration curve. Intra- and inter-examination analysis of dynamic echocardiographic measurements were computed as described previously¹⁸. Briefly, the coefficient of variation (CV) is calculated as the standard deviation of three consecutive end-expiratory measurements divided by their mean. The coefficient of error (CE) is derived by dividing by the number of total measurements. Precision is then two times the CE. The least significant change (LSC) between two measurements has been defined as $\text{LSC} = \text{CE} \times 1.96 \times \sqrt{2}$ ¹⁹. According to Jozwiak et al.¹⁸, intra-examination analysis was conducted within one respiratory cycle and inter-

examination analysis between measurements of the first and the third respiratory cycle.

Supplemental results

There were no significant differences in AUC between $\Delta V_{\max TP}$, ΔVTI_{TP} , and SVV_PCA (**Supplemental Content Table S2**).

Supplemental Content Table S3 shows the diagnostic capability of $\Delta V_{\max TP}$, ΔVTI_{TP} , and SVV_PCA with respect to providing optimized sensitivity or specificity. For $\Delta V_{\max TP}$ we found a cut-off of $> 2.5\%$ when optimizing for sensitivity and $> 15.5\%$ when optimizing for specificity. The corresponding values were $> 2.2\%$ and $> 16.9\%$ for ΔVTI_{TP} and $> 7.5\%$ and $> 19.5\%$ for SVV_PCA.

Positive and negative predictive values as well as the diagnostic odds ratio and likelihood ratio for $\Delta V_{\max TP}$, ΔVTI_{TP} , and SVV_PCA are provided in **Supplemental Content Table S4**.

Supplemental Content Figure S5 shows the cumulative fluid balance in responders and non-responders at each time point.

Supplemental Content Tables S5-S7 provide the sensitivity and specificity for different cut-off values for $\Delta V_{\max TP}$, ΔVTI_{TP} , and SVV_PCA.

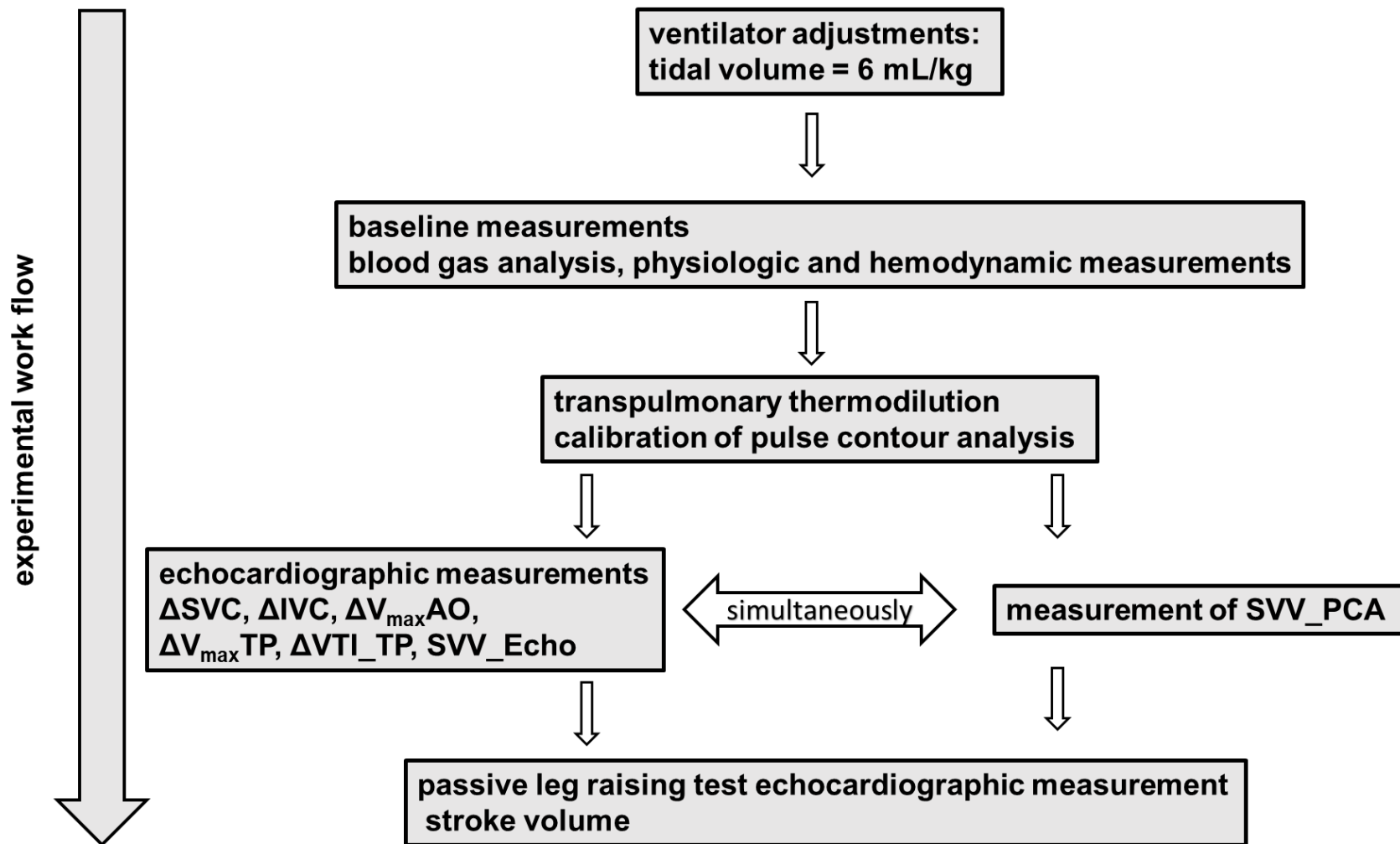


Fig. S1. Experimental workflow of the study

Table S1 Physiologic data of 20 patients immediately before the initiation of VV ECMO

Parameter	N = 20
Mechanical ventilation before VV ECMO (days)	4 ± 7
Out-of-house rescue cannulation, n	7
Indication for VV ECMO	
Hypoxemia, n	15
Hypercapnic failure/injurious mechanical ventilation, n	5
Systolic blood pressure (mmHg)	121 ± 15
Diastolic blood pressure (mmHg)	64 ± 9
Mean arterial pressure (mmHg)	83 ± 10
Central venous pressure (mmHg)	18 ± 4
Intraabdominal pressure (mmHg)	11 ± 6
Noradrenaline (µg/kg/min)	0.3 ± 0.4
Dobutamine (µg/kg/min)	0.0 ± 0.0
Fluid balance (ml)	1357 ± 2646
Respiratory rate (breaths/min)	22 ± 4
Tidal volume (mL)	451 ± 70
Tidal volume/kg bodyweight (mL/kg)	6.2 ± 1.1
Fraction of inspired oxygen (%)	85 ± 19
Peak airway pressure (cmH ₂ O)	38 ± 10
Airway plateau pressure (cmH ₂ O)	34 ± 9
Positive end-expiratory pressure (cmH ₂ O)	14 ± 4
Driving pressure (cmH ₂ O)	19 ± 11
Compliance of the respiratory system (mL/cmH ₂ O)	30 ± 18
Arterial partial pressure of oxygen (mmHg)	73 ± 27
Arterial oxygen saturation (%)	86 ± 15
Arterial partial pressure of carbon dioxide (mmHg)	69 ± 14
pHa	7.3 ± 0.0
Arterial lactate concentration (mmol/L)	2.8 ± 2.6
Central venous blood oxygen saturation (%)	73 ± 8

SV_TPTD (ml)	69 ± 19
Cardiac output TPTD (L/min)	6.5 ± 2.1
Cardiac index TPTD (L/min/m ²)	3.3 ± 1.1

Values are summarized as means ± standard deviation. **VV ECMO**, veno-venous extracorporeal membrane oxygenation; pHa, negative logarithm of the molar concentration of dissolved hydronium ions in arterial blood; SV, stroke volume; TPTD, transpulmonary thermodilution.

Table S2 Comparison of the area under the curve of dynamic parameters to predict preload responsiveness in patients managed with **VV ECMO**

Parameters compared	p value
$\Delta V_{\max TP}$ vs ΔVTI_{TP}	0.7225
$\Delta V_{\max TP}$ vs SVV_PCA	0.2422
ΔVTI_{TP} vs SVV_PCA	0.4144

Data are derived from non-parametric comparison of receiver operating characteristic curves derived from logistic regression of dynamic predictive parameters of 86 measurements in 20 patients with severe ARDS managed with **VV ECMO**. $\Delta V_{\max TP}$, respiratory variation of maximum Doppler velocity in the truncus pulmonalis; ΔVTI_{TP} , respiratory variation of velocity time integral in the truncus pulmonalis; SVV_PCA, stroke volume variation measured with pulse contour analysis after calibration with transpulmonary thermodilution.

Table S3 Diagnostic capability of dynamic parameters to predict preload responsiveness in patients with severe ARDS patients managed with **VV ECMO**

Parameters	Threshold value for optimized sensitivity	Optimized sensitivity (associated specificity), %	Threshold value for optimized specificity	Optimized specificity (associated sensitivity), %
$\Delta V_{\max TP}$ (%)	> 2.5	92 (23)	> 15.5	91 (22)
ΔVTI_{TP} (%)	> 2.2	89 (26)	> 16.9	91 (27)
SVV_PCA (%)	> 7.5	91 (47)	> 19.5	89 (34)

Threshold values for optimized sensitivity and specificity for $\Delta V_{\max TP}$, ΔVTI_{TP} , and SVV_PCA were calculated, and the diagnostic capabilities are shown as percentages. Values are presented as percentages and derived from the logistic regression of dynamic predictive parameters of 86 measurements in 20 patients with severe ARDS managed with **VV ECMO**. $\Delta V_{\max TP}$, respiratory variation of maximum Doppler velocity in the truncus pulmonalis; ΔVTI_{TP} , respiratory variation of velocity time integral in the truncus pulmonalis; SVV_PCA, stroke volume variation measured with pulse contour analysis after calibration with transpulmonary thermodilution.

Table S4 Diagnostic capability of dynamic parameters to predict preload responsiveness in patients managed with **VV ECMO** with corresponding indicators of test performance

Parameter	Sensitivity	Specificity	Cut-off, %	Positive predictive value	Negative predictive value	LHR	DOR
$\Delta V_{\max TP}$	91.89 (78.70–97.20)	23.40 (13.60–37.22)	> 2.5	48.57 (43.98–53.19)	78.57 (52.44–92.42)	1,20	3.46 (0.98–13.49)
$\Delta V_{\max TP}$	21.62 (11.39–37.20)	91.49 (80.07–96.64)	> 15.5	66.67 (39.48–85.98)	59.72 (55.07–64.21)	2.54	2.97 (0.82–10.77)
ΔVTI_{TP}	89.19 (74.58–96.97)	25.53 (13.94–40.35)	> 2.2	48.53 (43.53–53.56)	75.00 (51.30–89.52)	1.20	2.83 (0.83–9.65)
ΔVTI_{TP}	27.03 (13.79–44.12)	91.49 (79.62–97.63)	> 16.9	71.43 (46.00–88.00)	61.43 (56.24–66.37)	3.18	3.98 (1.14–13.97)
SVV_PCA	91.43 (77.62–97.04)	46.81 (33.33–60.77)	> 7.5	56.14 (49.00–63.03)	88.0 (70.44–95.76)	1.72	9.39 (2.52–34.96)
SVV_PCA	34.29 (19.13–52.21)	89.36 (76.90–96.45)	> 19.5	70.59 (48.21–86.09)	64.62 (58.50–70.29)	3.22	4.38 (1.37–13.99)

Data are derived from logistic regression of dynamic predictive parameters of 86 measurements in 20 patients with severe ARDS managed with **VV ECMO**. Cut-off values are presented as a percentage of the respiratory change of the respective parameter. Values are percentages with respective 95% CI for sensitivity, specificity, positive and negative predictive value, dimensionless value with respective 95% CI for DOR, or raw number for LHR. $\Delta V_{\max TP}$, respiratory variation of maximum Doppler velocity in the truncus pulmonalis; ΔVTI_{TP} , respiratory variation of the velocity time integral in the truncus pulmonalis; SVV_PCA, stroke volume variation measured with pulse contour analysis after calibration with transpulmonary thermodilution; LHR, likelihood ratio; DOR, diagnostic odds ratio.

Table S5 Predictive performance of respiratory variations of maximum Doppler velocity measured in the truncus pulmonalis ($\Delta V_{\max TP}$) at different cut-off values

Cut-off, %	Sensitivity	Specificity	Positive predictive value	Negative predictive value	DOR	Youden Index
> 2.5	91.89 (78.70–97.20)	23.40 (13.60–37.22)	48.57 (43.98–53.19)	78.57 (52.44–92.42)	3.46 (0.98– 13.49)	15.29
> 6.5	75.68 (59.88–86.64)	48.94 (35.28–62.76)	53.85 (45.51–61.97)	71.88 (57.43–82.88)	2.98 (1.16–7.66)	24.62
> 9.8	51.35 (35.89–66.55)	76.60 (62.78–86.40)	63.33 (48.54–75.98)	66.67 (58.09–74.27)	3.46 (1.36–8.79)	27.95*
> 14.0	27.03 (15.40–42.98)	87.23 (74.83–94.02)	62.50 (40.01–80.64)	60.29 (54.82–65.53)	2.53 (0.82–7.78)	14.26
> 15.5	21.62 (11.39–37.20)	91.49 (80.07–96.64)	66.67 (39.48–85.98)	59.72 (55.07–64.21)	2.97 (0.82– 10.77)	13.11

Data are derived from logistic regression of dynamic predictive parameters of 86 measurements of $\Delta V_{\max TP}$ in 20 patients with severe ARDS managed with **VV ECMO**. Cut-off values are presented as a percentage of the respiratory change of $\Delta V_{\max TP}$. Values are percentages with respective 95% CI for sensitivity, specificity, positive and negative predictive value, dimensionless value with respective 95% CI for the diagnostic odds ratio or raw number for Youden Index. DOR, diagnostic odds ratio.

*Maximum Youden Index.

Table S6 Predictive performance of respiratory variations of the velocity time integral measured in the truncus pulmonalis (Δ VTI_TP) at different cut-off values

Cut-off, %	Sensitivity	Specificity	Positive predictive value	Negative predictive value	DOR	Youden Index
> 1.8	91.89 (78.70–97.20)	25.53 (15.25–39.51)	49.28 (44.48–54.09)	80.00 (54.90–92.93)	3.9 (1.0–15.0)	17.42
> 5.3	78.38 (62.80–88.61)	51.06 (37.24–64.72)	55.77 (47.36–63.86)	75.00 (60.45–85.48)	3.8 (1.4–10.0)	29.44*
> 9.7	48.65 (33.45–64.11)	72.34 (58.24–83.06)	58.06 (43.95–70.97)	64.15 (55.52–71.95)	2.5 (1.0–6.1)	20.99
> 15.6	32.43 (19.63–48.54)	89.36 (77.41–95.37)	70.59 (48.13–86.12)	62.69 (56.83–68.20)	4.0 (1.3–12.8)	21.79
> 19.2	18.92 (9.48–34.20)	95.74 (85.75–99.24)	77.78 (43.57–94.07)	60.00 (55.94–63.93)	5.3 (1.0–27.0)	14.66

Data are derived from logistic regression of dynamic predictive parameters of 86 measurements of Δ VTI_TP in 20 patients with severe ARDS managed with **VV ECMO**. Cut-off values are presented as a percentage of the respiratory change of Δ VTI_TP. Values are percentages with respective 95% CI for sensitivity, specificity, positive and negative predictive value, dimensionless value with respective 95% CI for the diagnostic odds ratio or raw number for the Youden Index. DOR, diagnostic odds ratio.

*Maximum Youden Index.

Table S7 Predictive performance of stroke volume variation measured with pulse contour analysis after calibration with transpulmonary thermodilution (SVV_PCA) at different cut-off values

Cut-off	Sensitivity	Specificity	Positive predictive value	Negative predictive value	DOR	Youden Index
> 5.5	97.14 (85.47–99.85)	12.77 (5.99–25.17)	45.33 (42.30–48.40)	85.71 (43.06–97.94)	4.98 (0.57–43.73)	9.91
> 7.5	91.43 (77.62–97.04)	46.81 (33.33–60.77)	56.14 (49.00–63.03)	88.00 (70.44–95.76)	9.39 (2.52–34.96)	38.24*
> 10.5	68.57 (52.02–81.45)	68.09 (53.83–79.60)	61.54 (49.90–71.99)	74.42 (63.20–83.13)	4.66 (1.81–11.93)	36.66
> 14.5	48.57 (32.99–64.43)	76.6 (62.78–86.40)	60.71 (45.41–74.17)	66.67 (58.29–74.11)	3.10 (1.20–7.96)	25.17
> 16.5	42.86 (27.98–59.14)	82.98 (69.86–91.11)	65.22 (47.27–79.68)	66.10 (58.74–72.76)	3.66 (1.33–10.10)	25.84
> 20.5	34.29 (20.83–50.85)	93.62 (82.84–97.81)	80.00 (54.96–92.91)	65.67 (59.82–71.08)	7.65 (1.96–29.87)	27.91

Data are derived from logistic regression of 86 measurements of SVV_PCA in 20 patients with severe ARDS managed with **VV ECMO**. Cut-off values are presented as percentage of the respiratory change of the respective parameter. Values are percentage with respective 95% CI for sensitivity, specificity, positive and negative predictive value, dimensionless value with respective 95% CI for the diagnostic odds ratio or raw number for Youden Index. DOR = diagnostic odds ratio, * = maximum Youden Index.

Table S8 Intra- and inter-examination characteristics of dynamic echocardiographic measurements

Parameter	Intra-examination analysis			
	CV	CE	LSC, %	PE, %
SV_Echo	0.03 (0.02–0.04)	0.01 (0.01–0.02)	4 (2–6)	2 (–1- to 5)
V _{max} AO	0.02 (0.01–0.03)	0.01 (0.01–0.02)	3 (2–5)	0 (–3 to 3)
VTI_TP	0.04 (0.02–0.06)	0.02 (0.01–0.04)	5 (3–11)	–3 (–7 to 3)
V _{max} TP	0.03 (0.02–0.04)	0.02 (0.01–0.05)	5 (3–7)	–1 (–11 to 2)
SVC	Not applicable*			
IVC	Not applicable*			
Inter-examination, intra-observer analysis				
SV_Echo	0.03 (0.02–0.05)	0.01 (0.01–0.02)	5 (4–8)	0 (–3 to 2)
V _{max} AO	0.04 (0.02–0.04)	0.01 (0.01–0.01)	6 (3–6)	0 (–1 to 1)
VTI_TP	0.04 (0.03–0.06)	0.01 (0.01–0.04)	6 (4–8)	0 (–2 to 0)
V _{max} TP	0.04 (0.03–0.05)	0.02 (0.01–0.04)	6 (4–8)	0 (–1 to 0)
SVC	0.03 (0.00 –0.05)	0.02 (0.00–0.04)	6 (0–8)	0 (–1 to 0)
IVC	0.02 (0.02–0.04)	0.01 (0.01–0.05)	5 (3–9)	0 (–2 to 0)

Data are summarized as medians and the corresponding interquartile range. SV_Echo, cardiac stroke volume measured with echocardiography; V_{max} AO, maximum Doppler velocity in the left ventricular outflow tract; VTI_TP, velocity time integral in the truncus pulmonalis; V_{max}TP, maximum Doppler velocity in the truncus pulmonalis; SVC, diameter of the superior vena cava; IVC, diameter of inferior vena cava; CV, coefficient of variation; CE, coefficient of error; LSC, least significant change; PE, percentage error.

*SVC and IVC were measured once per expiration, and 3 times in total in different respiratory cycles. Therefore, the intra-examination analysis is not applicable.

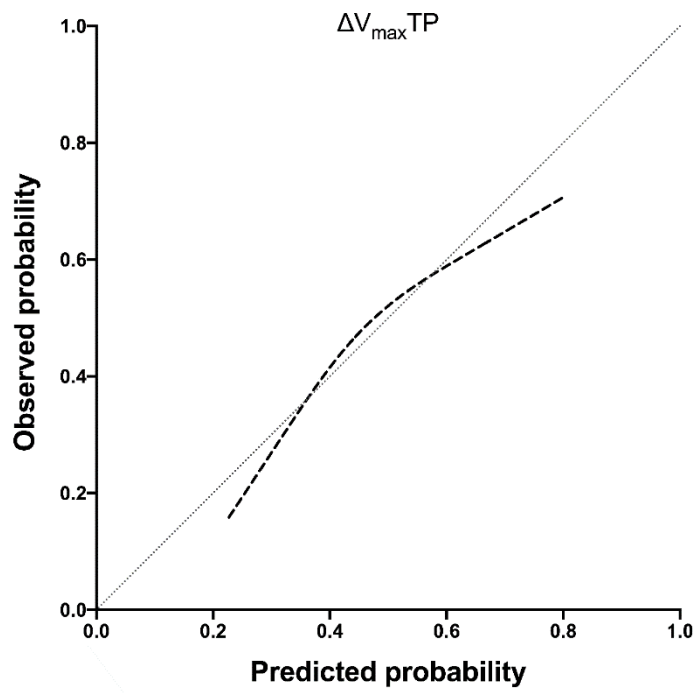


Fig. S2. Calibration curve of respiratory variations of the maximum Doppler velocity measured in the truncus pulmonalis ($\Delta V_{\max} TP$) of 86 measurements in 20 patients with severe ARDS managed with **VV ECMO**. Calibration curves were plotted using spline curve fitting

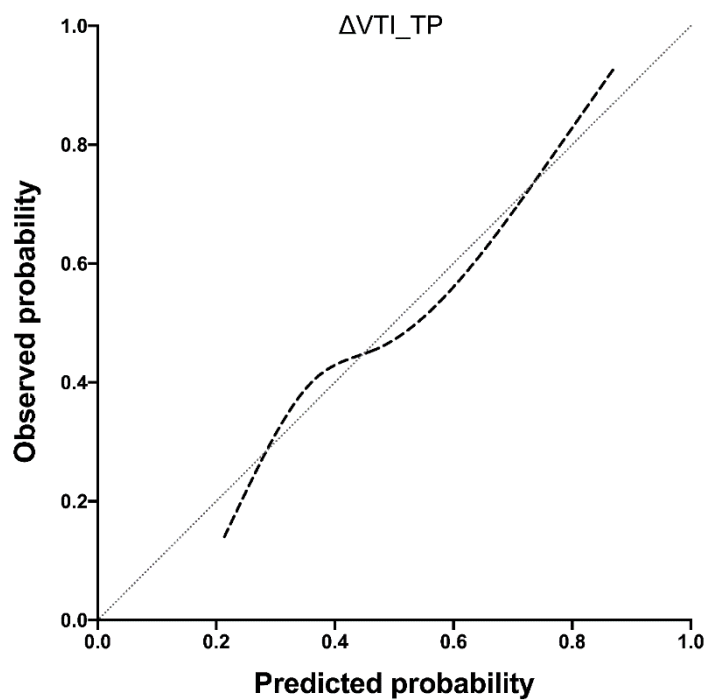


Fig. S3. Calibration curve of respiratory variations of the velocity time integral measured in the truncus pulmonalis ($\Delta\text{VTI_TP}$) of 86 measurements in 20 patients with severe ARDS managed with **VV ECMO**. Calibration curves were plotted using spline curve fitting

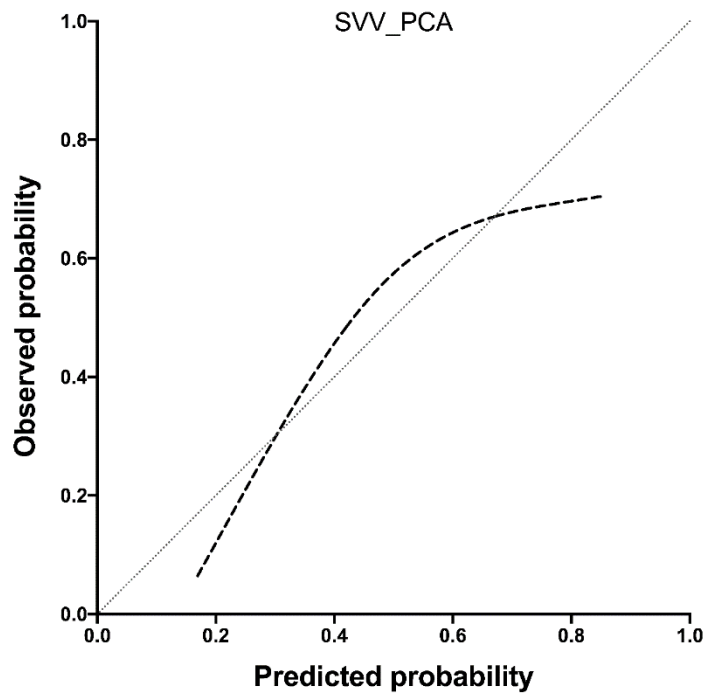


Fig. S4. Calibration curve of stroke volume variation measured with pulse contour analysis after calibration with transpulmonary thermodilution at distinctive cut-off values (SVV_PCA) of 86 measurements in 20 patients with severe ARDS managed with **VV ECMO**. Calibration curves were plotted using spline curve fitting

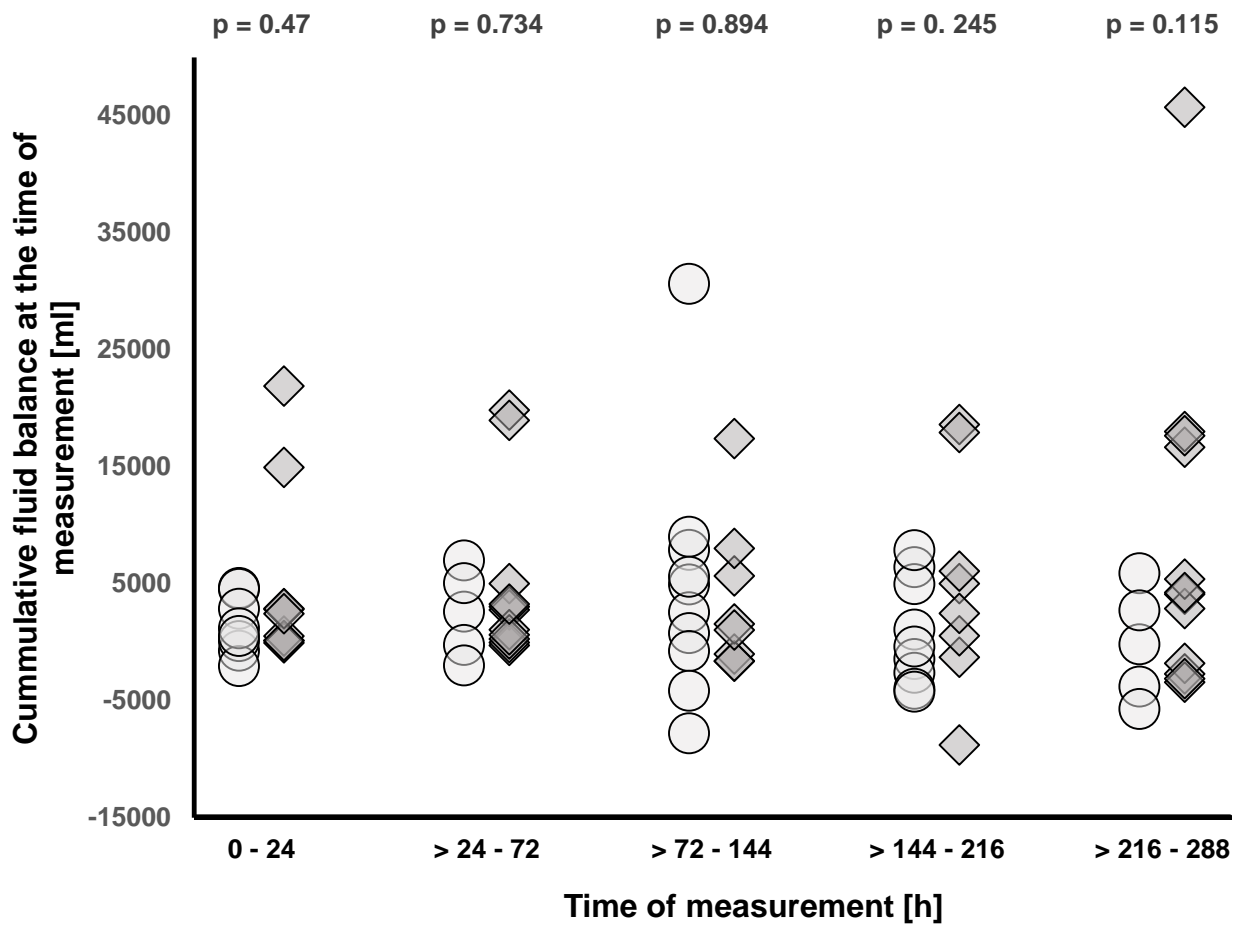


Fig. S5. Cumulative fluid balance of responders and non- responders at each time point. Light grey circles denote responders; dark grey rhombus denote non-responders

Abbreviations

(Δ)IVC	(respiratory variation of the) inferior vena cava
(Δ)SVC	(respiratory variation of the) superior vena cava
(Δ)V _{max} Ao	(respiratory variation of the) maximal Doppler velocity in the left ventricular outflow tract
(Δ)V _{max} TP	(respiratory variation of the) maximal Doppler velocity in the truncus pulmonalis
(Δ)VTI_TP	(respiratory variation of the) velocity time integral measured in the truncus pulmonalis
ARDS	acute respiratory distress syndrome
CE	coefficient of error
CI	confidence interval
CV	coefficient of variation
(d)LVOT	(diameter of the) left ventricular outflow tract
DOR	diagnostic odds ratio
EOLIA	ECMO to rescue Lung Injury in severe ARDS trial
FiO ₂	fraction of inspired oxygen
ICU	intensive care unit
IQR	interquartile range
LHR	likelihood ratio

LSC	least significant change
LV	left ventricle
non-responders	patients deemed to be in a state of fluid non-responsiveness to the PLRT
PLRT	Passive Leg Raise Test
PaCO ₂	partial pressure of carbon dioxide
PaO ₂	partial pressure of oxygen
PE	percentage error
pHa	negative logarithm of the molar concentration of dissolved hydronium ions in arterial blood
PLRT	Passive Leg Raise Test
responders	patients deemed to be in a state of fluid responsiveness to the PLRT
ROC	receiver operating characteristics
RV	right ventricle
SV	stroke volume
SVC	superior vena cava
SVV	stroke volume variation
SVV_Echo	stroke volume variation measured with echocardiography
SVV_PCA	stroke volume variation measured with pulse contour analysis after calibration with transpulmonary thermodilution
SVC	superior vena cava
TPTD	transpulmonary thermodilution

VTI velocity time integral

(VV) ECMO (veno-venous) extracorporeal membrane oxygenation

References

1. Tonna JE, Abrams D, Brodie D, *et al*: Management of Adult Patients Supported with Venovenous Extracorporeal Membrane Oxygenation (VV ECMO): Guideline from the Extracorporeal Life Support Organization (ELSO). *ASAIO journal* 67 (6): 601-610, 2021 doi: 10.1097/MAT.0000000000001432.
2. Combes A, Hajage D, Capellier G, *et al*: Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome. *The New England journal of medicine* 378 (21): 1965-1975, 2018 doi: 10.1056/NEJMoa1800385.
3. Acute Respiratory Distress Syndrome N, Brower RG, Matthay MA, *et al*: Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *The New England journal of medicine* 342 (18): 1301-8, 2000 doi: 10.1056/NEJM200005043421801.
4. Amato MB, Meade MO, Slutsky AS, *et al*: Driving pressure and survival in the acute respiratory distress syndrome. *The New England journal of medicine* 372 (8): 747-55, 2015 doi: 10.1056/NEJMsa1410639.
5. Shekar K, Badulak J, Peek G, *et al*: Extracorporeal Life Support Organization Coronavirus Disease 2019 Interim Guidelines: A Consensus Document from an International Group of Interdisciplinary Extracorporeal Membrane Oxygenation Providers. *ASAIO J* 66 (7): 707-721, 2020 doi: 10.1097/MAT.0000000000001193.
6. Brower RG, Lanken PN, MacIntyre N, *et al*: Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *The New England journal of medicine* 351 (4): 327-36, 2004 doi: 10.1056/NEJMoa032193.
7. Krebs J, Pelosi P, Rocco PRM, Hagmann M, Luecke T: Positive end-expiratory pressure titrated according to respiratory system mechanics or to ARDSNetwork table did not guarantee positive end-expiratory transpulmonary pressure in acute respiratory distress syndrome. *J Crit Care* 48: 433-442, 2018 doi: 10.1016/j.jcrc.2018.10.005.
8. Schmidt M, Pham T, Arcadipane A, *et al*: Mechanical Ventilation Management during Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome. An International Multicenter Prospective Cohort. *Am J Respir Crit Care Med* 200 (8): 1002-1012, 2019 doi: 10.1164/rccm.201806-1094OC.
9. Sandrio S, Krebs J, Leonardy E, Thiel M, Schoettler JJ: Vasoactive Inotropic Score as a Prognostic Factor during (Cardio-) Respiratory ECMO. *J Clin Med* 11 (9), 2022 doi: 10.3390/jcm11092390.
10. Graf PT, Boesing C, Brumm I, *et al*: Ultraprotective versus apneic ventilation in acute respiratory distress syndrome patients with extracorporeal membrane oxygenation: a physiological study. *J Intensive Care* 10 (1): 12, 2022 doi: 10.1186/s40560-022-00604-9.
11. Shah A, Menaker J, Mazzeffi MA, *et al*: Association of Volume Status During Venovenous Extracorporeal Membrane Oxygenation with Outcome. *Asaio j*, 2021 doi: 10.1097/mat.0000000000001642.
12. National Heart L, Blood Institute Acute Respiratory Distress Syndrome Clinical Trials N, Wiedemann HP, *et al*: Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 354 (24): 2564-75, 2006 doi: 10.1056/NEJMoa062200.
13. Seitz KP, Caldwell ES, Hough CL: Fluid management in ARDS: an evaluation of current practice and the association between early diuretic use and hospital mortality. *J Intensive Care* 8: 78, 2020 doi: 10.1186/s40560-020-00496-7.
14. Meierhenric R, Gauss A, Georgieff M, Schütz W: Use of multi-plane transoesophageal echocardiography in visualization of the main hepatic veins and acquisition of Doppler sonography curves. Comparison with the transabdominal approach. *Br J Anaesth* 87 (5): 711-7, 2001 doi: 10.1093/bja/87.5.711.
15. Glas AS, Lijmer JG, Prins MH, Bonsel GJ, Bossuyt PM: The diagnostic odds ratio: a single indicator of test performance. *J Clin Epidemiol* 56 (11): 1129-35, 2003 doi: 10.1016/s0895-4356(03)00177-x.
16. Youden WJ: Index for rating diagnostic tests. *Cancer* 3 (1): 32-5, 1950 doi: 10.1002/1097-0142(1950)3:1<32::aid-cnrcr2820030106>3.0.co;2-3.

17. Altman DG, Machin D, Bryant TN, Gardner MJ: *Statistics with confidence*. BMJ Books, 2000, pp 109.
18. Jozwiak M, Mercado P, Teboul JL, *et al*: What is the lowest change in cardiac output that transthoracic echocardiography can detect? *Critical care (London, England)* 23 (1): 116, 2019 doi: 10.1186/s13054-019-2413-x.
19. Cecconi M, Rhodes A, Poloniecki J, Della Rocca G, Grounds RM: Bench-to-bedside review: the importance of the precision of the reference technique in method comparison studies--with specific reference to the measurement of cardiac output. *Critical care (London, England)* 13 (1): 201, 2009 doi: 10.1186/cc7129.