Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

ECMO Configuration and Equipment

All participants had a 25 French multistage drainage ECMO cannula in the right or left femoral vein with a 21 French return cannula placed in either right or left internal jugular vein. The Maquet Cardiohelp ECMO circuit (Getinge, Germany), was utilized with the HLS 7.0-liter pump and oxygenator. The fractional concentration of oxygen delivered to the membrane oxygenator was 1.0 during the entire study period. The sweep gas flow was adjusted to maintain a normal plasma pH between 7.35-7.45.

Norepinephrine equivalent dose and mechanical work equations:

Norepinephrine equivalent dose = [norepinephrine (mcg/min)] + [dopamine (mcg/kg/min) ÷ 2] + [epinephrine (mcg/min)] + [phenylephrine (mcg/min) ÷ 10]

Mechanical Work (pressure ventilation) = RR * V_t * [PEEP + (pplat - PEEP)] * 0.098

RR: respiratory rate. V_t: tidal volume. PEEP: positive end-expiratory pressure. Pplat: plateau pressure. * Multiplication.

Sample	**Timing and Ventilator Setting**
Protocol Sample 1: Timing: Ventilator Setting:	Pre-ECMO with LTVV 30 minutes pre-ECMO initiation Volume Targeted Pressure Control LTVV - TV of ~6 ml/kg of PBW **(Standard of Care)**
Protocol Sample 2 Timing: Ventilator Setting:	Post-ECMO with LTVV 30 minutes post-ECMO initiation (immediately prior to LDVP) Volume Targeted Pressure Control LTVV - TV of ~6 ml/kg of PBW **(Standard of Care)**
Protocol Sample 3 Timing: Ventilator Setting:	Post-ECMO with LDPV Post-ECMO, ideally next calendar day (immediately prior to V-LDPV) Pressure Control Ventilation LDVP - ΔP 10-15 cmH_2O, PEEP of 10 cmH_2O, RR 10 **(ELSO guidelines)**
Protocol Sample 4 Timing: Ventilator Setting:	Post-ECMO with V-LDPV Post-ECMO, 2 hours post V-LDPV Pressure Control Ventilation V-LDPV - ΔP 1 cmH_2O, unchanged PEEP and RR **(Experiment)**
Protocol Sample 5 Timing: Ventilator Setting:	Post-ECMO with LDPV Post-ECMO, two hours after returning to LDPV from V-LDPV (main intervention) Pressure Control Ventilation LDVP - ΔP 10-15 cmH_2O, PEEP of 10 cmH_2O, RR 10 **(ELSO guidelines)**
Protocol Sample 6 Timing: Ventilator Setting:	24 hours post-ECMO 24 hours post-initiation of ECMO (drawn only if participant did not have V-LDPV protocol) Pressure Control Ventilation LDVP - ΔP 10-15 cmH_2O, PEEP of 10 cmH_2O, RR 10 **(ELSO guidelines)**

Table S1: Protocol sample timing and ventilator settings. Protocol sample 6 was obtained in 4 participants who did not have V-LDPV performed (thus missing protocol sample 4 and 5). LTVV, low tidal volume ventilation. TV, tidal volume. DP and ΔP: Driving Pressure. PBW, predicted body weight. RR, Respiratory Rate. ELSO, extracorporeal life support organization. LDPV, low driving pressure ventilation. V-LDPV, very low driving pressure ventilation. cmH_2O: centimeters of water. PEEP, positive end-expiratory pressure.

Safety and Tolerability Parameters	LDPV	V-LDPV	p-value
Heart Rate, beats per minute	83.3 ± 20.5	85.6 ± 15.6	0.447
Pulse Oximetry, %	96 ± 2	96 ± 2	0.369
Mean Arterial Pressure, mmHg	74.9 ± 7.6	73.4 ± 7.9	0.314
Norepinephrine equivalent dose, mcg/kg/min	0.099 ± 0.104	0.099 ± 0.143	0.985
ECMO circuit blood flow, L/min	4.8 ± 0.6	4.9 ± 0.6	0.297
ECMO sweep gas flow rate, L/min	4.8 ± 1.9	4.9 ± 2.0	0.162

Table S2: ECMO and vitals during LDPV and V-LDPV. LDPV, low-driving pressure ventilation. V-LVDP, very-low-driving pressure ventilation. Mcg/kg/min, micrograms per kilogram per minute. L/min, liters per minute. mmHg, millimeters of mercury. %, percent.

	N	Mean	SD	Min	Q1	Median	Q3	Max	p.value	BHadj.pval
logsRAGE										
preECMO	14	6.324	3.976	-2.303	6.802	7.162	7.837	12.345	0.024	0.062
postECMO	14	6.671	4.107	-2.303	6.941	7.74	8.061	12.492		
logIL.6										
preECMO	14	5.718	0.826	4.278	5.147	5.823	6.355	7.098	0.126	0.183
postECMO	14	5.804	0.892	4.18	5.23	5.842	6.358	7.527		
logIL.8										
preECMO	14	5.576	0.661	3.953	5.215	5.627	5.944	6.689	0.077	0.142
postECMO	14	5.787	0.849	3.885	5.319	5.868	6.235	7.23		
logCCL5										
preECMO	14	8.775	1.132	6.893	7.894	8.634	9.519	10.877	0.638	0.691
postECMO	14	8.679	1.175	7.085	7.592	8.789	9.378	11.127		
logAngio.2										
preECMO	14	7.693	0.865	5.991	7.245	7.647	7.935	9.819	0.18	0.234
postECMO	14	7.656	0.854	5.957	7.249	7.603	7.952	9.755		
logAngio.1										
preECMO	14	7.18	2.857	-2.303	7.077	7.829	8.511	9.225	0.292	0.345
postECMO	14	7.02	2.865	-2.303	6.535	8.015	8.352	8.944		
logIP.10										
preECMO	14	7.559	0.67	6.448	7.258	7.501	8.029	8.661	0.017	0.054
postECMO	14	7.79	0.532	6.962	7.491	7.66	8.018	8.918		
logTNF.alpha										
preECMO	14	3.425	0.954	1.675	3.136	3.312	3.552	5.793	0.002	0.011
postECMO	14	3.827	0.894	2.745	3.413	3.636	4.005	6.352		
logIFN.alpha										
preECMO	14	6.274	0.845	4.947	5.933	6.082	6.451	8.744	0.707	0.707
postECMO	14	6.187	0.52	5.267	5.821	6.197	6.513	7.054		
logCCL2										
preECMO	14	6.817	0.551	5.545	6.676	6.756	7.066	7.797	0.124	0.183
postECMO	14	6.984	0.573	6.271	6.657	6.779	7.108	8.445		
logCXCL9										
preECMO	14	7.817	0.929	5.895	7.339	7.958	8.043	9.743	<0.001	0.002
postECMO	14	8.598	1.066	6.268	8.309	8.704	9.163	10.148		
logIL.10										
preECMO	14	3.449	0.46	2.565	3.276	3.507	3.69	4.371	0.04	0.088
postECMO	14	3.31	0.489	2.56	3.116	3.206	3.596	4.435		
logVEGF										
preECMO	14	4.439	0.638	3.177	4.217	4.59	4.815	5.289	0.002	0.011
postECMO	14	3.564	0.789	1.89	3.274	3.739	4.023	4.532		

Table S3: Pre-ECMO (protocol sample 1 - LTVV) vs. Post-ECMO (protocol sample 2 - LTVV). Only participants with protocol sample 1 and 2 were included in this analysis, n = 14. LTVV, low tidal volume ventilation.

	N	Mean	SD	Min	Q1	Median	Q3	Max	p.value	BHadj.pval
logsRAGE										
LTVV	16	6.545	3.751	-2.303	6.835	7.402	7.92	12.345	0.607	0.657
LDPV	16	6.654	3.794	-2.303	6.581	7.518	8.187	11.65		
logIL.6										
LTVV	16	5.832	0.998	4.278	5.112	5.823	6.44	8.148	0.422	0.548
LDPV	16	5.966	0.926	4.77	5.199	5.746	6.394	7.57		
logIL.8										
LTVV	16	5.619	0.63	3.953	5.233	5.721	5.982	6.689	0.312	0.507
LDPV	16	5.691	0.792	3.947	5.414	5.803	6.085	7.432		
logCCL5										
LTVV	16	8.886	1.126	6.893	7.927	8.932	9.576	10.877	0.201	0.372
LDPV	16	8.583	1.089	7.229	7.725	8.332	9.403	10.637		
logAngio.2										
LTVV	16	7.693	0.806	5.991	7.278	7.694	7.921	9.819	0.16	0.372
LDPV	16	7.762	0.759	6.427	7.351	7.677	8.143	9.749		
logAngio.1										
LTVV	16	7.256	2.675	-2.303	7.176	7.829	8.497	9.225	0.182	0.372
LDPV	16	6.973	2.67	-2.303	6.811	7.488	8.425	9.422		
logIP.10										
LTVV	16	7.621	0.708	6.448	7.258	7.501	8.134	8.846	0.04	0.131
LDPV	16	7.777	0.607	6.881	7.232	7.761	8.155	8.888		
logTNF.alpha										
LTVV	16	3.41	0.901	1.675	3.068	3.312	3.615	5.793	0.836	0.836
LDPV	16	3.326	1.658	-2.303	3.042	3.411	4.436	4.67		
logIFN.alpha										
LTVV	16	6.29	0.788	4.947	5.936	6.212	6.424	8.744	0.501	0.592
LDPV	16	6.136	0.481	5.44	5.741	6.125	6.505	6.815		
logCCL2										
LTVV	16	6.912	0.575	5.545	6.703	6.803	7.445	7.797	0.01	0.068
LDPV	16	7.188	0.585	6.299	6.697	7.161	7.61	8.383		
logCXCL9										
LTVV	16	7.936	0.926	5.895	7.371	7.982	8.538	9.743	0.001	0.018
LDPV	16	8.345	0.938	6.297	7.862	8.294	8.811	10.301		
logIL.10										
LTVV	16	3.422	0.435	2.565	3.274	3.41	3.593	4.371	0.364	0.525
LDPV	16	3.354	0.412	2.462	3.09	3.36	3.588	4.185		
logVEGF										
LTVV	16	4.462	0.599	3.177	4.318	4.59	4.782	5.289	0.025	0.108
LDPV	16	4.126	0.691	2.645	3.739	4.099	4.518	5.314		

Table S4: Pre-ECMO (protocol sample 1 - LTVV) vs. Post-ECMO (protocol sample 3 - LDPV or protocol sample 6 - LDPV). Protocol sample 6 was used if participants (n=4) did not undergo V-LDPV. Only participants with protocol sample 1 - LTVV were included in this analysis, n = 16. LTVV, low tidal volume ventilation. LDPV, low-driving pressure ventilation.

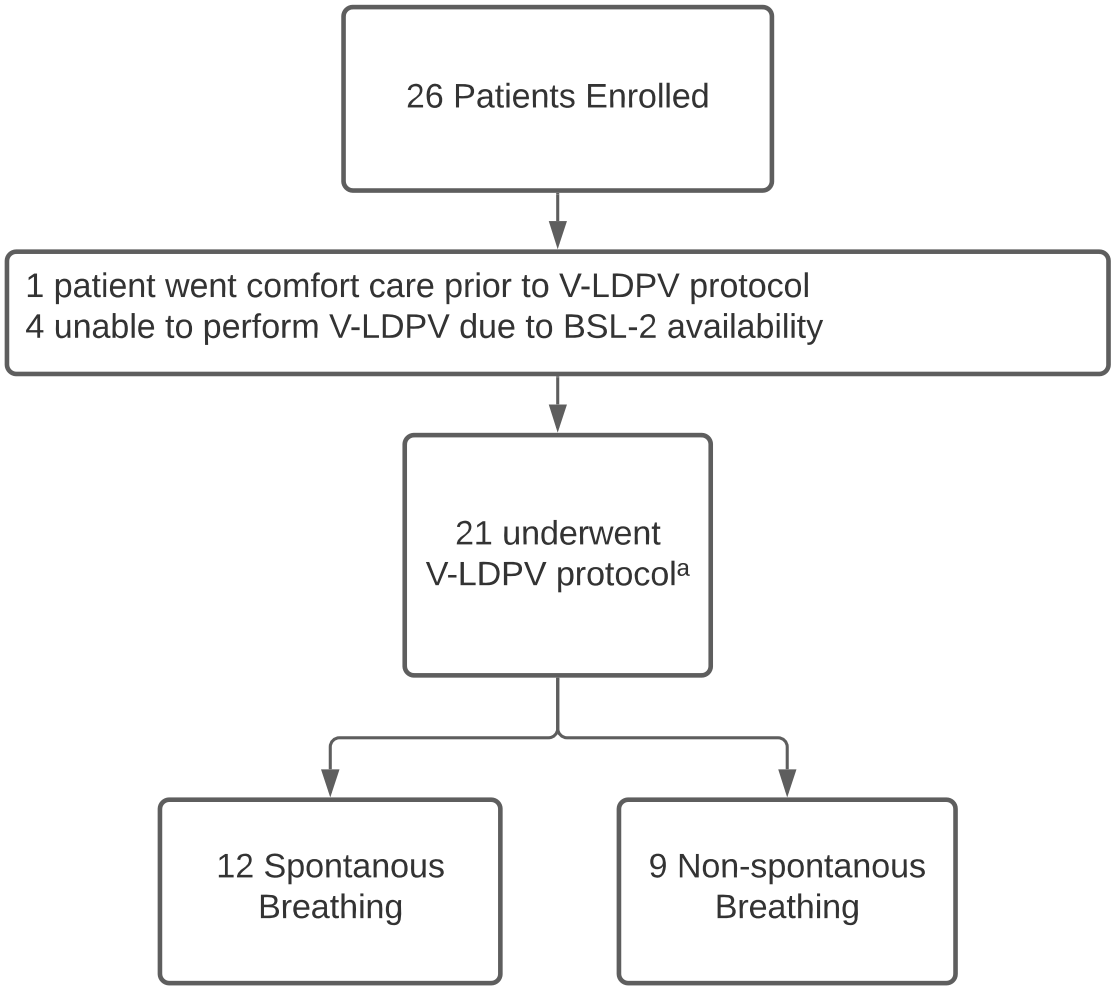

Figure S1: Consort diagram. Total 25 participants. Twenty-one participants had very-low driving pressure ventilation (V-LDPV). [a]Sixteen participants had protocol sample 1 (pre-ECMO sample), 9 participants without protocol sample 1 and 11 patients without protocol sample 2 due to mobile ECMO and BLS-2 unavailable respectfully. BSL-2, biosafety lab level-2.

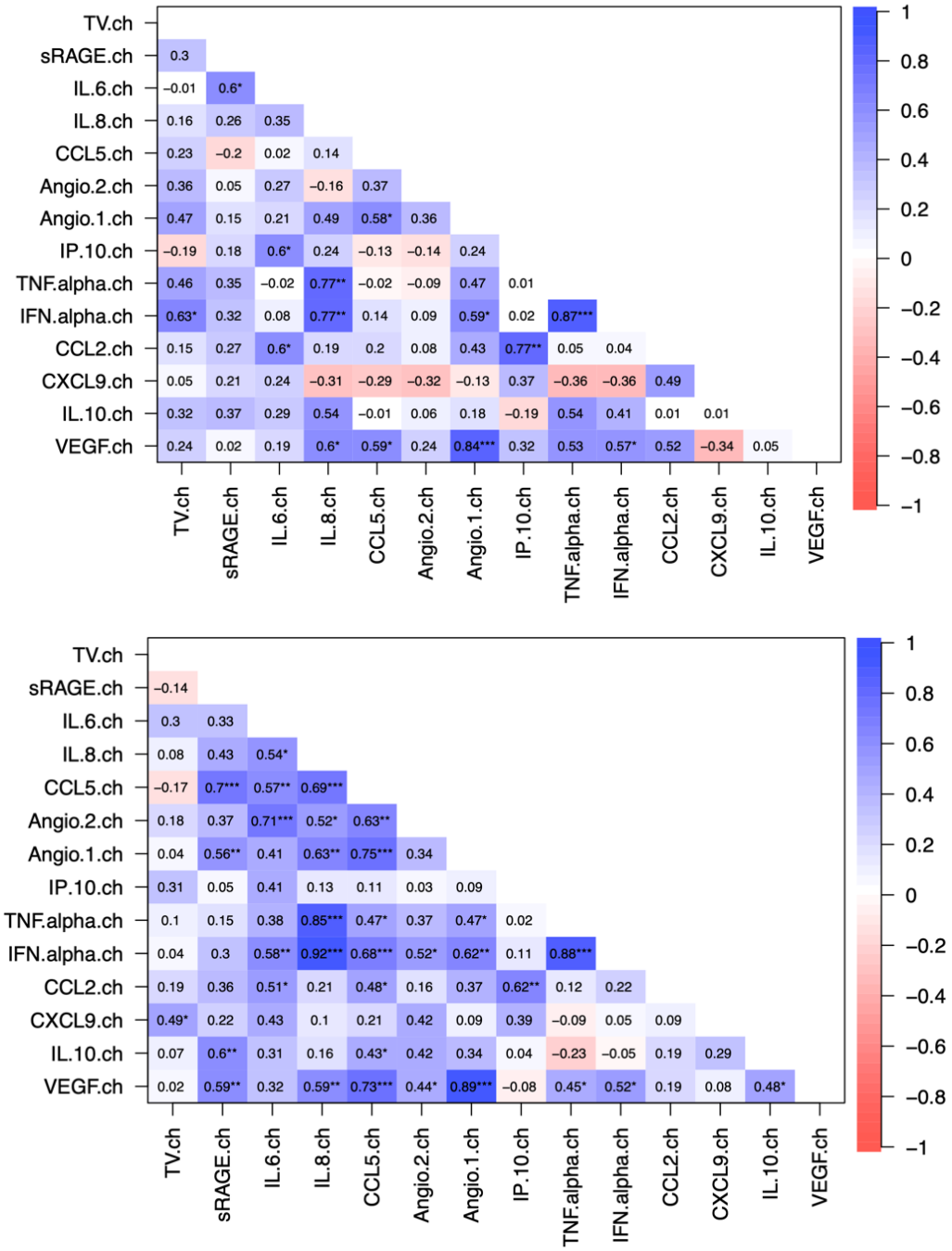

Figure S2: Pairwise Spearman's Correlation between biomarkers and change in tidal volume. Top graph represents changes from sample 1 (pre-ECMO with LTVV) to sample 3 (post-ECMO, LDPV), n=13. Bottom graph represents changes from sample 3 (LDPV) to sample 4 (V-LDPV), n=21. Blue and red boxes represent a positive and negative correlation respectfully. Darker blue or red colors represent a stronger correlation. LTVV, low tidal volume ventilation. LDPV, low-driving pressure ventilation. V-LVDP, very-low-driving pressure ventilation. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.