

Supplementary material

eTable 1 – Cerebrospinal fluid parameters in participants with neurological post-acute sequelae of SARS-CoV2 (Neuro-PASC)

<u>Participant</u>	<u>White blood cells in CSF</u> <u>(cells/mm³)</u>	<u>CSF protein</u> <u>(mg/dL)</u>	<u>CSF glucose</u> <u>(mg/dL)</u>	<u>CSF</u> <u>IgG-index</u>	<u>CSF-serum oligoclonal</u> <u>bands pattern^a</u>
<u>1</u>	4	52	60	0.64	4
<u>2</u>	0	35	74	0.58	1
<u>3</u>	1	30	60	0.52	1
<u>4</u>	1	30	72	0.51	2
<u>5</u>	2	33	62	0.47	1
<u>6</u>	2	31	59	0.52	4
<u>7</u>	1	21	66	0.48	1
<u>8</u>	3	38	66	1.10	2
<u>9</u>	1	24	50	0.51	1
<u>10</u>	2	30	65	0.55	1
<u>11</u>	0	35	76	0.48	3
<u>12</u>	1	27	55	0.51	1

^a CSF-serum oligoclonal bands pattern are as follows; 1 - no bands in CSF and serum; 2 - oligoclonal IgG bands in CSF but not in serum, indicative of intrathecal IgG synthesis; 3 – specific oligoclonal bands in CSF and also identical oligoclonal bands in serum and CSF, indicative of intrathecal IgG synthesis; 4 - identical pattern of oligoclonal bands in CSF and serum

Bold signifies a value outside the reference range.

CSF – cerebrospinal fluid; IgG – immunoglobulin G

eTable 2 – Serum and cerebrospinal fluid levels of Anti-SARS-CoV2 antibody levels in participants with neurological post-acute sequelae of SARS-CoV2 (Neuro-PASC)

<u>Participant</u>	<u>Serum</u>			<u>CSF</u>		
	<u>Spike-2- protein antibody</u>	<u>RBD antibody</u>	<u>Nucleocapsid antibody</u>	<u>Spike-2- protein antibody</u>	<u>RBD antibody</u>	<u>Nucleocapsid antibody</u>
<u>1</u>	161.56	172.03	296.1	0.7	0	0.88
<u>2</u>	203.16	191.40	7.05	0.77	0	0
<u>3</u>	223.57	286.13	229.33	0.47	0	0.4
<u>4</u>	0.51	4.51	12.21	0	0	0
<u>5</u>	81.81	107.32	66.14	0.8	0	0
<u>6^a</u>	11169.3	16855.8	114.21	17.6	25.9	0.21
<u>7</u>	0.63	4.15	0.66	0	0	0
<u>8</u>	55.13	74.47	62.45	0	0	0.19
<u>9</u>	41.49	37.25	4.09	0	0	0
<u>10</u>	52635.52	61860.14	28.79	64.12	75.91	0
<u>11</u>	0	0	0.64	0	0	0
<u>12</u>	52.17	70.95	88.71	0	0	0

^aparticipant was fully vaccinated for SARS-CoV2 with mRNA vaccine prior to being tested

Values are in international units per milliliter.

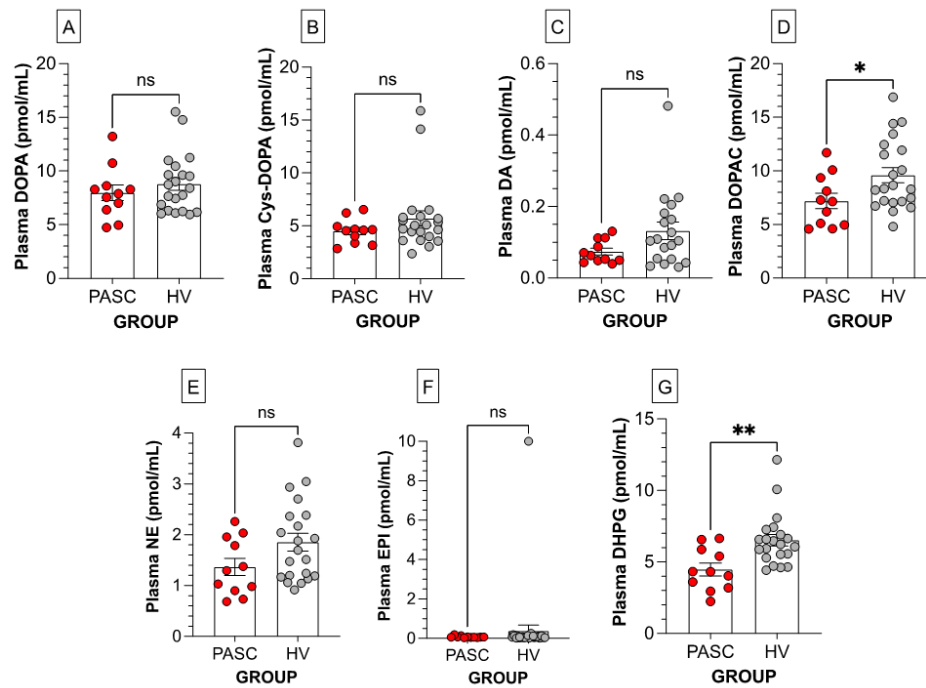
RBD – receptor binding domain

eTable 3 –Immunophenotyping of peripheral blood mononuclear cells (PBMCs) and cerebrospinal fluid (CSF) cells in patients with post-acute sequelae of SARS-CoV2 (PASC) compared to healthy volunteers (HV).

Immunological Markers		PBMC							CSF						
		HV			PASC			p-value	HV			PASC			p-value
		N	Mean	SD	N	Mean	SD		N	Mean	SD	N	Mean	SD	
	CSF cell (cells/ul)	-	-	-	-	-	-	-	27	1.357	0.866	11	2.232	1.764	0.0496
Lymphocytes	CD4/CD8 ratio	59	1.883	1.01	12	2.134	1.171	0.6796	27	3.537	1.317	11	3.012	1.82	0.1426
	B cell (%)	59	9.751	4.566	12	10.34	3.433	0.3479	27	0.826	0.774	11	1.864	1.725	0.0185
	B/monocyte ratio	59	0.954	0.654	12	1.188	0.805	0.2361	27	0.224	0.252	11	0.77	1.548	0.0183
	NK cell (%)	59	8.967	5.398	12	12.77	4.313	0.0151	27	3.185	2.039	11	5.82	2.819	0.0019
	CD56bright/dim ratio	59	0.076	0.061	12	0.093	0.092	0.4126	27	0.220	0.215	11	0.487	0.316	0.0092
	NKT cell (%)	59	1.483	1.546	12	1.345	1.182	0.9965	27	2.064	1.494	11	2.573	1.472	0.1667
	Monocyte (%)	59	12.76	5.696	12	10.47	3.707	0.2614	27	5.845	4.015	11	6.677	8.159	0.5677
CD4+ T-cell subsets	Naïve (%)	59	35.11	13.89	12	50.74	18.10	0.0033	27	4.183	3.495	11	7.229	4.754	0.0168
	Memory (%)	59	50.54	10.46	12	41.73	15.56	0.0189	27	72.4	8.623	11	78.64	9.081	0.0327
	Effector/memory (%)	59	12.86	7.176	12	6.141	3.435	<0.0001	27	22.15	7.423	11	11.83	4.676	<0.0001
	Effector (%)	59	1.489	1.453	12	1.398	1.487	0.6631	27	1.265	1.1	11	2.293	4.82	0.2929
	CD25high (%)	59	3.565	2.135	12	4.501	1.164	0.0248	27	2.476	1.91	11	3.632	2.655	0.2614
	Memory Tfh (%)	59	13.21	4.547	12	11.62	2.948	0.3787	27	13.61	3.736	11	15.28	5.506	0.4128
	CCR4 (%)	30	17.08	6.748	12	15.65	5.410	0.6752	14	7.061	5.843	11	9.405	3.640	0.1656
	PD-1 (%)	30	30.97	10	12	23.27	10.50	0.0336	14	79.53	8.216	11	73.8	14.46	0.3727
	CD244 (%)	30	7.990	5.058	12	10.10	9.257	0.6553	14	18.76	8.995	11	14.28	7.678	0.207
	TIGIT (%)	30	22.65	6.056	12	22.62	7.044	0.853	14	32.94	13.43	11	36.04	8.240	0.6092
	CD226 (%)	30	69.43	10.95	12	72.18	12.91	0.4821	14	71.21	12.68	11	74.42	19.70	0.373
CD8+ T-cell subsets	Naïve (%)	59	43.83	16.25	12	54.92	12.59	0.0240	27	26.67	10.36	11	33.09	12.36	0.1818
	Memory (%)	59	29.45	11.97	12	25.49	13.73	0.2681	27	56.89	12.99	11	55.58	18.24	0.918
	Effector/memory (%)	59	8.682	4.752	12	5.091	3.338	0.0057	27	10.77	5.505	11	5.327	3.153	0.0016
	Effector (%)	59	18.04	16.15	12	14.64	8.954	0.9844	27	5.681	4.358	11	6.012	6.601	0.6341
	CD25high (%)	59	0.423	0.611	12	0.913	1.017	0.0051	27	1.751	1.754	11	2.971	3.787	0.9042
	CCR5 (%)	59	3.151	1.813	12	4.518	2.285	0.0308	27	13.38	6.951	11	15.51	8.103	0.3687
	CCR4 (%)	30	5.814	4.447	12	5.028	4.771	0.4042	14	5.406	3.376	11	8.965	5.134	0.058
	PD-1 (%)	30	36.20	12.56	12	36.08	14.51	0.8422	14	81.93	9.183	11	79.4	16.64	0.9037
	CD244 (%)	30	50.00	15.52	12	50.58	10.55	0.9398	14	71.3	10.47	11	63.46	13.03	0.1072
	TIGIT (%)	30	38.24	11.53	12	43.26	11.95	0.1636	14	53.71	12.37	11	67.32	10.02	0.0062
B cell subsets	CD226 (%)	30	67.08	10.96	12	67.51	11.32	0.9365	14	45.73	12.68	11	49.71	16.93	0.5719
	Naïve (%)	59	34.21	10.53	12	36.22	8.675	0.5882	9	2.751	4.479	9	3.003	5.254	0.943
	Unswitched memory (%)	59	31.76	10.07	12	35.40	7.722	0.085	9	12.13	8.334	9	14.7	9.533	0.7131
	Switched memory (%)	59	26.55	12.37	12	22.65	11.76	0.2302	9	63.96	6.573	9	63.83	22.61	0.88
	Antibody secreting cell (%)	59	0.605	0.71	12	0.483	0.372	0.7938	9	0	0	9	7.563	15.77	0.009
Monocyte subsets	CD14+CD16- (%)	59	86.02	8.401	12	89.54	6.202	0.1856	10	38.19	22.84	8	40.24	10.73	0.3599
	CD14+CD16+ (%)	59	3.624	4.259	12	4.248	4.481	0.7939	10	48.14	24.32	8	45.31	16.64	0.7618
	CD14-CD16+ (%)	59	2.738	2.484	12	2.639	2.355	0.9307	10	0.656	1.077	8	3.816	7.835	0.4238
PD-L1	T cell (%)	30	1.592	1.851	12	5.673	5.607	0.0008	14	11.41	9.279	11	14.87	11.66	0.2671
	B cell (%)	30	1.394	1.02	12	1.786	1.124	0.1216	3	20.33	15.5	9	32.33	25.85	0.5773
	Monocyte (%)	30	10.35	11.36	12	31.32	28.66	0.0095	11	15.6	9.435	10	35.92	21.41	0.0197

P-value for Wilcoxon two-sample test. Bold signifies $p < 0.05$.

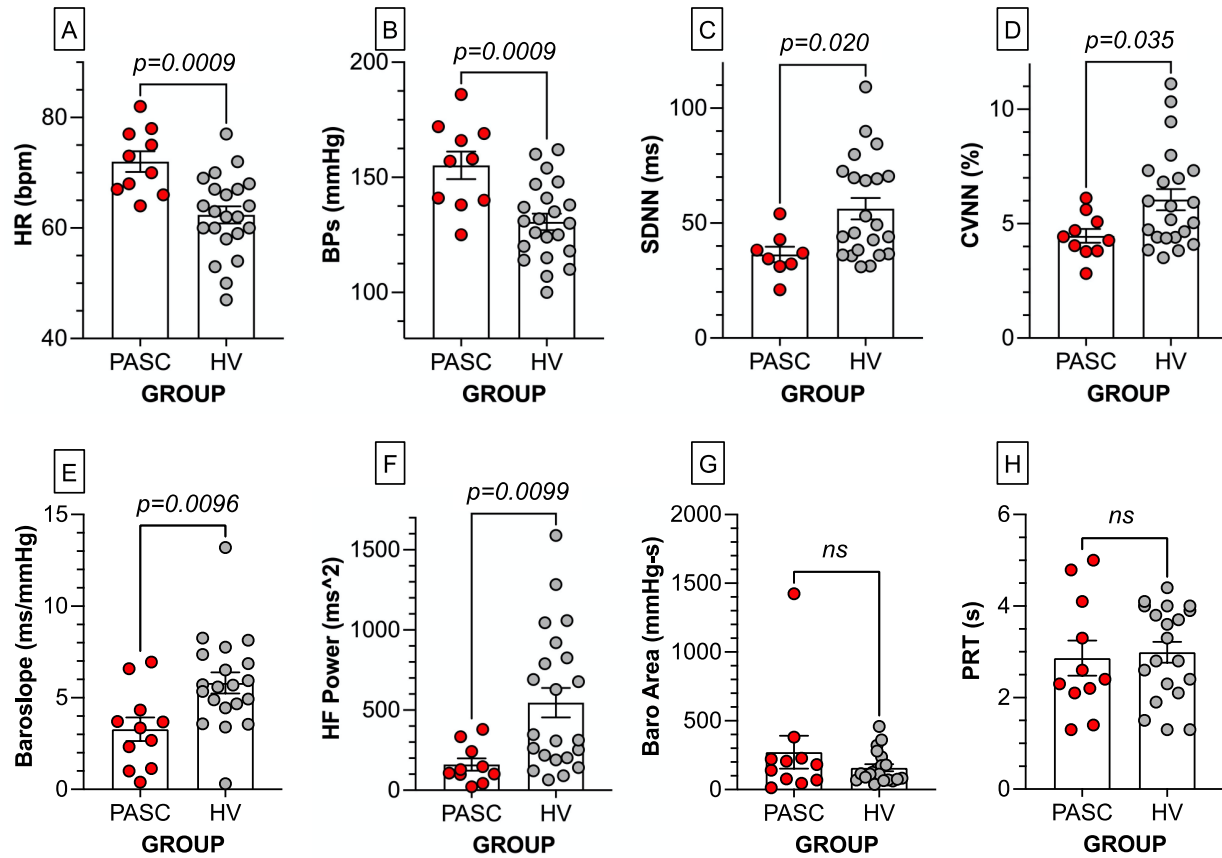
CCR – CC chemokine receptor; CD – cluster of differentiation; CSF – cerebrospinal fluid; NK – natural killer; PBMC – peripheral blood mononuclear cells; Tfh – T follicular helper; TIGIT - T-cell immunoglobulin and ITIM domains; PD-1 – programmed cell death protein 1; PD-L1 – programmed cell death protein ligand 1; SD – standard deviation



eFigure 1: Plasma levels of catecholamines in patients with post-acute sequelae of SARS-CoV2 infection (PASC, red) and healthy volunteers (HV, gray).

Each dot represents one participant, bars represent standard errors of the mean (top edge of rectangle). (*) $p < 0.05$ (**) $p < 0.01$ by independent means t-tests.

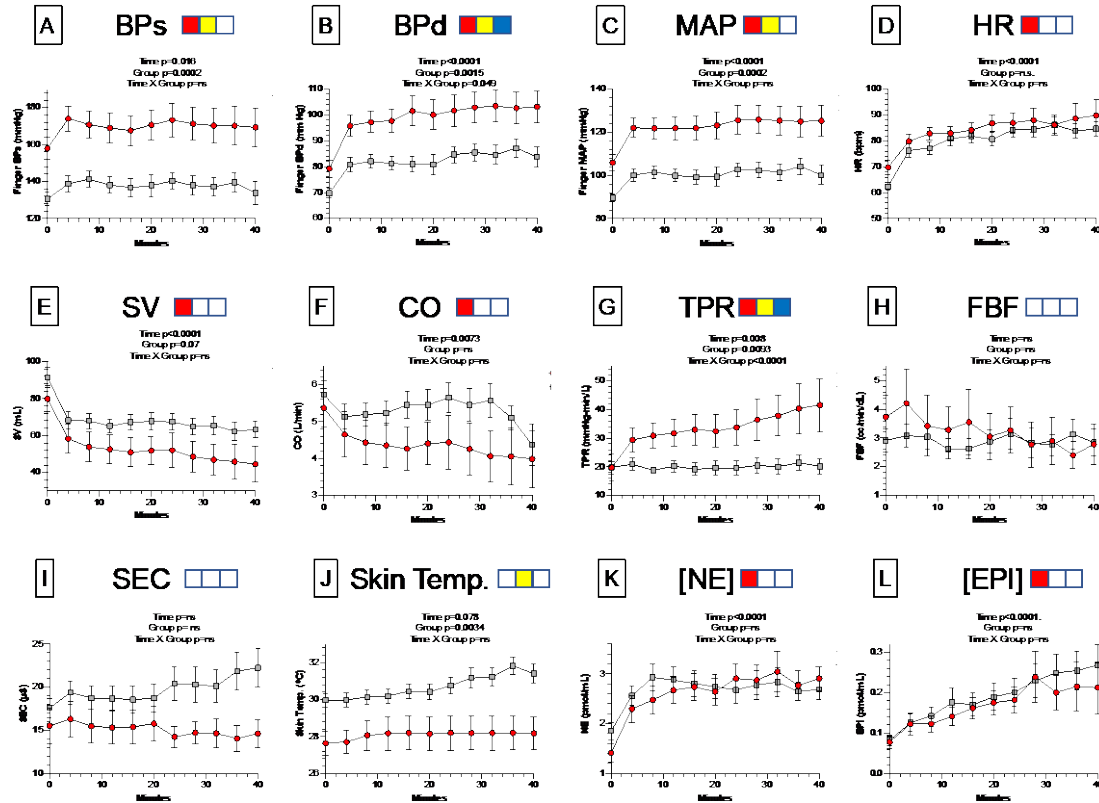
Abbreviations: Cys-DOPA - cysteinyl 3,4-dihydroxyphenylalanine; DA – dopamine; DHPG - 3,4-dihydroxyphenylglycol; DOPA - 3,4-dihydroxyphenylalanine; DOPAC - 3,4-dihydroxyphenylacetic acid; EPI – epinephrine; NE – norepinephrine ; ns – not significant



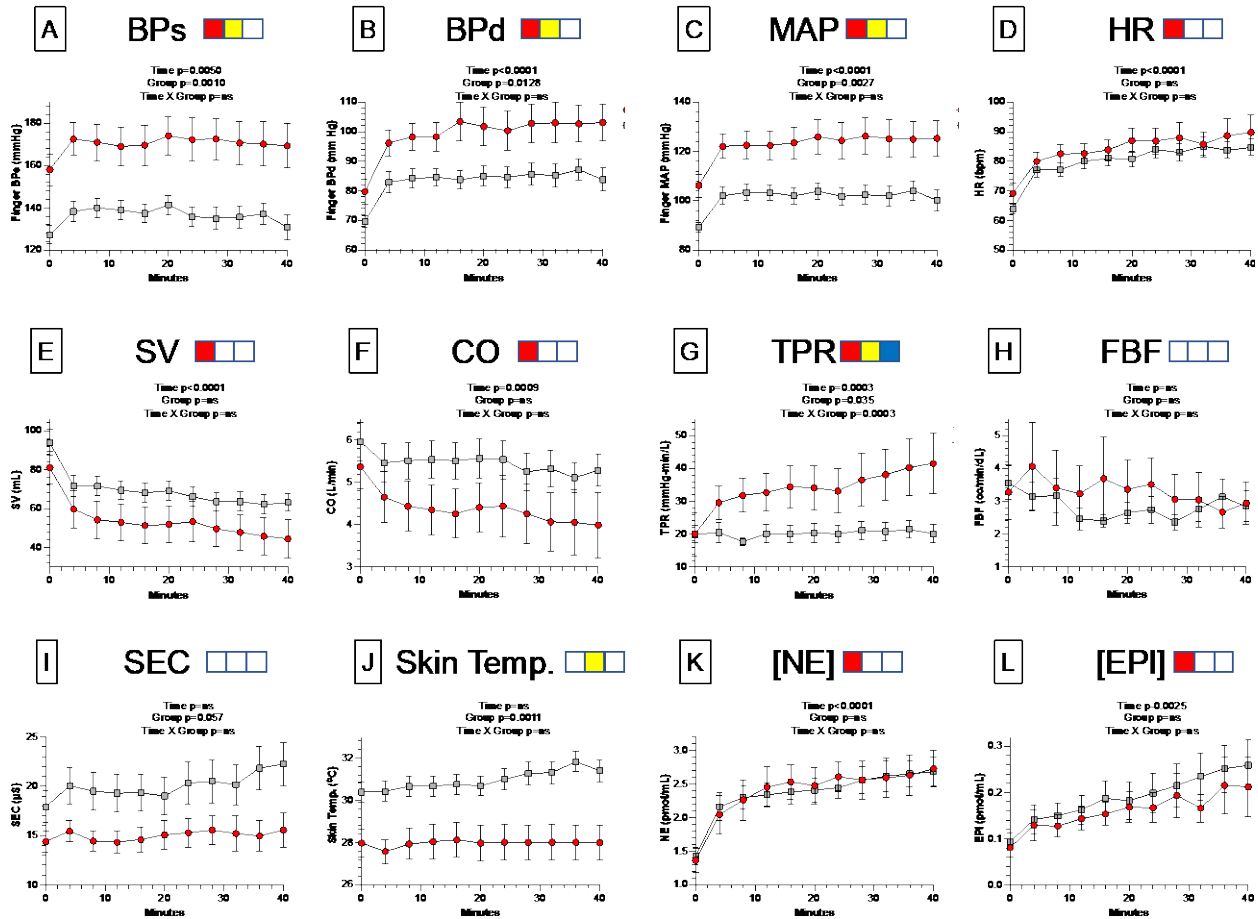
eFigure 2: Individual values for physiological variables in patients with post-acute sequelae of SARS-CoV2 infection (PASC, red) and healthy volunteers (HV, gray).

Each dot represents one participant, bars represent standard errors of the mean (top edge of rectangle). p values are for independent means t-tests. (A) heart rate (HR); (B) finger systolic blood pressure (BPs); (C) standard deviation of the interbeat interval for normal beats (SDNN); (D) coefficient of variation for the interbeat interval for normal beats (CVNN)); (E) baroreflex-cardiovascular gain; (F) high frequency (HF) power of heart rate variability; (G) total baroreflex area; (H) pressure recovery time (PRT).

ns – not significant



eFigure 3: Physiological variables and plasma catecholamines during head-up tilt table testing in patients with post-acute sequelae of SARS-CoV2 infection (PASC, red) and healthy volunteers (HV, gray). Data are from all subjects. Data at each time point is presented as mean (dot) and standard error of the mean (bars). (A) finger systolic blood pressure (BPs); (B) finger diastolic blood pressure (BPd) (C) mean arterial pressure (MAP); (D) heart rate (HR); (E) cardiac stroke volume (SV); (F) cardiac output (CO); (G) total peripheral resistance (TPR); (H) forearm blood flow (FBF); (I) skin electrical conductance (SEC); (J) skin temperature; (K) plasma norepinephrine ([NE]); (L) plasma epinephrine ([EPI]). Red symbols indicate significant Time effect, yellow symbols significant Group effect, and blue symbols significant Time-Group interaction effect in repeated-measures analyses of variance. Head-up tilting significantly increased BPs, BPd, MAP, HR, TPR, and plasma NE and EPI and decreased SV, CO. The PASC group had higher BPs, BPd, MAP, HR, and TPR and lower skin temperature than did the HV group. The PASC group had larger increases in BPd and TPR during head-up tilt.



eFigure 4: Physiological variables and plasma catecholamines during head-up tilt table testing in patients with post-acute sequelae of SARS-CoV2 infection (PASC, red) and healthy volunteers (HV, gray). Data are only from subjects who completed 40 minutes of tilting.

(A) finger systolic blood pressure (BPs); (B) finger diastolic blood pressure (BPd) (C) mean arterial pressure (MAP); (D) heart rate (HR); (E) cardiac stroke volume (SV); (F) cardiac output (CO); (G) total peripheral resistance (TPR); (H) forearm blood flow (FBF); (I) skin electrical conductance (SEC); (J) skin temperature; (K) plasma norepinephrine ([NE]); (L) plasma epinephrine ([EPI]). Red symbols indicate significant Time effect, yellow symbols significant Group effect, and blue symbols significant Time-Group interaction effect in repeated-measures analyses of variance. Head-up tilting significantly increased BPs, BPd, MAP, HR, TPR, and plasma NE and EPI and decreased SV, CO. The PASC group had higher BPs, BPd, MAP, HR,

and TPR and lower skin temperature than did the HV group. The PASC group had larger increases in BPd and TPR during head-up tilt.