

Supplemental Table 1. Cardiorespiratory and sympathetic parameters at rest and during head-up tilt in female patients on vs off medications.

	Off Medication (n=14)	On Medication (n=11)	P Value
<u>BASELINE</u>			
<u>Peripheral Hemodynamics</u>			
Heart rate (bpm)	77 ± 11	63 ± 10	0.002
Stroke volume (mL)	77 ± 18	82 ± 9	0.36
Cardiac output (L/min)	5.9 ± 1.2	5.2 ± 0.9	0.10
Mean arterial pressure (mmHg)	92 ± 15	91 ± 12	0.89
Systemic vascular resistance (dynes/cm ⁵)	1669 ± 555	1674 ± 586	0.98
Pulse pressure (mmHg)	62.1 ± 12.3	63.8 ± 8.6	0.71
Arterial pulsatility index	0.68 ± 0.12	0.70 ± 0.07	0.62
<u>Cerebral Hemodynamics</u>			
MCAv _{mean} (cm/s)	77 ± 15	78 ± 10	0.93
MCAv _{peak} (cm/s)	112 ± 21	116 ± 14	0.62
MCAv _{min} (cm/s)	60 ± 13	59 ± 8	0.80
MCAv pulsatility index	0.68 ± 0.1	0.73 ± 0.1	0.18
<u>Sympathetic</u>			
	(n=6)	(n=6)	
Burst frequency (bursts/min)	14 ± 4	11 ± 6	0.34
Burst amplitude (% of peak)	40 ± 12	43 ± 17	0.74
Total MSNA (a.u./min)	583 ± 312	550 ± 356	0.87
<u>Respiratory</u>			
Ventilation (L/min)	8.8 ± 2.5	9.7 ± 2.8	0.40
End tidal CO ₂ (mmHg)	38 ± 4	38 ± 3	0.93
End tidal O ₂ (mmHg)	92 ± 7	93 ± 7	0.53
<u>Δ HEAD-UP TILT</u>			
<u>Peripheral Hemodynamics</u>			
Δ Heart rate (bpm)	21 ± 9	19 ± 9	0.56
Δ Stroke volume (mL)	-26 ± 8	-25 ± 7	0.79
Δ Cardiac output (L/min)	-0.9 ± 0.6	-0.5 ± 0.6	0.09
Δ Mean arterial pressure (mmHg)	7 ± 10	10 ± 10	0.44
Δ Systemic vascular resistance (dynes/cm ⁵)	496 ± 399	334 ± 358	0.30
Δ Pulse pressure (mmHg)	-6.1 ± 4.3	-2.1 ± 6.5	0.07
Δ Arterial pulsatility index	-0.1 ± 0.05	-0.1 ± 0.02	0.25
<u>Cerebral Hemodynamics</u>			
Δ MCAv _{mean} (cm/s)	1 ± 6	0.3 ± 6	0.80
Δ MCAv _{peak} (cm/s)	-4 ± 8	-5 ± 8	0.76

Δ MCAv _{min} (cm/s)	3 ± 5	3 ± 6	0.84
Δ MCAv pulsatility index	-0.1 ± 0.06	-0.1 ± 0.04	0.97
<u>Sympathetic</u>	(n=5)	(n=4)	
Burst frequency (bursts/min)	23 ± 12	18 ± 11	0.53
Burst amplitude (% of peak)	38 ± 17	36 ± 13	0.82
Total MSNA (a.u./min)	2642 ± 2293	1562 ± 944	0.41
<u>Respiratory</u>			
Δ Ventilation (L/min)	2.9 ± 2.0	4.0 ± 2.7	0.26
Δ End tidal CO ₂ (mmHg)	-0.1 ± 0.4	-0.1 ± 0.2	0.67
Δ End tidal O ₂ (mmHg)	0.1 ± 1.6	0.03 ± 0.6	0.85
Data are reported as mean ± standard deviation. Group differences were compared using an independent samples two-tailed t-test. Abbr: POTS, Postural Orthostatic Tachycardia Syndrome; MCAv, middle cerebral artery velocity; MSNA, muscle sympathetic nerve activity; a.u., arbitrary units; CO, carbon dioxide; O ₂ , oxygen.			

Supplemental Table 2. Cardiorespiratory responses to hyperoxia during HUT in HC (n=11).

	Normoxia	Hyperoxia					
	Baseline	0-5 sec	6-10 sec	11-15 sec	16-20 sec	21-25 sec	26-30 sec
Respiratory							
V_E (L/min)	12.9 2.4	13.8 2.7	13.3 2.3	12.4 2.3	11.9* 2.2	11.7‡ 2.3	11.5‡ 2.1
ETCO ₂ (mmHg)	39.6 3.2	39.6 3.2	39.4 3.2	39.2 3.1	39.0 2.9	39.0 2.9	39.0 2.9
ETO ₂ (mmHg)	92.3 5.6	127.6† 15.6	234.4† 27.0	293.8† 27.2	334.7† 24.9	363.5† 19.6	380.9† 15.4
Cardiovascular							
MAP (mmHg)	101 13	100 12	100 13	99 13	98 11	98‡ 12	98 13
CO (L/min)	5.1 1.1	5.1 1.1	5.1 1.1	5.0 1.1	5.1 1.1	5.0 1.1	5.0 1.1
HR (bpm)	85 13	86 15	85 14	85 14	84 14	85 13	83 14
SV (mL)	60 14	59 14	60 14	60 14	60 14	60 14	60 14
SVR (dynes/cm ⁵)	1692 604	1678 609	1677 612	1687 638	1657 529	1672 603	1697 619
Data are reported as mean ± standard deviation (below). Cardiorespiratory responses to hyperoxia were compared using a 2-factor mixed-effects model: [Group: Control vs. Patient] x [Gas (repeated measure): Normoxia vs Hyperoxia] and Bonferroni post-hoc analysis. *p<0.05; ‡p<0.01; †p<0.001 represent values significantly different from normoxic baseline. Abbr: HC, healthy controls; HUT, head-up tilt; V_E , minute ventilation; ETCO ₂ , end-tidal carbon dioxide; ETO ₂ , end-tidal oxygen; MAP, mean arterial pressure; CO, cardiac output; HR, heart rate; SV, stroke volume; SVR, systemic vascular resistance.							

Supplemental Table 3. Cardiorespiratory responses to hyperoxia during HUT in patients with POTS (n=23)

	<u>Normoxia</u>	<u>Hyperoxia</u>					
	Baseline	0-5 sec	6-10 sec	11-15 sec	16-20 sec	21-25 sec	26-30 sec
<u>Respiratory</u>							
V _E (L/min)	15.1 4.2	16.5 5.0	16.1 5.0	15.3 5.1	15.2 5.8	14.7 5.0	14.1‡ 4.2
ETCO ₂ (mmHg)	37.6 3.7	37.7 3.7	37.5 3.6	37.4 3.6	37.3 3.6	37.3 3.6	37.3 3.6
ETO ₂ (mmHg)	93.7 7.7	127.7† 16.1	237.8† 34.7	298.1† 41.5	337.9† 42.6	365.6† 41.9	381.3† 41.9
<u>Cardiovascular</u>							
MAP (mmHg)	101 17	101 17	100 18	100 17	98† 17	99* 18	98† 17
CO (L/min)	5.3 1.0	5.3 1.0	5.4 0.9	5.3 0.9	5.3 1.0	5.2* 0.9	5.2 0.9
HR (bpm)	97 16	98 18	97 17	96 18	96 18	95 18	96 18
SV (mL)	55 12	54 11	55 12	55 12	55 12	55 12	55 12
SVR (dynes/cm ⁵)	1601 532	1598 530	1573 503	1587 527	1565* 524	1601 524	1582 526
<p>Data are reported as mean ± standard deviation (below). Cardiorespiratory responses to hyperoxia were compared using a 2-factor mixed-effects model: [Group: Control vs. Patient] x [Gas (repeated measure): Normoxia vs Hyperoxia]] and Bonferroni post-hoc analysis. *p<0.05; ‡p<0.01; †p<0.001 represent values significantly different from normoxic baseline. Abbr: POTS, postural orthostatic tachycardia syndrome; HUT, head-up tilt; V_E, minute ventilation; ETCO₂; end-tidal carbon dioxide; ETO₂, end-tidal oxygen; MAP, mean arterial pressure; CO, cardiac output; HR, heart rate; SV, stroke volume; SVR, systemic vascular resistance.</p>							

Supplemental Table 4. Supine cardiorespiratory responses to hyperoxia in HC (n=11)

	<u>Normoxia</u>	<u>Hyperoxia</u>					
	Baseline	0-5 sec	6-10 sec	11-15 sec	16-20 sec	21-25 sec	26-30 sec
<u>Respiratory</u>							
V _E (L/min)	11.1 2.2	11.4 2.55	10.6* 2.5	10.5‡ 2.4	10.3* 2.5	10.3‡ 2.6	10.4* 2.6
ETCO ₂ (mmHg)	39.6 2.9	39.6 3.0	39.4 2.9	39.1 2.8	39.0 2.8	38.9 2.8	38.9 2.9
ETO ₂ (mmHg)	94.1 5.9	137.9† 30.7	254.5† 25.9	307.6† 28.4	349.8† 23.6	376.4† 18.6	384.9† 27.7
<u>Cardiovascular</u>							
MAP (mmHg)	91 10	91 11	92 12	91 11	90 11	89 11	89 12
CO (L/min)	5.5 1.0	5.5 0.9	5.5 0.9	5.5 0.9	5.5 0.9	5.4 1.0	5.3* 1.0
HR (bpm)	69 11	69 12	69 11	68 12	68 12	68 11	67* 11
SV (mL)	80 13	80 13	79 12	80 12	80 14	80 13	80 12
SVR (dynes/cm ⁵)	1370 245	1355 230	1381 243	1364 245	1349 236	1356 238	1382 254
<p>Data are reported as mean ± standard deviation (below). Cardiorespiratory responses to hyperoxia were compared using a 2-factor mixed-effects model: [Group: Control vs. Patient] x [Gas (repeated measure): Normoxia vs Hyperoxia]] and Bonferroni post-hoc analysis. *p<0.05; ‡p<0.01; †p<0.001 represent values significantly different from normoxic baseline. Abbr: HC, healthy controls; V_E, minute ventilation; ETCO₂, end-tidal carbon dioxide; ETO₂, end-tidal oxygen; MAP, mean arterial pressure; CO, cardiac output; HR, heart rate; SV, stroke volume; SVR, systemic vascular resistance.</p>							

Supplemental Table 5. Supine cardiorespiratory responses to hyperoxia in patients with POTS (n=25)

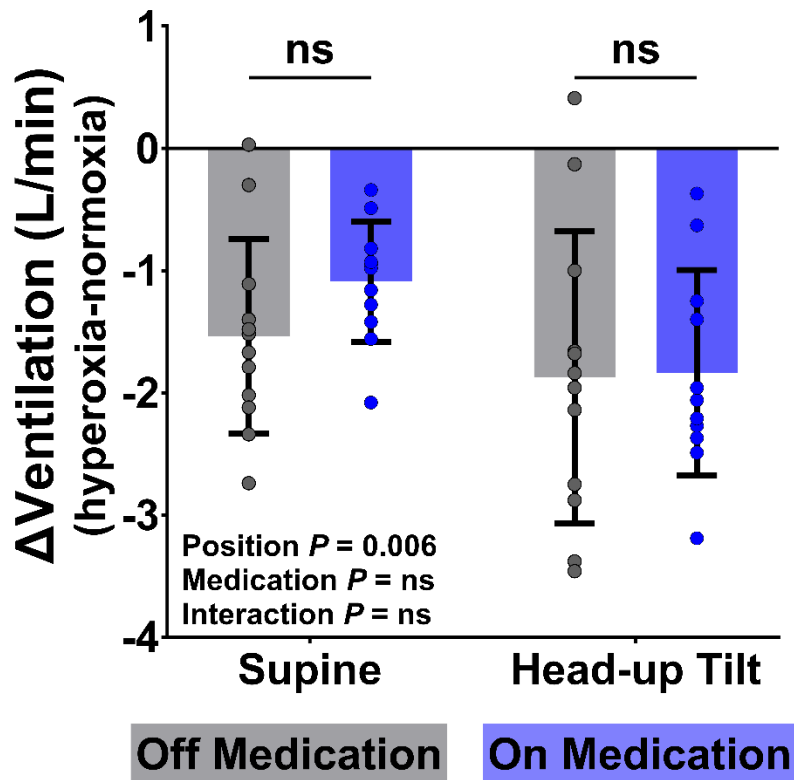
	<u>Normoxia</u>	<u>Hyperoxia</u>					
	Baseline	0-5 sec	6-10 sec	11-15 sec	16-20 sec	21-25 sec	26-30 sec
<u>Respiratory</u>							
V _E (L/min)	10.3 2.3	10.5 2.6	10.4 2.4	9.9 2.4	9.7* 2.3	9.4† 2.1	9.5† 2.3
ETCO ₂ (mmHg)	38.2 3.6	38.1 3.8	37.9 3.7	37.8 3.8	37.6 3.7	37.6 3.7	37.5 3.6
ETO ₂ (mmHg)	94.3 8.9	124.7† 20.8	232.9† 37.6	289.6† 38.5	329.0† 39.7	356.5† 37.8	371.3† 36.7
<u>Cardiovascular</u>							
MAP (mmHg)	90 13	90 13	89 13	89* 13	88† 12	88† 12	88† 12
CO (L/min)	5.7 1.1	5.7 1.1	5.7 1.1	5.7 1.1	5.7 1.1	5.6 1.1	5.6 1.1
HR (bpm)	70 12	70 12	70 13	70 12	70 12	69‡ 13	69‡ 13
SV (mL)	81 14	81 14	81 14	81 14	81 15	82* 15	82* 15
SVR (dynes/cm ⁵)	1319 330	1312 326	1314 330	1299 312	1296* 320	1308 320	1312 332
<p>Data are reported as mean ± standard deviation (below). Cardiorespiratory responses to hyperoxia were compared using a 2-factor mixed-effects model: [Group: Control vs. Patient] x [Gas (repeated measure): Normoxia vs Hyperoxia]] and Bonferroni post-hoc analysis. *p<0.05; ‡p<0.01; †p<0.001 represent values significantly different from normoxic baseline. Abbr: POTS, postural orthostatic tachycardia syndrome; V_E, minute ventilation; ETCO₂, end-tidal carbon dioxide; ETO₂, end-tidal oxygen; MAP, mean arterial pressure; CO, cardiac output; HR, heart rate; SV, stroke volume; SVR, systemic vascular resistance.</p>							

Supplemental Table 6. Respiratory and sympathetic nerve activity at baseline in rats with (intact) and without (denervated) peripheral chemoreceptor and baroreceptor afferents.

	Baseline		
	<u>Intact (n=5)</u>	<u>Denervated (n=5)</u>	<u>P</u>
Pressure (mmHg)	90±0 90 (90, 90)	90±0 90 (90, 90)	>0.99
Respiratory (phrenic) nerve activity			
Total nerve activity (a.u.)	51±29 37 (30, 79)	62±42 60 (29, 69)	>0.99
Neural tidal volume (a.u.)	2.3±1.2 2.1 (1.3, 3.5)	2.7±1.5 2.6 (1.6, 3.6)	0.84
Neural frequency (burst/min)	22±2 22 (21 - 23)	22±5 23 (19, 26)	0.69
Inspiratory time (s)	0.9±0.2 0.8 (0.8, 0.9)	1.0±0.1 1.0 (0.9, 1.0)	0.22
Expiratory time (s)	1.9±0.4 1.9 (1.8, 2.0)	1.8±0.7 1.4 (1.2, 2.4)	0.69
Inspiratory: Expiratory time ratio	0.51±0.24 0.44 (0.39, 0.45)	0.68±0.30 0.85 (0.38, 0.87)	0.84
Eupneic index	0.69±0.03 0.69 (0.67, 0.72)	0.69±0.03 0.70 (0.67, 0.71)	0.69
Sympathetic (splanchnic) nerve activity			
Total across respiratory cycle (a.u.)	1065±1121 453 (341, 1440)	1154±479 1029 (1021, 1144)	0.55
Inspiratory phase (a.u.)	981±1087 465 (268, 1300)	1064±370 481 (953, 1089)	0.55
Expiratory phase (a.u.)	1134±1186 1059 (375, 1541)	1261±532 1213 (1017, 1269)	0.55
Data are reported as mean ± standard deviation and the median (25 th , 75 th percentiles) below. Baseline group differences between preparations with intact (n=5) and denervated (n=5) peripheral chemoreceptor and baroreceptor afferents were compared using a Mann-Whitney two-tailed t-test. a.u., arbitrary units.			

Supplemental Table 7. Respiratory and sympathetic nerve activity in response to low and high perfusion in rats with (intact) and without (denervated) peripheral chemoreceptor and baroreceptor afferents.

	Response to Low Pressure			Response to High Pressure		
	<u>Intact</u> (n=5)	<u>Denervated</u> (n=5)	<i>P</i>	<u>Intact</u> (n=5)	<u>Denervated</u> (n=5)	<i>P</i>
Pressure (Δ mmHg)	-26\pm3\ddagger	-28\pm3\ddagger	0.27	27\pm3\ddagger	25\pm3\ddagger	0.50
Respiratory (phrenic) nerve activity						
Total nerve activity (%)	17\pm3\ddagger	18\pm6\ddagger	>0.99	-43\pm9\ddagger	-16\pm9\ddagger	<0.001
Neural tidal volume (%)	16\pm4*	17\pm11*	>0.99	-17\pm10*	-12 \pm 12	>0.99
Neural frequency (Δ burst/min)	0 \pm 1	0 \pm 2	>0.99	-6\pm1\ddagger	-1 \pm 1	<0.001
Inspiratory time (Δ s)	0.0 \pm 0.1	0.0 \pm 0.0	0.58	0.1 \pm 0.2	0.0 \pm 0.0	>0.99
Expiratory time (Δ s)	0.0 \pm 0.0	-0.1 \pm 0.3	>0.99	1.2\pm0.6\ddagger	0.0 \pm 0.1	<0.001
Inspiratory: Expiratory time ratio (Δ)	-0.04 \pm 0.08	0.06 \pm 0.04	0.009	-0.14\pm0.04\ddagger	0.00 \pm 0.05	<0.001
Eupneic index (Δ)	-0.01 \pm 0.06	-0.00 \pm 0.01	>0.99	0.00 \pm 0.06	0.04 \pm 0.04	>0.99
Sympathetic (splanchnic) nerve activity						
Total across respiratory cycle (%)	30\pm22*	38\pm26\ddagger	>0.99	-70\pm15\ddagger	-21 \pm 12	<0.001
Inspiratory phase (%)	42\pm43*	43\pm33*	>0.99	-64\pm16\ddagger	-21 \pm 15	0.028
Expiratory phase (%)	27\pm18*	32\pm26*	>0.99	-72\pm15\ddagger	-20 \pm 12	<0.001
Data are reported as mean \pm standard deviation (below). Responses to pressure challenges in preparations with intact (n=5) and denervated (n=5) peripheral chemoreceptor and baroreceptor afferents were compared using a 2-factor mixed-effects model: [Group: Intact vs. Denervated] x [Pressure (repeated measure): Baseline vs. Low Pressure vs. High Pressure] and Bonferroni post-hoc analysis. *p<0.05; \ddagger p<0.01; \ddagger p<0.001 represent values significantly different from baseline.						



Supplemental Figure 1. Interactions between ventilatory response to hyperoxia and medication use. Between group comparisons showed that the magnitude of ventilation inhibition during hyperoxia was not different between patients on medications vs off medication in either position. Data are presented as mean \pm SD. Medication main effect: $p=0.46$; Interaction: $p=0.25$. Group differences in ventilation inhibition during hyperoxia were compared using a two-factor mixed-effects model with Bonferroni post-hoc testing correction.