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Leg vasoconstriction during head-up tilt in patients with autonomic failure is not abolished

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Groothuis JT, Thijssen DH, Lenders JW, Deinum J, Hopman MT. Leg vasoconstriction during head-up tilt in patients with autonomic failure is not abolished. *J Appl Physiol* 110: 416–422, 2011. First published December 2, 2010; doi:10.1152/japplphysiol.01098.2010.—Maintaining blood pressure during orthostatic challenges is primarily achieved by baroreceptor-mediated activation of the sympathetic nervous system, which can be divided into preganglionic and postganglionic parts. Despite their preganglionic autonomic failure, spinal cord-injured individuals demonstrate a preserved peripheral vasoconstriction during orthostatic challenges. Whether this also applies to patients with postganglionic autonomic failure is unknown. Therefore, we assessed leg vasoconstriction during 60° head-up tilt in five patients with pure autonomic failure (PAF) and two patients with autonomic failure due to dopamine-β-hydroxylase (DBH) deficiency. Ten healthy subjects served as controls. Leg blood flow was measured using duplex ultrasound in the right superficial femoral artery. Leg vascular resistance was calculated as the arterial-venous pressure gradient divided by blood flow. DBH-deficient patients were tested off and on the norepinephrine pro-drug L-threo-dihydroxyphenylserine (L-DOPS). During 60° head-up tilt, leg vascular resistance increased significantly in PAF patients [0.40 ± 0.38 (+30%) mmHg·ml^{-1}·min^{-1}]. The increase in leg vascular resistance was not significantly different from controls [0.88 ± 1.04 (+72%) mmHg·ml^{-1}·min^{-1}]. In DBH-deficient patients, leg vascular resistance increased by 0.49 ± 0.01 (+153%) and 1.52 ± 1.47 (+234%) mmHg·ml^{-1}·min^{-1} off and on L-DOPS, respectively. Despite the increase in leg vascular resistance, orthostatic hypotension was present in PAF and DBH-deficient patients. Our results demonstrate that leg vasoconstriction during orthostatic challenges in patients with PAF or DBH deficiency is not abolished. This indicates that the sympathetic nervous system is not the sole or pivotal mechanism inducing leg vasoconstriction during orthostatic challenges. Additional vasoconstrictor mechanisms may compensate for the loss in sympathetic nervous system control.

leg vascular resistance; sympathetic nervous system

THE UPRIGHT POSTURE in humans leads to a gravitational displacement of blood into the dependent vasculature of the splanchnic area and lower limbs, leading to a decrease in venous return to the heart and an immediate drop in blood pressure (11, 34). The decrease in blood pressure unloads baroreceptors, resulting in decreased vagal nerve activity and increased sympathetic outflow (11, 34). Activation of the sympathetic nervous system increases heart rate, cardiac contractility, and peripheral vascular resistance (11, 34).

The sympathetic nervous system can be anatomically and functionally divided into preganglionic and postganglionic parts (11, 28). Despite preganglionic autonomic failure, spinal cord-injured individuals demonstrate an increase in leg vascular resistance during orthostatic challenges (15, 16, 18, 26). These results suggest that the sympathetic nervous system is not obligatory for peripheral vasoconstriction during orthostatic challenges. Whether this also applies to patients with postganglionic autonomic failure is unknown. Therefore, we assessed leg vasoconstriction during an orthostatic challenge in two distinctive patient groups with autonomic disorders who demonstrate selective failure of the postganglionic part of the sympathetic nervous system.

For this purpose, we measured leg vascular resistance at baseline and during 60° head-up tilt (HUT) in patients with pure autonomic failure (PAF) and dopamine-β-hydroxylase (DBH) deficiency as well as a group of healthy controls. PAF represents a chronic primary autonomic disorder with a postganglionic lesion with sympathetic denervation (Table 1) (13, 37). DBH deficiency is an extremely rare hereditary autonomic disorder characterized by the complete absence of norepinephrine with an intact sympathetic nervous system (Table 1) (32). We hypothesized that leg vasoconstriction will be present in patients with PAF and DBH deficiency, which supports the idea that the sympathetic nervous system is not obligatory for leg vasoconstriction during orthostatic challenges.

METHODS

Subjects. Seven patients with chronic autonomic failure, including five PAF and two DBH-deficient patients, and ten age-matched healthy controls (7 men and 3 women) participated in this study (Table 2). PAF is characterized by reduced levels of norepinephrine and widespread autonomic failure with no other neurological features present (5a) (Table 1) and was diagnosed by an experienced internist (J. Deinum or J. W. M. Lenders). Diagnosis of DBH deficiency was confirmed by the complete absence of plasma and urine norepinephrine and adrenaline (Table 1), increased plasma dopamine levels, a significant improvement of clinical symptoms of autonomic failure upon L-threo-dihydroxyphenylserine (L-DOPS; droxidopa) treatment, and verification of the genetic disorder (9, 32). None of the subjects smoked. All PAF patients continued their medication (Table 2), and four of them were put on extra sodium intake. DBH-deficient patients were measured before and 2 wk after cessation of their daily L-DOPS treatment, which was confirmed by undetectable plasma and urine norepinephrine levels. Autonomic failure in PAF patients was confirmed by Valsalva maneuver testing.

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Table 1. *Pathophysiological classification*

	PAF	DBH
Sympathetic nerves	Degenerative	Intact
Baseline norepinephrine	Low	Absent
Norepinephrine response during tilt	Low	Absent
Response to norepinephrine	Increased	Increased

PAF, pure autonomic failure; DBH, dopamine-β-hydroxylase deficiency.

This study was performed in accordance with the Declaration of Helsinki and was approved by the medical ethical committee of our institution. All subjects gave written informed consent.

Experimental procedures and protocol. All subjects refrained from caffeine-containing food and beverages, vitamin C supplements, nicotine, and alcohol for >12 h and from heavy physical activity for >24 h before the experiment. Subjects fasted for >2 h before the experiment. All experiments were performed in the morning in a quiet, temperature-controlled (23 ± 1°C) room.

Subjects rested in the supine position on a manually driven tilt table with a footboard. After a supine resting period of at least 30 min, subjects were tilted manually, within 5 s, to a passive 60° HUT position for a 10-min period. Subjects supported their body weight during the 60° HUT by standing on their left leg, allowing the nonweight-bearing right leg to be relaxed for blood flow measurements.

Measurements. Blood pressure was measured continuously using a noninvasive blood pressure device (Nexfin, BMEYE). A finger cuff was attached to the middle phalanx of the right third finger to measure finger arterial blood pressure, which accurately reflects intra-arterial blood pressure changes (22). A built-in heart reference system was in operation to correct for hydrostatic influences. Mean arterial blood pressure (MAP) was derived beat to beat, and heart rate was the inverse of the interbeat interval. Stroke volume and systemic vascular resistance were determined by a three-element model of arterial input impedance using Modelflow (19). Cardiac output was calculated as stroke volume times heart rate.

Superficial femoral arterial blood flow during supine rest and 60° HUT was measured using duplex ultrasound, with a coefficient of variance of 14% (8). Mean red blood cell velocity (V_{mean}) and systolic and diastolic diameter of the right superficial femoral artery, ~2 cm distal of the bifurcation, were measured with a duplex ultrasound device (Picus, ESAOTE, and WAKI, Atys Medical). V_{mean} was calculated as the average of 20 consecutive Doppler waveforms. Automated software was used for operator-independent analyses of waveforms (Matlab 6.1, Mathworks). For diameter measurements, the average of six consecutive mean diameters was obtained. Real-time automated analyses were performed using the ARTLAB system (Pie Medical). Leg blood flow was calculated with the following formula: $(\pi \times r^2 \times V_{mean}) \times 60$, where $r = 0.5 \times$ diameter of the superficial femoral artery.

Data analysis. All variables were measured in the supine position (baseline) and in the last minute of 60° HUT. Leg vascular resistance was calculated as the arterial-venous pressure gradient divided by blood flow. Supine venous pressure was set at 9 mmHg, and during 60° HUT, the arterial-venous pressure gradient was replaced by MAP, since hydrostatic pressure makes an identical contribution to leg venous pressure as well as leg arterial pressure (17).

Statistical analysis. Statistical analyses were performed using SPSS 16.0 (SPSS) software. Data are presented as means ± SD unless otherwise stated. The level of statistical significance was set at $\alpha < 0.05$. Differences in baseline parameters between PAF patients and controls were assessed using independent *t*-tests. Repeated-measures ANOVAs were used to assess differences in the effect of 60° HUT on leg vascular resistance between PAF patients and controls. Post hoc *t*-tests were performed when the ANOVA reported a significant effect. The Bonferroni correction was used to correct for multiple comparisons. Baseline values and effects of 60° HUT in DBH-deficient patients were not statistically analyzed.

RESULTS

Baseline leg vascular resistance, leg blood flow, and superficial femoral artery diameter were not significantly different between PAF patients and controls, whereas MAP and heart rate were significantly higher in PAF patients compared with controls ($P = 0.01$ and $P < 0.001$, respectively; Table 3). In DBH-deficient patients, baseline supine leg vascular resistance was lower compared with controls (Table 3). Baseline supine MAP and heart rate were comparable between DBH-deficient patients and controls (Table 3). Although leg vascular resistance increased during L-DOPS treatment, leg vascular resistance remained lower in DBH-deficient patients compared with controls (Table 3).

60° HUT. All subjects completed the 10-min period of 60° HUT. During 60° HUT, leg vascular resistance significantly increased in PAF patients (30 ± 22%) and controls (72 ± 69%,

Table 2. *Subject and group characteristics*

	Sex	Age, yr	Height, cm	Weight, kg	Systolic Blood Pressure, mmHg	Diastolic Blood Pressure, mmHg	Heart Rate, beats/min	Medication(s)
				DBH patients (n = 2)				
DBH-deficient *patient 1*	Female	26	159	60	136	72	52	L-DOPS
DBH-deficient *patient 2*	Female	41	167	55	120	90	56	L-DOPS
Means ± SD		34 ± 11	163 ± 6	58 ± 4	128 ± 11	81 ± 3	54 ± 3	
				PAF patients (n =5)				
PAF *patient 1*	Female	69	154	52	140	76	85	Midodrine and fludrocortisone
PAF *patient 2*	Male	75	184	61	120	86	78	
PAF *patient 3*	Female	76	172	60	144	86	68	Midodrine and fludrocortisone
PAF *patient 4*	Female	64	167	74	192	98	68	Midodrine and fludrocortisone
PAF *patient 5*	Male	67	172	54	180	90	68	Fludrocortisone
Means ± SD		70 ± 5	170 ± 11	60 ± 9*	155 ± 30*	87 ± 8	73 ± 8	
				Controls (n = 10)				
Means ± SD		69 ± 4	177 ± 9	80 ± 9	128 ± 18	81 ± 8	60 ± 8	

Values are individual values and means ± SD; *n*, no. of subjects/group. Blood pressure and heart rate values for DBH-deficient patients were after a 14-day interruption of L-threo-dihydroxyphenylserine (L-DOPS) treatment. *Significantly different from controls.

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Table 3. *Systemic and peripheral cardiovascular parameters at baseline and during 60° HUT*

	Mean Arterial Blood Pressure, mmHg		Heart Rate, beats/min		Leg Blood Flow, ml/min		Leg Vascular Resistance, mmHg·ml^{-1}·min^{-1}		Superficial Femoral Artery Diameter, mm
	Baseline	60° HUT	Baseline	60° HUT	Baseline	60° HUT	Baseline	60° HUT	
				DBH-deficient patients (n = 2)					
DBH-deficient *patient 1*	99	81	51	58	332	109	0.27	0.77	6.8
With L-DOPS	95	82	47	55	140	35	0.62	3.17	6.1
DBH-deficient *patient 2*	86	52	56	78	199	59	0.39	0.87	5.3
With L-DOPS	101	87	68	69	111	67	0.83	1.31	5.7
				PAF patients (n = 5)					
PAF *patient 1*	97	86	85	89	55	45	1.66	1.77	9.0
PAF *patient 2*	119	98	79	94	72	54	1.53	1.87	6.2
PAF *patient 3*	133	54	63	69	80	22	1.61	2.66	6.5
PAF *patient 4*	150	64	70	63	180	61	0.79	1.06	9.5
PAF *patient 5*	121	80	69	75	104	62	1.08	1.32	9.0
Means ± SD	124 ± 19*	76 ± 18*†	73 ± 9*	78 ± 13	98 ± 49	49 ± 16†	1.33 ± 0.38	1.74 ± 0.61†	8.0 ± 1.6
				Controls (n = 10)					
Means ± SD	101 ± 12	101 ± 13	59 ± 8	71 ± 12†	96 ± 33	63 ± 30†	1.17 ± 0.39	2.04 ± 1.23†	8.0 ± 1.2
ANOVA	Time <0.01	Interaction <0.01	Time <0.01	Interaction 0.12	Time <0.01	Interaction 0.34	Time 0.02	Interaction 0.34	

Values are individual values and means ± SD; *n*, no. of subjects/group. HUT, head-up tilt. ANOVA indicates the *P* values of repeated-measures ANOVA between PAF patients and controls. *Post hoc significantly different from controls; †significantly different from baseline.

post hoc $P = 0.04$ and $P = 0.01$, respectively), whereas the increase in leg vascular resistance was not significantly different between groups (Table 3 and Fig. 1). Controls showed no change in MAP (Table 3 and Fig. 1), whilereas MAP significantly decreased during 60° HUT in PAF patients (post hoc $P = 0.02$; Table 3 and Fig. 2). Heart rate increased significantly during 60° HUT in PAF patients and controls (Table 3). The increase in heart rate was not significantly different

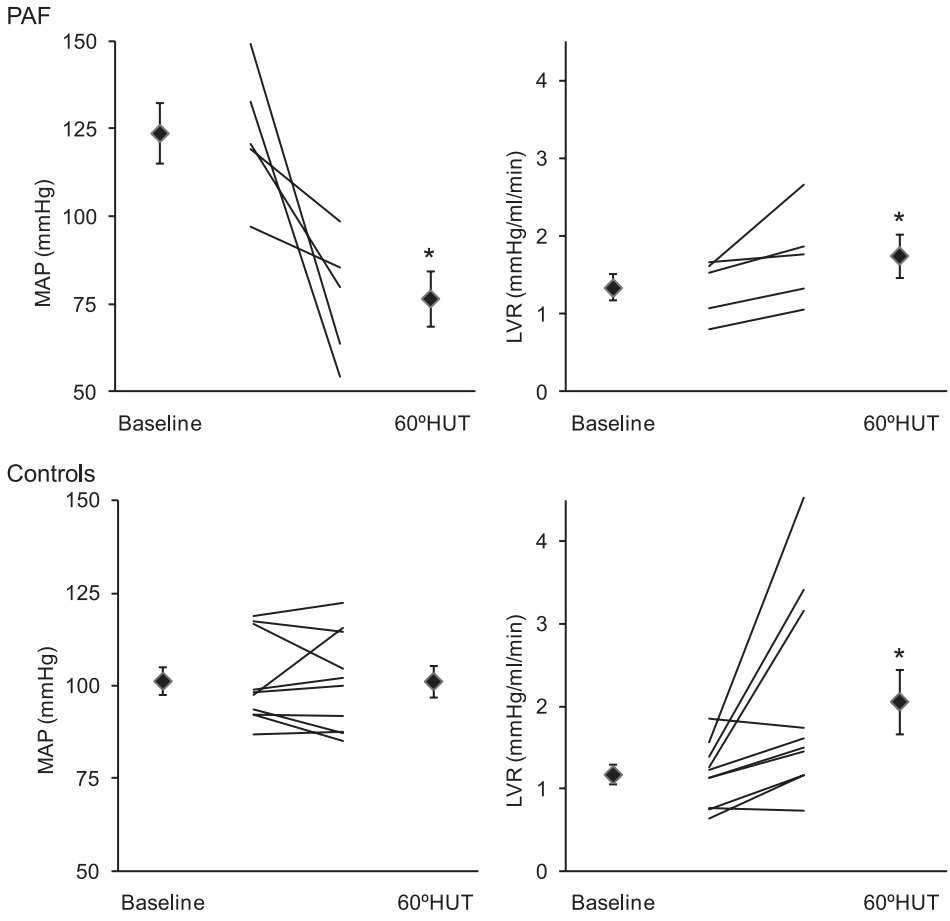

Fig. 1. Group (♦) and individual (solid lines) mean arterial blood pressure (MAP) and leg vascular resistance (LVR) values at baseline and during 60° head-up tilt (HUT) in pure autonomic failure patients (PAF; $n = 5$) and controls ($n = 10$). Group values represent means ± SE. *Significantly different from baseline.

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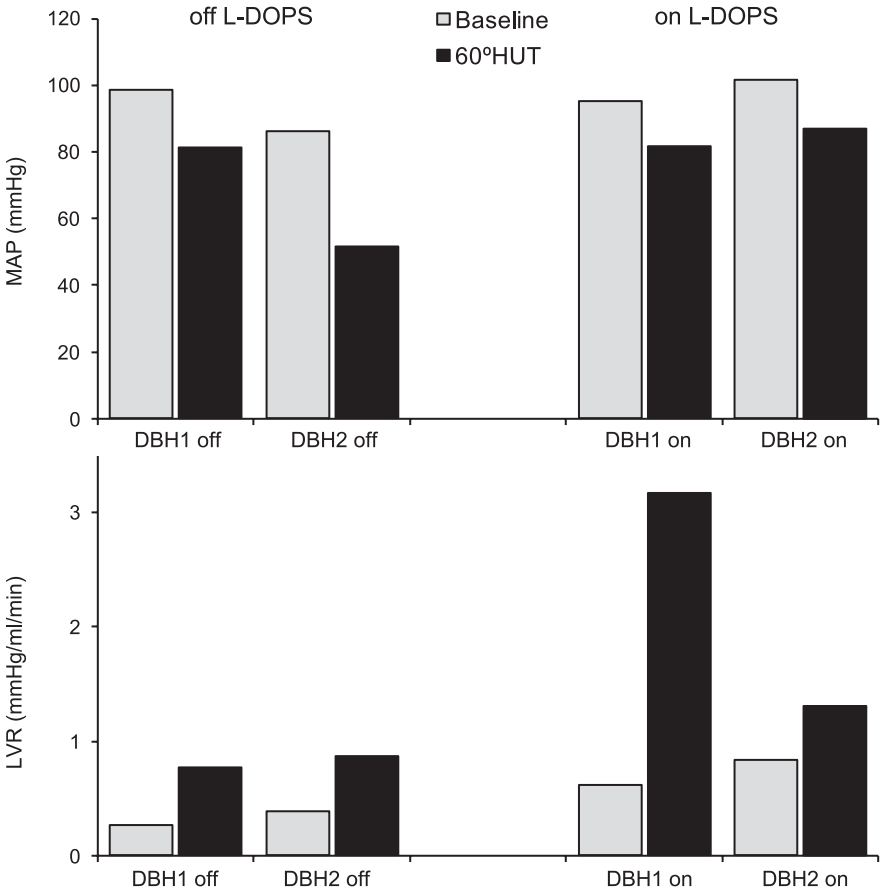

Fig. 2. MAP and LVR values at baseline and during 60° HUT in dopamine-β-hydroxylase-deficient *patient 1* (DBH1) and *patient 2* (DBH 2) off and on l-threo-dihydroxyphenylserine (L-DOPS).

between groups (Table 3). In DBH-deficient patients off and on L-DOPS treatment, leg vascular resistance increased during 60° HUT (DBH-deficient *patient 1*: 184% and 413% and DBH-deficient *patient 2*: 123% and 57%, respectively; Table 3 and Fig. 2). DBH-deficient patients off and on L-DOPS showed a decrease in MAP during 60° HUT (Table 3 and Fig. 2). Heart rate increased in DBH-deficient patients off and on L-DOPS (Table 3).

Stroke volume significantly decreased during 60° HUT in PAF patients and controls (Table 4). Systemic vascular resistance decreased significantly in PAF patients but did not change in controls during 60° HUT (Table 4). Controls showed

Table 4. *Systemic cardiovascular parameters at baseline and during 60° HUT*

	Stroke Volume, ml		Cardiac Output, l/min		Systemic Vascular Resistantce, dyn·s·cm^{-5}	
	Baseline	60° HUT	Baseline	60° HUT	Baseline	60° HUT
			DBH-deficient patients (n = 2)			
DBH-deficient *patient 1*	152	106	7.8	6.1	767	799
With L-DOPS	129	85	6.0	4.7	961	1,050
DBH-deficient *patient 2*	93	47	5.2	3.7	1,312	1,134
With L-DOPS	97	75	6.6	5.2	1,249	1,343
			PAF patients (n = 5)			
PAF *patient 1*	56	46	3.8	3.2	2,892	1,847
PAF *patient 2*	53	42	4.2	4.0	2,285	1,988
PAF *patient 3*	39	29	2.5	2.0	4,416	2,175
PAF *patient 4*	61	48	4.3	3.1	2,794	1,655
PAF *patient 5*	68	55	4.7	4.2	2,064	1,584
Means ± SD	55 ± 13	44 ± 11†	3.9 ± 0.9	3.3 ± 0.9†	2m890 ± 920*	1,850 ± 242†
			Controls (n = 10)			
Means ± SD	70 ± 14	59 ± 14†	4.1 ± 1.1	4.2 ± 1.0*	2,158 ± 608	2,100 ± 597
	Time	Interaction	Time	Interaction	Time	Interaction
ANOVA	<0.01	0.85	0.02	<0.01	<0.01	0.01

Values are individual values and means ± SD; *n*, no. of subjects/group. ANOVA indicates the *P* values of repeated-measures ANOVA between PAF patients and controls. *Post hoc significantly different from controls; †significantly different from baseline.

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no change in cardiac output, whereas cardiac output decreased during 60° HUT in PAF patients (post hoc $P = 0.02$; Table 4). DBH-deficient patients showed a decrease in stroke volume and cardiac output during 60° HUT off and on L-DOPS (Table 4). Systemic vascular resistance decreased during 60° HUT only in DBH-deficient *patient 2* off L-DOPS (Table 4).

DISCUSSION

To study the importance of the sympathetic nervous system during orthostatic challenges, we examined leg vascular responses during 60° HUT in two distinct groups of chronic postganglionic autonomic disorders. The major findings were *1*) an increase in leg vascular resistance during 60° HUT was observed in both postganglionic autonomic failure groups; *2*) the increase in leg vascular resistance in PAF patients seemed to be lower, although not significantly different from healthy controls; and *3*) orthostatic hypotension during 60° HUT was still present in the postganglionic autonomic failure groups, despite the preserved leg vasoconstriction. These findings indicate that the sympathetic nervous system is not the sole or pivotal mechanism for leg vasoconstriction during orthostatic challenges.

Leg vasoconstrictor mechanisms. To maintain blood pressure during orthostatic challenges, peripheral vasoconstriction is induced by baroreceptor-mediated activation of the sympathetic nervous system (11, 34), which can be anatomically divided into preganglionic and postganglionic parts (11, 28). We demonstrated that leg vasoconstriction in patients with PAF and DBH deficiency is not abolished. In parallel to our findings, preserved leg vasoconstriction was demonstrated in spinal cord-injured individuals (15, 16, 18, 26) with preganglionic autonomic failure due to disruption of the spinal cord. Indeed, the increase in leg vascular resistance during HUT in spinal cord-injured individuals, but also in healthy controls, was unaffected during an intra-arterial infusion of phentolamine (α-adrenergic antagonist) (26). The major finding of our study is that an intact sympathetic nervous system is not obligatory for leg vasoconstriction during orthostatic challenges in humans, which reinforces the findings of previous studies.

As an intact sympathetic nervous system is not obligatory, one may question which mechanism(s) contributed to the leg vasoconstriction in our subjects during 60° HUT. In autonomic disorders with intact sympathetic nerve endings, as in DBH deficiency (32), nonadrenergic neurotransmitters, such as ATP and neuropeptide Y (NPY) (29) may contribute to the demonstrated leg vasoconstriction. DBH-deficient patients have an intact sympathetic nervous system with a normal increase in baroreflex-mediated sympathetic activity during 60° HUT (Table 1) (31). Nonadrenergic neurotransmitters may, therefore, induce vasoconstriction during HUT in DBH deficiency (Table 5). In PAF patients, however, nonadrenergic neurotransmitters are unlikely to contribute to the leg vasoconstriction, given the generalized sympathetic denervation and consequent loss of sympathetic nerve terminals (Tables 1 and 5) (13, 36, 37). The nonadrenergic neurotransmitters ATP and NPY are costored with norepinephrine, are simultaneously released from the sympathetic nerve terminal into the synaptic cleft, and are thought to have a coordinated action with norepinephrine (2). Animal studies have demonstrated the vasoconstrictor capacities of ATP, whereas NPY modulates the action of norepinephrine and ATP (2, 3). However, the exact role of noradrenergic neurotransmitters in humans is still unclear.

Table 5. *Possible peripheral vasoconstrictor mechanisms in PAF and DBH deficiency*

Vasoconstrictor mechanisms	PAF	DBH
Baroreflex	−	−
Nonadrenergic neurotransmission*	−	+
Venoarteriolar axon reflex	−	−
Myogenic response	+	+

*ATP and neuropeptide Y.

In addition, local vasoconstrictor mechanisms may induce vasoconstriction, such as the venoarteriolar axon reflex (VAR). The VAR is triggered when venous pressure exceeds 25 mmHg, which results in vasoconstriction of the corresponding arteriole, and may importantly contribute to peripheral vasoconstriction during orthostatic challenges (20). The VAR runs through a sympathetic axon and is thought to be α-adrenergically mediated (10). Due to the denervation of the sympathetic postganglionic axons in PAF, the VAR cannot contribute to leg vasoconstriction during 60° HUT (Table 1 and 5). In DBH deficiency, based on the absence of norepinephrine, the VAR may only contribute to leg vasoconstriction if it is mediated by nonadrenergic neurotransmitters (Tables 1 and 5). This would challenge the general view of the VAR being α-adrenergically mediated (10). However, recent studies have suggested that the VAR is not fully α-adrenergically mediated (6, 26).

Finally, peripheral vasoconstriction may also be induced via the myogenic response, which is triggered by an increase in transmural pressure across an arteriole (10, 21), and is independent of humoral or neuronal influences (7). Therefore, the myogenic response is independent of the sympathetic nervous system. The myogenic response may explain the observed leg vasoconstriction in both PAF and DBH deficiency (Table 5). Similarly, the myogenic response has been hypothesized to be responsible for the leg vasoconstriction during HUT and limb dependency in spinal cord-injured individuals (24, 26). This redundant local vasoconstrictor mechanism may compensate for the loss of sympathetic-mediated vasoconstriction and explain the preserved leg vasoconstriction in patients with autonomic failure.

The results of our study clearly demonstrate that the sympathetic nervous system is important but is not obligatory for leg vasoconstriction during orthostatic challenges. While alternative vasoconstrictor mechanisms may compensate for the loss of sympathetic α-adrenergic vascular control, it is unknown whether and to which extend these mechanisms are present during normal situations or only become active when the sympathetic nervous system fails. Most likely, leg vasoconstriction during orthostatic challenges is caused by a combination of central and local vasoconstrictor mechanisms. When one of these mechanisms fails, the other vasoconstrictor mechanisms can compensate for its loss. The results demonstrate that without control of the sympathetic nervous system, leg vascular resistance can increase by 30% in PAF patients. This 30% increase in leg vascular resistance may be considered as the maximal capacity of nonadrenergic vasoconstrictor mechanisms, most likely the myogenic response, to contribute

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to leg vasoconstriction. However, this needs to be studied in detail in future studies.

Orthostatic hypotension. Despite the leg vasoconstriction during 60° HUT, orthostatic hypotension [≥20-mmHg decrease in systolic pressure or ≥10-mmHg decrease in diastolic pressure within 3 min of standing or 60° HUT (5a)] was present in all PAF and DBH-deficient patients. Interestingly, the increase in leg vascular resistance during 60° HUT in DBH-deficient patients was even larger compared with controls. Orthostatic hypotension in autonomic failure can, therefore, only be partly attributed to changes in the leg vascular response. Potential contributing mechanisms for the orthostatic hypotension in autonomic failure could relate to alterations in the splanchnic vascular bed, an attenuated venoconstriction, and/or inadequate plasma volumes. In PAF patients, the large decrease in systemic vascular resistance suggests a lack of vasoconstriction in other vascular beds, in contrast to the increase in leg vascular resistance. The vascular resistance of the superior mesenteric artery does not change during HUT in PAF patients, nor does forearm vascular resistance (5), suggesting a lack of vasoconstriction of the upper limb and splanchnic vascular bed, although the superior mesenteric artery is only one of three large splanchnic blood vessels. However, systemic vascular resistance decreases, indicating that there should be vasodilation in other vascular beds in PAF patients. Which vascular beds actually demonstrate vasodilation is unknown. Nevertheless, the decrease in systemic vascular resistance during 60° HUT seems to be the major cause of orthostatic hypotension in PAF patients (1, 4, 5). Future studies should further examine the exact mechanism explaining the orthostatic hypotension in autonomic failure, which may contribute to the clinical management of these patients.

Baseline values. Baseline leg vascular resistance was not different between PAF patients and controls, despite the generalized sympathetic denervation and low norepinephrine levels in PAF patients. This could be explained by the use of midodrine (α-adrenoceptor agonist) and, to a lesser extent, fludrocortisone in PAF patients, which both increase baseline leg vascular resistance. Similarly, the higher MAP in PAF patients compared with controls may be explained by the increased blood volume by prescribed fludricortisone and sodium. Alternatively, PAF patients may demonstrate physiological adaptations to try to prevent orthostatic intolerance (14, 33).

Limitations. In our 60° HUT protocol, subjects supported their body weight on one leg, allowing the nonweight-bearing leg to be relaxed for blood flow measurements. This protocol has been used before (18, 25, 27) but might increase muscle tensing in the weight-bearing leg (35) and, thereby, increase muscle sympathetic nerve activity by the exercise pressor reflex (30). We tried to minimize the muscle tensing during 60° HUT by supporting the thigh of the weight-bearing leg by a strap to keep it extended and supporting straps around the waist and chest. Muscle tensing in the weight-bearing leg might result in vasoconstriction in this leg, although it seems to decrease systemic vascular resistance in controls and PAF patients (35). It could, therefore, be that muscle tensing in the weight-bearing leg leads to vasoconstriction and at the same time to systemic vasodilation, explaining our lack of increase in systemic vascular resistance in controls. The demonstrated increase in leg vascular resistance of the nonweight-bearing leg could, in that case, be underestimated. Nevertheless, the differences between standing on one or two legs during 60° HUT on central and peripheral vascular responses are unknown.

Our small group sizes resulted in less powerful statistical analyses, especially in DBH deficiency. However, both disorders represent rare autonomic disorders with often serious comorbidities, and DBH-deficient patients rarely cease their medication. Moreover, these unique and carefully selected groups demonstrated comparable cardiovascular responses during 60° HUT. Therefore, increasing our sample size is unlikely to change the major outcomes of our study.

Four of five PAF patients used medication to manage their orthostatic hypotension (Table 2). The use of an α-adrenoceptor agonist (midodrine) increases basal vascular tone. However, whether this drug altered the vascular tone during orthostatic challenges is unknown. Fludrocortisone and sodium have an effect on circulating volume, and fludricortisone has also a lesser effect on vascular tone. It is, therefore, unlikely that the observed leg vasoconstriction during 60° HUT in PAF is the result of medication. Furthermore, one PAF patient did not use any medication but demonstrated similar results as the other PAF patients.

Clinical relevance. The initial cardiovascular responses to orthostatic challenges, i.e., increase in heart rate, cardiac contractility, and peripheral vascular resistance, have been allocated to the sympathetic nervous system (4, 12, 23, 28, 34). Our results challenge this widely adopted view, since an increase in leg vascular resistance was observed in specific disorders of the postganglionic part of the sympathetic nervous system. Alternative vasoconstrictor mechanisms may compensate for the loss of sympathetic α-adrenergic-mediated vasoconstriction in patients with autonomic failure. Furthermore, our results indicate that, despite the increase in leg vascular resistance and optimal pharmacotherapy, orthostatic hypotension was still present in all PAF and DBH-deficient patients. This suggests that orthostatic intolerance is unlikely to be caused by changes in leg vascular resistance.

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DISCLOSURES

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