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Systemic Hemodynamics during Orthostasis in Multiple System Atrophy

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Multiple System Atrophy; Total peripheral resistance; Stroke volume; Orthostatic hypotension; Autonomic failure; Systemic Hemodynamics

To the Editor

We are writing with respect to the recent article by Suzuki et al., "Impaired peripheral vasoconstrictor response to orthostatic stress in patients with multiple system atrophy," [1] in which the authors report an overall decrease in total peripheral resistance to blood flow (TPR) during orthostasis in multiple system atrophy (MSA). This is potentially important, because if this interpretation of the data were correct then MSA might involve a heretofore unrecognized reflexive systemic vasodilator response to decreased venous return to the heart. Such paradoxical vasodilation might not only contribute to the orthostatic hypotension (OH) attending MSA but also incite attempts to identify the causative factors and develop novel treatments.

To evaluate TPR the authors used mean arterial pressure (MAP) measured by a non-invasive finger cuff device, divided by cardiac output measured by impedance cardiography. The cardiac output is the cardiac stroke volume (SV) times the heart rate. During orthostasis SV and cardiac output fall, and MAP normally is maintained by increased TPR due to reflexively increased sympathetic noradrenergic system outflows.

Calculation of SV by impedance cardiography is based on an empirical formula applied to the peak change in trans-thoracic electrical impedance during the heartbeat. The impedance cardiographic method has been validated against invasive measures, including situations in which the heart rate and SV change in opposite directions, such as orthostasis [2]. The authors appropriately express caution, however, because impedance cardiography has not been compared with other measures of SV in MSA, and the study did not involve other patient groups with neurogenic OH.

If the orthostatic decrease in SV by the impedance cardiographic method underestimated the actual decrease, then the magnitude of the orthostatic fall in blood pressure would be greater

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than accounted for by the fall in cardiac output, and so MSA patients would appear to have a fall in TPR when they actually did not.

The findings and their interpretation by Suzuki et al. incited us to review our data from IRB-approved protocols at the NIH Clinical Center involving systemic hemodynamic responses to orthostasis using impedance cardiography and the Modelflow algorithm as applied to the finger pressure signal [3], in MSA patients with OH and in patients with OH in the setting of Parkinson's disease (PD+OH) and pure autonomic failure (PAF). Control subjects were healthy volunteers or referred patients without signs of central neurodegeneration or OH.

Our results using impedance cardiography (Table 1) confirm those of Suzuki et al. in indicating an orthostatic decrease in TPR ($p<0.0001$ compared both to zero and to controls) in MSA. Moreover, there was an orthostatic decrease in TPR by the finger cuff method, albeit smaller than that by impedance cardiography.

The findings in the other patient groups, however, lead to concern that *both* techniques underestimate the orthostatic fall in SV, with the extent of underestimation greater for impedance cardiography than by the finger cuff method.

As shown in Table 1, in both PD+OH and in PAF the orthostatic fall in SV was smaller by impedance cardiography, and accordingly the orthostatic fall in TPR was greater, than by the finger cuff method. The magnitudes of decline in SV seemed suspiciously small by both techniques but especially by impedance cardiography. Among the controls the mean decrease in SV and increase in TPR during orthostasis were smaller by impedance cardiography than by the finger cuff method.

Findings based on the change in forearm vascular resistance (FVR) as assessed by impedance plethysmography, a method independent of both impedance cardiography and the Modelflow method to calculate SV, suggest that both the impedance cardiographic and finger cuff methods underestimate the extent of reflexive vasoconstriction during orthostasis. FVR increased by 54% in the controls, whereas the TPR increased by only 30% using the Modelflow method and by only 18% using the impedance cardiography method. Moreover, all the groups with OH had orthostatic decreases in calculated TPR by the impedance cardiography method, yet without concomitant decreases in FVR. If there were a generalized decrease in vascular resistance, one would expect TPR and FVR to change in the same direction.

We think it would be best to withhold judgment about whether MSA patients have systemic vasodilation during orthostasis, until a gold standard method such as acetylene re-breathing or cardiac Doppler-ultrasound is applied.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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TABLE 1

Systemic Hemodynamics during 90 Degrees of Head-Up Tilt in Primary Chronic Autonomic Failure

Numbers of patients are in parentheses. Data were taken at 5 minutes of orthostasis but earlier in the event of a progressive, large decrease in blood pressure.

Group	ΔBPs	ΔSV IMP CARD	ΔSV FINGER	FxΔTPR IMP CARD	FxΔTPR FINGER	FxΔFVR
	mmHg	*mL*	*mL*			
CON	7 ± 1	−16 ± 2	−21 ± 1	0.18 ± 0.05	0.30 ± 0.06	0.54 ± 0.10
	(117) ****	(93) ****	(91) ****	(92) **	(90) ****	(97) ****
		IMP v FINGER: 0.013		*IMP v FINGER: 0.004*		
MSA	−53 ± 4	−11 ± 2	−16 ± 2	−0.24 ± 0.03	−0.13 ± 0.04	0.24 ± 0.11
	(38) ****	(35) ****	(20) ****	(35) ****	(20) **	(34)
	++++	n.s.	n.s.	++++	++	+
		IMP v FINGER: 0.17		*IMP v FINGER: 0.45*		
PD+OH	−58 ± 5	−7 ± 3	−21 ± 3	−0.34 ± 0.04	−0.04 ± 0.08	−0.02 ± 0.15
	(24) ****	(21) *	(14) ****	(21) ****	(14)	(23)
	++++	+	n.s.	++++	+	+
		IMP v FINGER: 0.012		*IMP v FINGER: 0.022*		
PAF	−57 ± 5	−3 ± 2	−22 ± 3	−0.18 ± 0.14	0.05 ± 0.18	0.48 ± 0.13
	(17) ****	(16)	(123) ****	(15)	(12)	(16)
	++++	++	n.s.	++	n.s.	+
		IMP v FING: 0.002		*IMP v FING: 0.017*		

Notes:

(*) Different from zero, p<0.05;

(**) p<0.01;

(***) p<0.001;

(****) p<0.0001.

(+) Different from CON, p<0.05;

(**) p<0.01;

(***)p<0.001;

(****)p<0.0001;

n.s.=no significant difference from CON.

Abbreviations: ΔBPs=change in systolic blood pressure; ΔSV=change in cardiac stroke volume; FxΔTPR=fractional change in total peripheral resistance; CON=controls; FING=finger cuff; IMP and IMP CARD=impedance cardiography; MSA=multiple system atrophy; PD+OH=Parkinson's disease with orthostatic hypotension; PAF=pure autonomic failure.