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EDITORIAL

Baroreflex sensitivity and its implication in neurally mediated syncope in children

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Neurally mediated syncope (NMS) refers to an entity of syncopal disorders that can be triggered by a psychological stimulus, standing for a long time, sudden position change from supine to upright, or a muggy environment. Vasovagal syncope (VVS), also known as acute orthostatic intolerance (OI), is the main form of NMS [1] and seriously affects the quality of life of children. However, the pathogenesis of NMS has not yet been fully clarified. The mechanisms underlying NMS are considered to involve autonomic regulation abnormalities, low blood volume, abnormal vascular function, etc. Baroreflex sensitivity (BRS) is the sensitivity of baroreceptor reflex regulation, which controls cardiovascular autonomic function. Abnormal regulation of the baroreflex has been identified as a fundamental mechanism underlying NMS. Arterial BRS describes the effectiveness of baroreflex during an alteration in blood pressure (BP) and is determined by evaluating changes in heart rate (HR) in response to BP alterations.

Physiology and measurement of baroreflex sensitivity

Baroreflex control is a crucial reflex adjustment in the human body that keeps BP, HR, and blood volume within a restricted physiologic range in response to changes in environmental stimuli [2]. Baroreceptors are triggered by stretching when BP and/or blood volume increase and signals to the nucleus of the solitary tract (NTS) are increased through the vagus and glossopharyngeal nerves. To counteract the increase and decrease in pressure, baroreceptors cause vasodilation by inhibiting the efferent sympathetic impulse to target organs such as the heart, muscle, and vessels. At the same time, increased parasympathetic activity at the sinoatrial node slows the HR. Additionally, baroreceptors are unloaded when position changes from supine to standing, resulting in vascular constriction and HR increase to prevent the drop in BP [3]. The effectiveness of the baroreflex can be described as BRS.

The conventional methods of measuring arterial BRS include injection of vasoactive drugs, the Valsalva maneuver, and the neck chamber; while there is a more recent method involving the analysis of spontaneous variations in BP and the RR interval [4]. It is worth mentioning that baroreceptors are affected by modest variations in BP that occur continuously throughout the day as well as by rapid changes in BP. The baroreceptor-heart rate reflex can be precisely analyzed through computer-based techniques. There are two basic approaches used, time domain-based and frequency domain-based measurements.

Arterial baroreceptors located in the carotid sinuses and aortic arch are sensitive to pressure changes, and cardiopulmonary baroreceptors located in the thoracic veins and heart are sensitive to blood volume changes. Efferent sympathetic neurons are inhibited by both arterial and cardiopulmonary baroreceptors, resulting in vasodilation. However, only arterial baroreceptors directly affect HR. Furthermore, the ability of the baroreflex to modulate HR on a beat-by-beat basis is mediated by the vagus nerve rather than the sympathetic nerves [4]. Therefore, the quantification of arterial BRS or the so-called parasympathetic BRS can be calculated by changes in HR in response to the changes in BP caused by vasoactive medication or alteration of body position. Some studies were conducted to detect sympathetic BRS by measuring the activity of sympathetic nerves in muscles in reaction to changes in BP [5].

Remarkably, the responses of the carotid baroreflex to orthostatic stress are influenced not only by changes in the carotid baroreceptors but also by an interaction with the responses of the cardiopulmonary baroreceptors. Arterial

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baroreceptors are also called high-pressure baroreceptors, while cardiopulmonary baroreceptors are also called low-pressure baroreceptors or volumetric receptors. Arterial baroreceptors are inactivated by central volume unloading, while extreme hypovolemia and consequent central volume unloading may paradoxically stimulate cardiopulmonary baroreceptors, which is a model of the vasovagal response [6]. Variations in muscle sympathetic nervous activity (MSNA) reflect the sympathetic component of the baroreflex, which is also reflected in alterations in cardiac BRS [7]. Impaired sympathetic baroreflex function during an upright position seems to contribute to the pathophysiology of NMS [8]. In 1998, Furlan et al. found that patients with chronic OI had decreased MSNA and an exaggerated HR, both of which indicate abnormal sympathetic outflow to the vessels but not the heart [9]. Not only arterial BRS but also cardiopulmonary BRS and sympathetic BRS should be investigated to explain autonomic dysfunction in NMS. However, some studies have shown that the sensitivities of cardiac and sympathetic efferent arms do not appear to be correlated, probably because cardiac and sympathetic BRS share unique pathways [7]. Therefore, we need to explore the underlying pathways deeply in future studies.

The arterial baroreceptor reflex system is crucial in maintaining BP and avoiding wide fluctuations in BP within a short time. Abnormal baroreceptor reflex system causes unstable BP and leads to cardiovascular diseases [10]. Abnormal BRS, which reflects abnormal cardiovascular autonomic function, has been identified as an underlying mechanism for NMS. However, there are controversies regarding the role of the changes in BRS in the pathophysiology of NMS.

Baroreflex sensitivity in patients with neurally mediated syncope

When VVS patients are in a supine position or a resting state, the resting BRS is increased, as reported in most studies. El-Sayed et al. used the addition of graded lower body suction to assess orthostatic tolerance and found that subjects who were more susceptible to syncope had significantly low blood volumes and significantly high BRS at rest [11]. Pitzalis et al. found that VVS patients with positive head-up tilt test (HUTT) had greater baseline supine BRS at rest than those with negative HUTT and controls [12]. Lee et al. described that BRS in patients suffering from NMS during the pretest period was significantly higher than that in healthy subjects [13]. The results of studies on children were similar to those on adults. In 2018, Li et al. revealed that BRS and total peripheral vascular resistance (TPVR) in the supine position were both higher in children with VVS than in the controls [14]. They hypothesized that an individual's vulnerability to tilt-induced VVS could be measured by the degree to which their HR was controlled by the baroreflex after baroreceptor inactivation. In contrast, Flevari et al. [15] found that BRS was impaired in the supine position in patients with syncope, especially in those suffering from VVS with vasodepressor type. Studies on BRS are conflicting [16–20]. Some investigators thought that the carotid BRS of VVS patients did not differ from that of healthy controls in the supine position. The reasons for the discrepancies in BRS status in the supine position at rest among different studies were numerous: (1) different methods to measure BRS [4]; (2) a small number of subjects in most of the studies; (3) different and complex clinical conditions of research subjects, such as a history of recurrence syncope or only mild symptoms; (4) different HUTT protocols, tilt time, and tilt angle [4]; (5) individual differences in BRS, and (6) complex pathophysiology of NMS. Therefore, how the arterial baroreflex plays a role in the pathophysiology of VVS merits further studies.

In almost all studies, a reduction in arterial BRS was observed during the upright position in comparison to the supine position, no matter whether the participants were healthy people or patients with NMS. Researchers revealed a reduced BRS at positive reaction time compared with the supine position in adults with NMS [21–23], and Alnoor et al. also reported a similar result in children with NMS at tilt and positive time [24, 25]. Yang et al. [26] showed that BRS dropped markedly from the supine to the upright position in children with orthostatic hypertension compared with controls. In addition, changes in BRS in patients with NMS and controls were inversely correlated to mean arterial pressure changes when subjects moved from supine to upright positions. A decreased BRS at tilt might contribute to the development of NMS by making it more difficult to adequately counteract hypotension. In addition, the decline in BRS seems to be more pronounced in HUTT-positive patients than in HUTT-negative patients and healthy people. Mitro et al. also demonstrated that BRS and CO were reduced at the time of syncope in the HUTT-positive group [27]. Lee et al. found that the reduction in BRS from the pretest of the HUTT to the positive period in the patients was greater than that in the controls [13]. This means that NMS-prone individuals appear to demonstrate functional diminution of baroreceptor responsiveness at the time of syncope. Several studies have shown that arterial BRS decreases in response to orthostatic posture in healthy volunteers as well [28, 29]. These findings also illustrate that the importance of BRS in the maintenance of BP may explain the pathogenesis in patients with NMS (Table 1).

Ogoh et al. indicated that arterial BRS mediated by the carotid sinus controls HR via parasympathetic activity when central blood volume decreases during the HUTT; however, the maintenance of BP benefits from the sympathetic

Table 1 Baroreflex sensitivity in patients with neurally mediated syncope

References	Conditions	Group	Age (year)	*N*	BRS (ms/mmHg)	Main findings
El-Sayed et al. [11]	Resting	HUTT	42.1 (18–68)	9	13.1 ± 2.7	Subjects who were more susceptible to syncope had significantly high BRS
		HUTT + LBNP-20		25	7.2 ± 3.3	
		HUTT + LBNP-40		15	5.8 ± 2.4	
Pitzalis et al. [12]	Resting	HUTT (+)	30 ± 14	94	17.4 ± 9.8	Patients with HUTT (+) showed greater BRS than those with HUTT (−) and controls
		HUTT (−)	38 ± 15	216	13.2 ± 7.9	
		Control	37 ± 14	100	12.8 ± 8.2	
Lee et al. [13]	Resting	Syncope	34.8 ± 11.9	55	20.1 ± 10.9	BRS was significantly higher than that in controls during the pretest and recovery period in syncope patients
		Control	38.1 ± 9.8	77	13.0 ± 8.1	
	Recovery	Syncope	34.8 ± 11.9	55	20.3 ± 8.9	
		Control	38.1 ± 9.8	77	13.5 ± 7.4	
Li et al. [14]	Resting	Syncope	11 ± 3	77	15.5 ± 7.5	BRS was higher in children with VVS than in the controls
		Control	11 ± 2	28	9.9 ± 5.6	
Thomson et al. [16]	Positive	Syncope	43.6 ± 16.7	40	4 ± 6	There was no significant difference between the two groups
		Control	41.8 ± 17.0	32	4 ± 2	
Sneddon et al. [17]	Resting	Syncope	50.6 ± 14.8	17	16.4 ± 12.2	There was no significant difference between the two groups
		Control	47.5 ± 19.8	17	15.1 ± 13.0	
Sneddon et al. [17]	Resting	HUTT (+)	42.0 ± 19.3	18	14.9 ± 11.7	There was no significant difference between the two groups
		HUTT (−)	43.4 ± 21.2	19	16.2 ± 11.4	
		Control	42.8 ± 14.2	17	15.2 ± 8.5	
Morillo et al. [20]	Baroreflex gain during pressure reduction	HUTT (+)	48 ± 3	21	4.4 ± 0.8	BRS in patients with HUTT (+) was decreased than with HUTT (−)
		HUTT (−)		32	8.5 ± 1.3	
	Baroreflex gain during pressure elevation	HUTT (+)	48 ± 3	21	4.2 ± 1.5	
		HUTT (−)		32	11.0 ± 1.5	
Hu et al. [21]	Supine	HUTT (+)	42 ± 12	22	7.55 ± 3.79	There was no significant difference between the two groups
		HUTT (−)		20	8.66 ± 3.95	
		Control	36 ± 11	20	9.62 ± 3.67	
	HUTT positive	HUTT (+)	42 ± 12	22	5.08 ± 2.14	BRS in patients with HUTT (+) was decreased than those with HUTT (−)
		HUTT (−)		20	7.05 ± 3.29	
		Control	36 ± 11	20	8.42 ± 3.38	
Samniah et al. [22]	HUTT at 3 min	HUTT (+)	47 ± 4.37	12	6.0 ± 2.02 (BRR)	There was no significant difference between the two groups
		HUTT (−)	55 ± 3.85	16	3.37 ± 1.56 (BRR)	
	HUTT positive or at 45 min	HUTT (+)	47 ± 4.37	12	−3.30 ± 0.81 (BRR)	BRS in patients with HUTT (+) was decreased than with HUTT (−)
		HUTT (−)	55 ± 3.85	16	4.92 ± 1.36 (BRR)	
Mitro et al. [26]	HUTT positive	HUTT (+)	48.4 ± 17.1	28	0.54 ± 0.27	BRS in patients with HUTT (+) was decreased than with HUTT (−)
		HUTT (−)	44.6 ± 21	23	0.72 ± 0.35	

HUTT (+) positive response in head-up tilt test, *HUTT (−)* negative response in head-up tilt test, *LBNP-20* lower body suction at − 20 mmHg, *LBNP-40* lower body suction at − 40 mmHg, *BRR* baroreceptor responsiveness

activity and its effects on the heart, vessels, and muscles [30]. When changing from a supine to an upright position, the venous return and CO decrease immediately, which lowers the frequency of the transmission of impulses via arterial baroreceptors to the NTS, resulting in an unloading of vagal tone and an increase in sympathetic efferent impulses. Ventricular contraction caused by the increased sympathetic activity will be sensed by inhibitory mechanoreceptors in the left ventricular wall and activated high-pressure C-fiber afferents, causing reflexive bradycardia, vasodilation, and hypotension [31], which is called the Bezold-Jarisch reflex (BJR) [32]. Indeed, syncope sometimes starts with a period of excessive increase in HR and myocardial contractility, which can be detected immediately before the occurrence of syncope by echocardiography [33]. As a result, traditional ideas have stated that an overactivated sympathetic nervous system is one of the important mechanisms causing VVS [34]. However, as arterial pressure, cerebral blood flow, and

brainstem perfusion all decrease, a pattern of progressive baroreflex dysfunction becomes apparent. Therefore, arterial and sympathetic BRS decrease when a positive response occurs during the HUTT. In addition, Jardine et al. found that arterial baroreflex control of the HR starts to become weaker earlier than sympathetic baroreflex control during the HUTT [35].

Baroreflex sensitivity acts as a predictor of treatment efficacy in children with neurally mediated syncope

BRS predicts response to tilt training in children with VVS

Tilt training is a common treatment option for patients with VVS, and studies have shown that autonomic tone is increased in subjects after orthostatic training. In 2016, Tao et al. indicated that BRS in the supine position was significantly higher in children with VVS who responded to training therapy than in nonresponders. They also found that a baseline supine BRS cutoff value of 8.945 ms/mmHg may predict with a sensitivity of 86.5% and specificity of 80.0% whether children with VVS will benefit from tilt training as therapy or not [36]. However, Mitro et al. demonstrated that responders had lower BRS values than nonresponders in the standing position [37]. Previous findings of an increase in BRS at rest and an exaggerated drop in BRS during the HUTT might be associated with VVS mechanisms [16]. Accordingly, both BRS in the supine position and BRS in the standing position can be good predictors of the efficacy of training for pediatric VVS.

BRS predicts response to metoprolol in children with VVS

For years, the efficacy of β-adrenergic receptor blockers for patients with VVS has been controversial. Previous studies reported different results [38]. Our research team found that BRS during the HUTT could predict the efficacy of metoprolol in children with VVS [39, 40]. Children who responded to metoprolol had a significantly increased supine BRS value and a remarkable decrease in BRS from supine to syncope compared with nonresponders. Using a supine BRS of 10.3 ms/mmHg during the HUTT as the cutoff value, the sensitivity and specificity to predict therapeutic efficacy of metoprolol in children with VVS were 82% and 83%, respectively. Similarly, using a 4 ms/mmHg decrease in BRS as the threshold, the sensitivity and specificity were 71% and 83%, respectively, to predict therapeutic efficacy of metoprolol in children with VVS. Based on previous research, overactivated sympathetic activity is one of the main mechanisms for VVS [40, 41]. Therefore, the increased supine BRS and the great decrease in BRS during the HUTT could be a helpful indicator of the therapeutic response to β-blockers, which might help clinicians improve the efficiency of treatment.

BRS predicts response to metoprolol in children with postural tachycardia syndrome

A high BRS at baseline is associated with a positive therapeutic response to metoprolol, and these findings should help direct the individualized administration of β-adrenoceptor blockers to children with postural tachycardia syndrome (POTS). Cui et al. [42] reported that supine BRS was significantly higher in metoprolol responders than in nonresponders. The ROC curve showed that a cutoff value of 8.045 ms/mmHg predicted the treatment effectiveness for POTS with a sensitivity and specificity of 75.8% and 95.2%, respectively (Table 2).

Perspectives

Patients with NMS have a variety of imbalanced humoral factors that regulate autonomic nervous system function. Studies have shown that endogenous hydrogen sulfide can activate the carotid sinus baroreflex [43]. Yang et al. showed that the production of hydrogen sulfide from erythrocytes of children with VVS was higher than in the controls, which

Table 2 Baroreflex sensitivity predicts the therapeutic effectiveness in children with neurally mediated syncope

References	Disease	Treatment	Predictor	Cutoff value (mmHg)	Sensitivity (%)	Specificity (%)
Tao et al. [36]	VVS	Training	Supine BRS	> 8.9	86.5	80.0
Tao et al. [40]	VVS	Metoprolol	Supine BRS	> 10.3	82.0	83.0
Tao et al. [40]	VVS	Metoprolol	BRS decreases from supine position to syncopal attack	> 4.0	71.0	83.0
Cui et al. [42]	POTS	Metoprolol	Supine BRS	> 8.045	75.8	95.2

VVS vasovagal syncope, *POTS* postural orthostatic tachycardia syndrome, *BRS* baroreflex sensitivity

indicated that increased endogenous hydrogen sulfide might be involved in the development of VVS in association with BRS [44]. Neuropeptide Y (NPY) was found to inhibit the release of the neurotransmitter acetylcholine by stimulating presynaptic Y2 receptors on cardiac vagal nerve terminals [45], which may affect vagal tone and sensitivity. Liao et al. found that children with VVS had significantly lower levels of plasma NYP than healthy children [46]. However, no evidences have revealed that NYP can affect BRS.

VVS is classified into three types according to different hemodynamic responses during HUTT: VVS-mixed, VVS-cardioinhibitory, and VVS-vasodepressor [47, 48]. Different types of VVS may have different BRS changes during the syncope episode. Interestingly, Thomson et al. indicated that patients with VVS-cardioinhibitory and VVS-vasodepressor types had comparable cardiopulmonary BRS at rest [16]. Similarly, Sneddon et al. also found no difference in autonomic tone at rest between VVS-cardioinhibitory and VVS-vasodepressor types of VVS [17]. However, Flevari et al. [15] found that supine arterial BRS was significantly impaired in patients suffering from vasodepressor-type VVS. Data suggest that bradycardia is preceded by a rapid fall in BP, but some individuals become asystolic early during a positive HUTT [49, 50]. This may be the mechanism for different statuses and changes among different types of VVS. More studies are needed to clarify the function of BRS in different hemodynamic changes.

It is important to remember that BRS levels decrease with age, which has a documented effect on the reflex control of HR [51]. The effect of other factors, such as aldosterone [52], cyclooxygenase [53], and carbohydrate loading [54], on the impairment of BRS has been proven and requires further in-depth investigation.

In conclusion, the role of BRS in NMS pathogenesis is significant and is closely related to clinical diagnosis and treatment decisions. We expect that in the future, more studies can be carried out on BRS in children with NMS to better help with clinical diagnosis and treatment.

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Author contribution statement CYX collected and analyzed data, drafted the initial manuscript, and revised the manuscript. DJB and JHF conceptualized and designed the study, and critically reviewed and revised the manuscript. All authors agreed to accept responsibility for this work and agreed with the final manuscript as submitted.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest No financial or non-financial benefits have been received or will be received from any party related directly or indirectly to the subject of this article. Junbao Du is a member of the Editorial Board for the *World Journal of Pediatrics*. The paper was handled by the other Editor. Junbao Du was not involved in the journal's review of or decisions related to this manuscript.

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