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INSIGHT

Autonomic Nervous Function in Vasovagal Syncope of Children and Adolescents

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Syncope is defined as a transient loss of consciousness due to global cerebral hypoperfusion, accompanied by loss of muscle tone and failure to maintain an active position. Vasovagal syncope (VVS) is the most common presentation of syncope, and its diagnostic criteria include: (1) absence of any other evident etiology for syncope or pre-syncope, (2) positive response to head-up tilt test with evident vasovagal reaction (hypotension and/or bradycardia), and (3) no concomitant chronic or acute disease [1, 2]. The onset of VVS peaks initially in childhood and adolescence, and accounts for 60%–70% of all syncopal cases. Clinicians pay great attention to syncope among children and adolescents, due to its high prevalence and its impact on patients' quality of life. Affected individuals often experience mental stress, economic burdens, and accidental bodily injuries related to syncope [2]. While the pathogenesis of VVS is not fully understood, autonomic nervous dysfunction has been identified as a contributing mechanism. The examination of autonomic nervous function can provide important information about patients with syncope. When autonomic nervous dysfunction participates in the pathogenesis of VVS, autonomic function training serves as an efficient method for treating patients with syncope [3]. Therefore, examination of autonomic nervous function in VVS patients is useful for understanding the mechanisms of VVS as well as diagnosis and treatment. This review focuses on the evaluation of autonomic nervous function in children and adolescents with VVS.

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Altered Autonomic Nervous Function in Pediatric VVS Patients Under Non-provocative Conditions (Table 1)

Several studies have reported that sympathetic function is dominant in pediatric VVS patients under non-provocative conditions. Akçaboy *et al.* analyzed the 24-h heart rate variability in pediatric patients and healthy controls, and found that patients were characterized by a much higher standard deviation of normal-to-normal intervals [4]. In addition to a higher low-frequency power value, patients had a lower square root of the mean squared differences of successive normal-to-normal intervals, proportion of differences in consecutive normal-to-normal intervals that are longer than 50 ms, and high-frequency power values in comparison to normal reference ranges [1]. These results indicated that patients not only had stronger sympathetic activity, but also lower parasympathetic activity under non-provocative conditions. Longin *et al.* also found that VVS patients demonstrated augmentation in basal sympathetic activity based on the analysis of heart rate variability. Moreover, they divided their patients into two groups according to age: 5–11 years old (n = 12) and 12–15 years old (n = 17). They discovered that both groups had higher very low-frequency power values than healthy participants,

Table 1 Studies on autonomic nervous function in vasovagal syncope in children and adolescents.

Study groups	Number of participants	Age (years)	Conditions	Indicators	Alteration in patients *vs.* controls	
					Sympathetic function	Parasympathetic function
Sehra *et al*. 1999 [11]	Patients (n = 8)	13.2 ± 3.2 (mean ± SD)	Tilting/	R–R intervals	–	↓
	Controls (n = 10)	13.0 ± 2.9 (mean ± SD)	Pre-syncope		–	–
Zygmunt *et al*. 2004 [1]	Patients (n = 73)	11–18 (range)	Non-provocative	pNN50	–	↓
				RMSSD	–	↓
				HF	–	↓
				LF	↑	–
Kula *et al*. 2004 [7]	Patients (n = 38)	14.0 ± 0.7 (mean ± SD)	Non-provocative	QTcd	↑	–
	Controls (n = 24)	14.6 ± 0.7 (mean ± SD)			–	–
Xue *et al*. 2007 [6]	Patients (n = 46)	7–17 (range)	Non-provocative	QTd	↑	–
	Controls (n = 30)	6–12 (range)			–	–
Longin *et al*. 2008 [5]	Patients (n = 29)	5–15 (range)	Non-provocative	VLF	↑	–
	Controls (n = 72)	5–15 (range)			–	–
Akçaboy *et al*. 2011 [4]	Patients (n = 27)	8–17 (range)	Non-provocative	SDNN	↑	–
	Controls (n = 27)	10–17 (range)			–	–
Cui *et al*. 2012 [9]	Patients (n = 72)	11.0 ± 1.9 (mean ± SD)	Non-provocative	Ambulatory BP	↑	–
	Controls (n = 40)	10.0 ± 2.0 (mean ± SD)			–	–
Li *et al*. 2018 [10]	Patients (n = 77)	11 ± 3 (mean ± SD)	Non-provocative	BRS	–	↑
	Controls (n = 28)	11 ± 2 (mean ± SD)			–	–

BP, blood pressure; BRS, baroreflex sensitivity; HF, high-frequency; LF, low-frequency; pNN50, normal-to-normal intervals > 50 ms; QTcd, rate-corrected QT interval dispersion; QTd, QT interval dispersion; RMSSD, square root of the mean squared differences of successive normal-to-normal intervals; SDNN, standard deviation of normal-to-normal intervals; VLF, very low-frequency; ↑, relevant function greater in patients than in the other group; ↓, relevant function lower in patients than in the other group; –, nothing in the blanks.

which indicated that, irrespective of patients' age, their sympathetic activity was stronger than that of healthy individuals [5]. Xue *et al.* studied the QT interval dispersion (QTd) in pediatric VVS patients and healthy controls. They found that patients had a prolonged QTd compared to that of controls and that there was no significant difference between the QTds of patients with a vasodepressor response and a mixed response. The results elucidated that patients had higher sympathetic tone and that similar sympathetic tone might exist in patients with different hemodynamic types [6]. A further study on rate-corrected QTd (QTcd) at different times within one day showed that QTcd was significantly higher in the early morning in VVS cases than in healthy controls. This study might explain why VVS patients frequently suffer from syncopal attacks early in the morning [7, 8]. Cui *et al.* discussed the changes of ambulatory blood pressure (BP) in children with VVS. The 24-h mean systolic BP, 24-h mean diastolic BP, daytime mean systolic BP, and nighttime mean systolic BP of patients were higher than those of the control group. In the patient group, the proportion of non-spoon BP pattern was higher than that in the healthy control group. More importantly, the non-spoon BP pattern served as the diagnostic cutoff of VVS and yielded a sensitivity of 82.5% and a specificity of 66.7% [9]. These studies suggested that patients have a predominance of basal sympathetic activity, although an increased cardiovagal baroreflex sensitivity of VVS patients in the supine position has also been reported [10].

Altered Autonomic Nervous Function in Pediatric VVS Patients During the Tilt Test (Table 1)

The tilt test, an important diagnostic method, is widely used to mimic the hemodynamic change before and during a VVS attack. Sehra *et al.* conducted a study focusing on the alteration of autonomic nervous function during the tilt test. They found that the R–R intervals of syncopal patients were significantly shorter than those of controls at 2 min, 5 min and 10 min after tilting, and 2 min before the onset of syncope. This elucidated that sympathetic activity is predominant during the progression of the tilt test and upon the onset of syncope [11]. Current understanding of the Bezold-Jarisch reflex indicates that it is a crucial part in the pathogenesis of VVS, in which sympathetic activity plays an important role [12, 13].

Value of Autonomic Nervous Function Alteration in Predicting the Effectiveness in Treatment with Autonomic Function Training

Orthostatic training, which improves autonomic nervous function, is regarded as an important treatment option for pediatric VVS, although its efficacy is controversial [14, 15]. Therefore, it may be beneficial to predict the efficacy of orthostatic training in advance. In 2018, Tao *et al.* conducted a study of the ability of the acceleration index to predict the efficacy of orthostatic training. They found that lower acceleration index values correlated with increased therapeutic efficacy of orthostatic training. Specifically, an acceleration index cutoff value of 26.77 yielded a sensitivity of 85.0% and a specificity of 69.2% [16].

Limitations

In fact, different indicators have different capacities of reflecting autonomic nervous function. The capacity of QTd, QTcd, BP, frequency domain of heart-rate variability, and cardiovagal baroreflex sensitivity in reflecting autonomic nervous function requires further justification and several papers have warned of their poor reproducibility [2, 17]. In addition, indicators have been found to change with many factors such as age, gender, body mass index, and time of assessment, and some studies had a relatively small sample size contributing to potential bias of their results [18–20]. On the other hand, given the complexity of the autonomic system, there may be no single test that precisely reflects the function of a specific branch of this system. So, batteries of autonomic tests like the Ewing battery should be recommended.

Conclusion

In conclusion, many studies on VVS suggest that sympathetic activity is predominant at baseline as well as during tilting. Meanwhile, other mechanisms such as central hypovolemia, endothelial dysfunction, or neurohormonal disturbance may be primarily involved in the pathogenesis of some VVS cases. Therefore, further studies including pathogenesis-based stratification, and multi-center-based standardized test conditions and test protocols are needed to elucidate the autonomic nervous activity alteration in VVS of children and adolescents, especially those with different hemodynamic patterns.

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