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ORIGINAL COMMUNICATION

Diagnostic efficacy of transcranial Doppler combined with upright tilt test in vasovagal syncope

Jingyi Wang[1,2] · Hua Li[1,2] · Liming Cao[3,4]

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Abstract

Background Vasovagal syncope (VVS) is the most common subtype of syncope, and it significantly impacts patients' quality of life and incurs substantial healthcare costs. Although the head-up tilt table test (HUTT) is the gold standard method for diagnosing VVS, its sensitivity and specificity are limited, which leads to diagnostic challenges. Combining HUTT with transcranial Doppler (TCD) can improve diagnostic accuracy by addressing limitations in monitoring cerebral blood flow during syncope evaluation. In this study, we aimed to analyze the diagnostic efficacy of combining the HUTT and TCD in patients with VVS.

Methods In this prospective study, we enrolled 102 patients with suspected VVS who underwent combined HUTT and TCD evaluation. The diagnostic performance of the combined approach was compared to that of the standalone HUTT, with a focus on sensitivity, specificity, and accuracy.

Results The multimodal testing group showed a 25.61% increase in sensitivity for diagnosing VVS compared to the standalone HUTT group, albeit with a 10.00% reduction in specificity. The false-negative rate decreased by 25.61%, while the false-positive rate increased by 10.00%. Furthermore, the positive likelihood ratio increased by 0.151, and the negative likelihood ratio decreased by 0.3701. The overall accuracy increased by 7.8%. Notably, the areas under the curve for systolic and mean cerebral blood flow velocities were 0.717 and 0.744, respectively.

Conclusions The combination of HUTT and TCD significantly enhanced the diagnostic efficacy in patients with VVS, improving the prediction of syncope and reducing the risks associated with testing.

Keywords Vasovagal syncope · Head-up tilt testing · Transcranial Doppler · Multimodal test · Cerebral blood flow

Introduction

Vasovagal syncope (VVS) is the most common syncope subtype, accounting for 66.67% of cases [1]. Key symptoms of VVS include sweating, a sensation of warmth, nausea, pallor, associated hypotension, and tachycardia [2]. It is more prevalent among younger individuals than among older adults [3]. Studies from Vienna, Austria, have demonstrated that the average cost of assessing a single episode of syncope is approximately €7756 [4]. Syncope is a frequent and costly complaint in emergency departments, accounting for 740,000 visits annually and an estimated expenditure of $2.4 billion in the United States alone [5]. Beyond the financial burden, syncope significantly diminishes patients'quality of life, contributing to anxiety and depression [6]. Recurrence rates for VVS vary depending on the frequency of prior episodes, ranging from 15 to 20% at 1 and 2 years for those with

✉ Liming Cao
caolm-2007@163.com

1 Department of Neurology, Zhuhai Hospital Affiliated to Faculty of Chinese Medicine, Macau University of Science and Technology, Zhuhai 519000, Guangdong, China

2 Department of Neurology, Zhuhai Hospital of Integrated Traditional Chinese and Western Medicine, Zhuhai 519000, Guangdong, China

3 Department of Neurology, The First Affiliated Hospital of Shenzhen University, Shenzhen 518000, Guangdong, China

4 Hunan Provincial Key Laboratory of the Research and Development of Novel Pharmaceutical Preparations, Changsha Medical University, Changsha, China

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one or two episodes to 36% and 42% for those with three episodes over the same periods [7].

An early and accurate diagnosis of VVS is essential for improving patient outcomes. The head-up tilt table test (HUTT) is the gold standard method for evaluating VVS [8, 9]. However, its sensitivity and specificity are limited. In patients with suspected VVS, HUTT often has a low diagnostic yield, making it insufficient for establishing a reliable diagnosis in some cases. For example, the HUTT demonstrates a positivity rate of 65% in patients with established VVS but only 36% in those with likely VVS [10]. This discrepancy highlights the risk of false negatives, particularly in patients exhibiting atypical symptoms or those with comorbidities that may mask the results. Furthermore, in patients with recurrent, unexplained syncope, 65% tested positive on the HUTT [11].

The HUTT has some limitations. First, it primarily relies on changes in blood pressure and heart rate for assessment, which does not directly monitor cerebral blood flow, leaving critical diagnostic information unaddressed. Second, the lack of continuous blood pressure monitoring reduces the temporal resolution of measurements, posing significant risks for patients who experience sudden blood pressure drops. Third, clinical observations indicate that many patients with presyncopal symptoms may not exhibit obvious hypotension, despite substantial reductions in cerebral blood flow, leading to false-negative results. Integrating transcranial Doppler (TCD) into the HUTT procedures allows for the dynamic monitoring of middle cerebral artery blood flow velocity, potentially overcoming these limitations. However, research on the combined efficacy of the HUTT and TCD in diagnosing VVS remains limited. We hypothesize that combining the HUTT and TCD will improve the diagnostic sensitivity and accuracy for VVS compared to using the HUTT alone. Few studies have comprehensively assessed the diagnostic value of this multimodal approach for suspected VVS cases. In this study, we aimed to address the limitations of this approach to further promote the application of the HUTT combined with TCD.

Methods

Study design

The study was designed as a prospective diagnostic test.

Study participants

This prospective study involved 102 patients with VVS from the First Affiliated Hospital of Shenzhen University between September 2022 and April 2024. Assessments were conducted using a head-up tilt table and monitoring system (Beijing Juchi Medical Technology Co., Ltd., HUT822-A, Beijing, China) and a transcranial Doppler ultrasound system (Shenzhen Delika Medical Equipment Co., Ltd., MS-9D,Shenzhen, China).

Grouping and comparison

This study included 102 patients suspected of having VVS who could complete both the HUTT and TCD examinations simultaneously. When considering both the HUTT and TCD data, this group of 102 patients was designated as the multimodal group. When considering only the HUTT data, the same 102 individuals were referred to as the HUTT-only group. We compared the diagnostic efficacy for VVS between the two groups.

This study was approved by the Ethics Review Committee of the First Affiliated Hospital of Shenzhen University (Approval no. 202304133010). The experiments were undertaken with the understanding of and written consent from each participant. The study adheres to the principles of the World Medical Association's Declaration of Helsinki.

Eligibility criteria

The inclusion criteria were:

1. Clinical diagnosis of suspected syncope. Patients were considered to have suspected syncope if they presented with a history of Transient Loss of Consciousness, based on the initial clinical assessment.
2. Ability to complete both the TCD and HUTT assessments
3. Provision of informed consent by the patient or their legal guardian

The exclusion criteria were:

1. Presence of severe stenosis in the intracranial, carotid, or coronary arteries; severe stenosis of the aortic or mitral valve; severe obstructive hypertrophic cardiomyopathy; severe anemia; significant arrhythmias; moderate-to-severe hypertension; or pregnancy. Particularly, patients with severe MCA stenosis were excluded during the TCD screening process. Severe Stenosis is defined as $\geq 70\%$ luminal narrowing in intracranial, carotid, or coronary arteries [12]. Severe structural heart disease: left ventricular ejection fraction $< 40\%$, significant valvular disease (moderate to severe stenosis or regurgitation), hypertrophic cardiomyopathy with outflow tract obstruction. Severe obstructive hypertrophic cardiomyopathy was defined as resting left ventricular outflow tract gradient ≥ 30 mmHg [13]. Significant cardiac arrhythmias, including but not limited to sustained ventricular tachy-

cardia, supraventricular tachycardia with rapid ventricular response (> 100 bpm) [14], symptomatic bradycardia (< 40 bpm) [15], second-degree Mobitz type II or third-degree atrioventricular block, and sick sinus syndrome. Moderate-to-severe hypertension was defined as systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg at screening [16]. These exclusions were determined through comprehensive pre-enrollment investigations, including a 12-lead electrocardiogram, 24-h Holter monitoring (for patients with abnormalities on routine 12-lead electrocardiogram or a history of cardiovascular disease), brain magnetic resonance imaging/computed tomography, electroencephalography (for suspected seizure history), carotid ultrasound, TCD, and blood count.
2. Patients without an available temporal ultrasound window.

The exclusion criteria were primarily established to ensure patient safety and test reliability, eliminating conditions that would either contraindicate HUTT (such as severe cardiovascular diseases) or potentially interfere with accurate TCD measurements (such as inadequate temporal bone windows).

Data collection

Demographic data were collected from all the patients, including sex, age, height, weight, and body mass index (BMI) [BMI = weight (kg)/height $(m)^2$]. Additional data included primary clinical diagnoses, comorbidities, and results from the HUTT and TCD examinations.

Gold standard method for diagnosing VVS [17]

1. Transient and reversible loss of consciousness caused by insufficient cerebral perfusion
2. Patient falls to the ground due to loss of muscle tone during syncope.
3. The exclusion of other causes of loss of consciousness, such as epilepsy, hypoglycemia, metabolic disorders, drug overdose, alcohol intoxication, head trauma, and other reasons, was conducted through comprehensive pre-enrollment investigations. These investigations included a review of medical records and targeted clinical inquiries to identify symptoms or signs of severe comorbidities, along with diagnostic tests such as 12-lead electrocardiogram, transthoracic echocardiography, 24-h Holter monitoring, brain magnetic resonance imaging/computed tomography, electroencephalogram, carotid ultrasound, TCD, and complete blood count.

Modified nitroglycerin provocation protocol for HUTT [18, 19]

1. Patients fasted for at least 4 h and were examined in a quiet, temperature-controlled room. They were placed in the supine position for 10 min before tilting to establish baseline blood pressure, heart rate, and cerebral blood flow measurements.
2. Patients were tilted at an angle of 70° for 20 min. During this time, non-invasive blood pressure was recorded every minute using an automatic sphygmomanometer, while continuous electrocardiography and cerebral blood flow monitoring were performed. Cerebral blood flow monitoring was performed using TCD, as described below. If presyncope or syncope occurred, the patient was immediately returned to the supine position.
3. If the initial HUTT results were negative, the patient remained tilted, and sublingual nitroglycerin (0.3 mg) was administered. The tilt was maintained for 20 min or until presyncope or syncope occurred. In either case, the patient was promptly returned to the supine position.

Criteria for positive HUTT results [20]

1. During the HUTT procedure, any of the following physiological changes accompanied by presyncope or syncope qualified as a positive result: contraction pressure < 80 mmHg, diastolic pressure < 50 mmHg, mean arterial pressure drop > 25%, or systolic pressure < 90 mmHg, sinus bradycardia (< 40 beats/min), sinus arrest lasting > 3 s, heart rate decrease > 20%, transient second-degree or higher atrioventricular block, or junctional rhythm.
2. A significant reduction in cerebral blood flow velocity (CBFV) > 20% from baseline, leading to presyncope or syncope, was also considered a positive result [21]. TCD as an Additional Criterion. During the course of a HUT test, when there is a positive TCD result, it is also necessary to have symptoms of presyncope and syncope to determine a positive HUT result.

TCD cerebral blood flow monitoring

During the HUTT, a 2 MHz TCD probe was used to monitor CBFV in the middle cerebral artery M1 segment through the temporal window, with a monitoring depth of 50–60 mm. Both the left and right MCA M1 segments are simultaneously monitored during the HUTT. If bilateral monitoring was possible, the average CBFV from both sides was calculated to represent the patient's CBFV. In cases where only one side provided a clear signal, the measurable CBFV from that side was used as representative of the patient's MCA blood flow velocity. To ensure stable detection of cerebral

Table 1 Clinical Characteristics of Study Participants

Variable	Patients with VVS, $N = 84$	Non-VVS patients, $N = 18$	*P* value
Age, years	47.81 ± 18.48	56.27 ± 8.86	0.005
Male/female	55/29, 65.5%/34.5%	12/6, 66.7%/33.3%	0.009
Hypertension	26, 31%	5, 27.8%	0.071
Diabetes Mellitus	12, 14.3%	3, 16.7%	0.067
Hyperlipidemia	16, 19.0%	6, 33.3%	1.788
History of Stroke	10, 11.9%	4, 22.2%	1.333

Continuous variables are presented as mean ± standard deviation (SD). Categorical variables are presented as number and percentage (*n*/%).

VVS vasovagal syncope

Table 2 The results of testing should be correlated with clinical features

	Results of HUTT		*P* value
	Positive	Negative	
Frequency of syncope	1.07 ± 2.07	0.46 ± 0.61	0.024
Hypertension	26, 31%	5, 27.8%	0.071
Diabetes mellitus	12, 14.3%	3, 16.7%	0.067
Baseline systolic blood pressure	122.76 ± 17.04	131.42 ± 11.15	0.042
Baseline diastolic pressure	79.63 ± 20.99	82.59 ± 11.14	0.564
Baseline heart rate	67.88 ± 12.12	65.39 ± 14.22	0.446
Baseline mean CBFV	58.17 ± 15.07	50.14 ± 15.29	0.229

CBVF cerebral blood flow velocity, *HUTT* head-up tilt test

Baseline blood pressure, heart rate, and CBFV were defined as the average values during the initial supine phase of the HUTT

blood flow signals, a self-developed multilayer elastic net cap (Chinese Patent No. 202310468404.2) was used to secure the TCD head frame and probe.

Statistical methods

Data analyses were performed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY). The normality of continuous variables was evaluated using the Kolmogorov–Smirnov test. Normally distributed data are reported as mean ± standard deviation ($\overline{\chi} \pm s$), while non-normally distributed data are presented as median (interquartile range). The Chi-square (χ^2) test was used to compare categorical data between groups. Diagnostic tests were analyzed using a 2×2 contingency table, with the main performance indicators being sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and accuracy. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of cerebral blood flow velocity parameters. The optimal cut-off values were determined using Youden's index (J = sensitivity + specificity − 1) [22], which serves as the diagnostic index for evaluating test performance. The area under the curve (AUC) was calculated to assess the discriminative ability of systolic, diastolic, and mean cerebral blood flow velocities in identifying vasovagal syncope.

Table 3 Diagnostic tests of upright tilt table-only test

HUTT-only group	Patients with VVS	Patients without VVS	Total
Positive	54	7	61
Negative	28	13	41
Total	82	20	102

Results

Sixty-seven male patients (65.69%) and 35 female patients (34.31%) were included, with a mean age of 49.30 ± 17.45 years. The age distribution was as follows: nine patients were aged 11–20 years, eight patients were aged 21–30 years, nine patients were aged 31–40 years, 20 patients were aged 41–50 years, 27 patients were aged 51–60 years, 19 patients were aged 61–70 years, nine patients were aged 71–80 years, and one patient was aged 81–90 years. The results are summarized in Tables 1, 2 and 3.

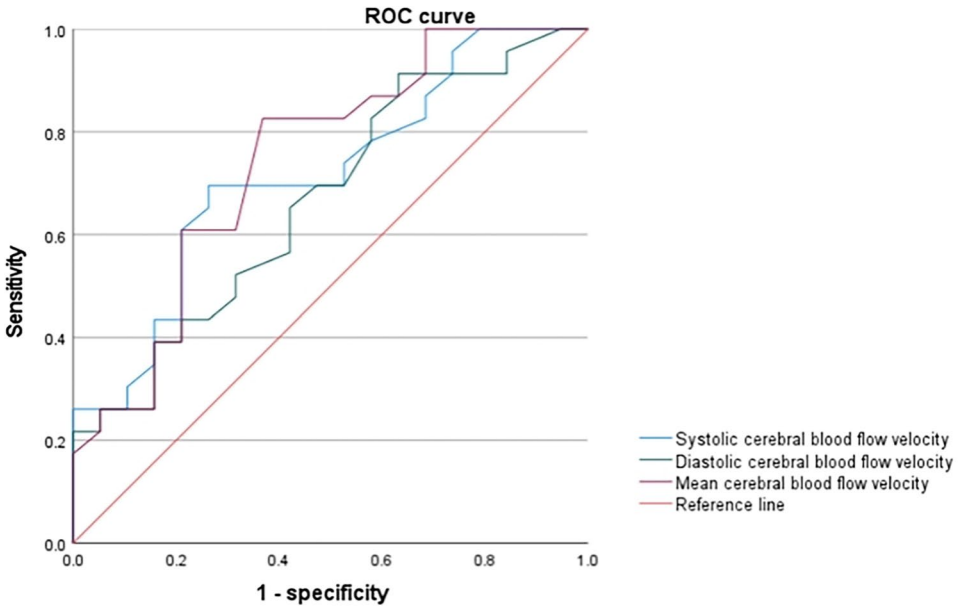

Fig. 1 ROC curve of the diagnostic test. The area under the curve (AUC) for systolic cerebral blood flow velocity (CBFV) was 0.717. At the optimal cut-off value of 58.5 cm/s, the sensitivity was 0.696 and the specificity was 0.737

Table 4 Diagnostic performance of multimodal testing for vasovagal syncope

Multimodal tests	Patients with VVS	Patients without VVS	Total
Positive	75	9	84
Negative	7	11	18
Total	82	20	102

Table 5 Comparison of diagnostic efficacy of multimodal tests and upright tilt table-only test for vasovagal syncope

Diagnostic performance indicators	HUTT-only	Multimodal testing
Sensitivity	0.6585	0.9146
Specificity	0.65	0.55
False negative rate	0.3415	0.0854
False positive rate	0.35	0.45
Positive likelihood ratio	1.8814	2.0324
Negative likelihood ratio	0.5254	0.1553
Accuracy	0.6543	0.7323
Diagnostic index	0.3085	0.4646

The ROC curve was used to evaluate the diagnostic test: the AUC for systolic cerebral blood flow velocity was 0.717. At the optimal cut-off value of 58.5 cm/s, the sensitivity was 0.696, and the specificity was 0.737. The AUC for diastolic CBFV was 0.667. At the optimal cut-off value of 31 cm/s, the sensitivity was 0.913, and the specificity was 0.368. Furthermore, the AUC for mean CBFV was 0.744. At the optimal cut-off value of 47.5 cm/s, the sensitivity was 0.826, and the specificity was 0.632. (Fig. 1). For the summary of the patient clinical profiles, see Table 1.

The correlation between head-up tilt test results and clinical features is detailed in Table 2.

The positive rate of the HUTT-only and multimodal testing for vasovagal syncope are presented in Tables 3 and 4, respectively.

Comparison of diagnostic efficacy of multimodal tests and upright tilt table-only test for vasovagal syncope (see Table 5).

Discussion

The combined use of the HUTT and TCD enables the assessment of hemodynamic indicators from both cardiac and cerebral perspectives, thereby improving the diagnostic accuracy for VVS. This study revealed that the combined HUTT and TCD examination was significantly more effective than the HUTT-only test in diagnosing VVS. Furthermore, it allowed for the direct visualization of the impact of decreased cerebral blood flow on patients, thereby assisting in the diagnosis.

Comparison of diagnostic efficacy for multimodal testing versus HUTT-only test

This study demonstrates that multimodal testing significantly enhances the diagnosis of VVS compared to

standalone HUTT. Specifically, the sensitivity of VVS diagnosis increased by 25.61% and the false-negative rate decreased by 25.61% when using the combination approach. Additionally, the specificity improved by 10.0%, the false-positive rate decreased by 10.0%, and the overall diagnostic accuracy increased by 7.8%. Previous studies have reported the sensitivity of HUTT for diagnosing VVS to be 65.9% [23]. In an earlier study, the sensitivity of the HUTT was estimated to range from 67 to 83%, with the specificity ranging from 75 to 100% [24]. More recent research indicates the specificity of the HUTT using common protocols to be between 92 and 94% [25]. These findings highlight that while the specificity of the HUTT is relatively high, its sensitivity remains relatively low. The diagnostic determination by the HUTT primarily relies on changes in blood pressure, heart rate, and electrocardiography results, without routine monitoring of cerebral blood flow.

In our experience with the HUTT, we observed cases where patients exhibited premonitory symptoms of syncope during the test, yet their blood pressure did not reach the positive result threshold, leading to misclassification as negative results. Attempts to reach the diagnostic threshold for blood pressure during testing may result in significant hypotension becoming apparent only after severe cerebral perfusion insufficiency occurs, increasing the risks associated with the test, particularly in the absence of continuous blood pressure or cerebral blood flow monitoring.

The primary cause of syncope or premonitory symptoms during the HUTT is a significant drop in CBFV, which leads to inadequate cerebral perfusion. Incorporating TCD monitoring during the HUTT allows for the detection of critical changes in CBFV and the vascular resistance index with high temporal resolution, facilitating timely diagnosis. Therefore, the combination of the HUTT and TCD is essential [26]. This synchronous application integrates the advantages of both standalone tests, enhancing the diagnostic sensitivity and accuracy for VVS while addressing the limitations of using the HUTT alone and improving the safety of the procedure.

Safety of HUTT in patients with suspected VVS

The safety of the HUTT depends on several factors, including the testing protocol and appropriate patient selection. While the HUTT is generally considered a relatively safe procedure for patients with VVS [27], it can occasionally trigger cardiovascular and cerebrovascular complications. These may include transient aphasia, seizures, and myocardial ischemia and may even lead to severe arrhythmias, such as significant bradycardia and sinus arrest. The probability of inducing seizures during the HUTT is 3.74–11.6% [27, 28]. The incidence of transient aphasia during the HUTT is 3.18%, with higher rates observed in adults than in children (7.0% vs. 1.6%) [29]. This discrepancy may be attributed to underlying cerebrovascular diseases in adults, such as cerebrovascular stenosis and neurodegenerative diseases. Patients with a history of severe cardiovascular conditions, significant autonomic dysfunction, and prior episodes of severe syncope may require alternative diagnostic approaches or additional precautions during the tilt test [30]. The HUTT is often conducted on a diverse range of patients with suspected VVS, including those with comorbidities such as severe cerebral artery stenosis, coronary artery stenosis, or severe arrhythmias, which are not always strictly excluded. This practice inadvertently increases the risks associated with the test.

Additionally, some patients required more than 10 min to regain consciousness during the HUTT, indicating prolonged cerebral ischemia and a slow recovery process due to impaired self-regulatory capacity (Fig. 2). To ensure patient safety during the HUTT, inducing syncope requires careful monitoring, such as continuous monitoring of cerebral blood flow using TCD and preparedness for immediate intervention, which relies on the operator's experience and professional judgment.

Advantages of combined testing over HUTT-only in assessing cerebral hemodynamics

Combined testing enables earlier prediction of syncope and premonitory symptoms. In patients with VVS, premonitory symptoms and changes in CBFV occur earlier than the onset of syncope does [31]. In this study, 28 patients with primary cerebrovascular dysregulation were identified; these patients tested negative on the standalone HUTT but showed significant decreases in CBFV on TCD. While blood pressure and cerebral blood flow homeostasis are closely related, they are not entirely consistent or parallel. Notably, significant decreases in CBFV can occur even when the blood pressure remains relatively stable, leading to symptoms of inadequate cerebral perfusion. Currently, this phenomenon is not fully understood by many physicians. TCD provides a useful, non-invasive, and dynamic tool for assessing the status of and changes in intracranial circulation [32]. During the HUTT, patients experiencing syncope or premonitory symptoms exhibited a significant reduction in CBFV, with a 76% decrease in diastolic flow and a 33% decrease in systolic flow. Performing TCD imaging during the HUTT is valuable for detecting these changes [26]. These alterations in cerebral blood flow often precede blood pressure changes, providing a better prediction of VVS onset and addressing the limitations of relying solely on blood pressure monitoring during the HUTT [33]. This is particularly useful in patients with primary cerebrovascular dysregulation that is not caused by blood pressure drops.

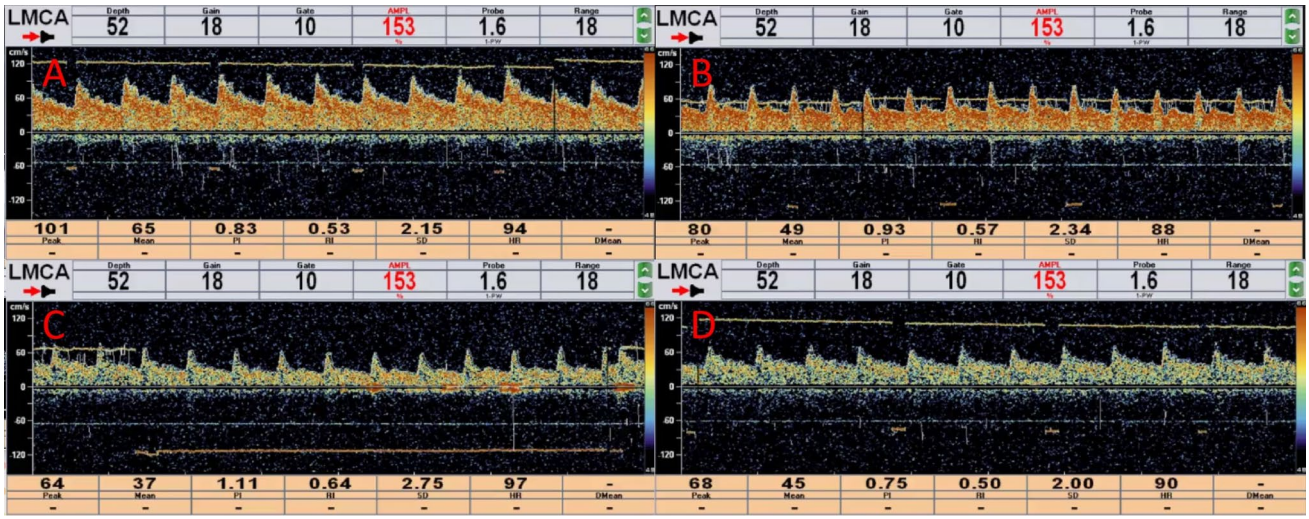

Fig. 2 Cerebral blood flow changes in patients with vasovagal syncope during nitroglycerin-induced upright tilt table testing. **A** At baseline, the mean cerebral blood flow velocity (CBFV) was 65 cm/s and the vascular pulse index (PI) was 0.83; **B** mean CBFV was 49 cm/s in the upright position; **C** after taking nitroglycerin in the upright tilt position, the mean CBFV was 37 cm/s, and the PI was 1.11; **D** after returning to the supine position, the mean CBFV and the PI were 45 cm/s and 0.75, respectively

The diagnostic utility of the HUTT lies in its ability to reproduce symptoms associated with VVS, including premonitory signs such as nausea, pallor, and diaphoresis. The HUTT effectively induces syncope in patients with a history of VVS, allowing clinicians to observe the hemodynamic changes that occur during these episodes. Additionally, it allows direct observation of symptoms that arise when CBFV decreases, thereby confirming suspected VVS episodes. This is particularly important as it provides direct evidence of the patient's susceptibility to vasovagal reflexes, which is essential for an accurate diagnosis.

Limitations

The combination of the HUTT and TCD offers notable advantages in VVS diagnosis but is not without the following limitations:

1. The combined HUTT and TCD examinations require a high level of operator expertise, including proficiency in both the HUTT and TCD techniques.
2. The results are highly dependent on the interpreter's experience. The reporting physician must possess substantial knowledge of neurology and neurosonology to interpret the test results accurately and comprehensively.
3. The technical details and criteria for interpreting the results of this combined examination are still being refined and standardized.
4. Some patients may lack an adequate temporal acoustic window for MCA-CBFV assessment.

Conclusion

The findings of this study contribute to the understanding of VVS diagnosis and the integration of diagnostic tools. Combining the HUTT and TCD imaging enables simultaneous assessment of the hemodynamic status and changes from both the cardiac and cerebral perspectives. This approach aids in the diagnosis of VVS, enhances diagnostic efficacy, and improves examination safety. Our findings highlight the significant value of multimodal testing using the HUTT and TCD in diagnosing VVS. While multimodal testing is a valuable diagnostic tool, the technical details and criteria for interpreting the results of this combined examination are still being refined and standardized. In future research, assessing the percentual decrease of CBFV between supine and standing positions will better reflect changes in cerebral blood flow.

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Author contributions Wang Jingyi: writing—original draft (lead); Cao Liming: writing—review and editing (lead), methodology (lead); Li Hua: conceptualization (supporting). All authors have read and approved the final manuscript.

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Data, material and/or code availability The materials used and/or analyzed during the present study are available from the corresponding author upon reasonable request.

Declarations

Conflicts of interest The authors declare that they have no conflict of interest.

Ethics approval Approval was obtained from the Ethics Review Committee of the First Affiliated Hospital of Shenzhen University (Approval no. 202304133010). The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent to publish Not applicable

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