Venous capacitance and venous return in young adults with typical vasovagal syncope: a cross-sectional study

Ely Fish,[1] Sapir Barak Lanciano,[2] Itay Shavit,[2] Hagar Palacci,[2] Chen Chaiat,[2] Ishay Avivi,[2] Ella Haber Kaptsenel,[2] Udi Nussinovitch [3]

[1]Department of Psychiatry, Westchester Medical Center, Valhalla, NY, USA
[2]Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[3]Division of Cardiovascular Medicine, Stanford University, Palo Alto, CA, USA

Correspondence to
Dr Udi Nussinovitch, Division of Cardiovascular Medicine, Stanford University, Palo Alto, CA, USA;
udi.nussinovitch@gmail.com

Accepted 3 August 2021

To cite: Fish E, Barak Lanciano S, Shavit I, *et al*. *J Investig Med* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/jim-2021-001906

ABSTRACT

Vasovagal syncope (VVS) has a high prevalence in the general population and is associated with potential complications. There is limited information on the possible association between venous capacitance (VC) and venous return (VR), important determinants of preload and VVS. Since the tilt test was reported to yield a high rate of false positive results, the aim of this study was to evaluate whether abnormal VC and VR at baseline could predispose individuals to VVS.

To this end, 88 young, healthy volunteers were recruited and classified to 26 (29.5%) who experienced typical VVS and 62 (70.5%) who did not. VC and VR were evaluated with a commercial device and plethysmography applied to the elevated legs. Maximum venous outflow (MVO), segmental venous capacitance (SVC) and MVO/SVC ratio were calculated and averaged.

No significant differences between MVO (5.0±0.5 vs 5.6±0.8, p>0.05), SVC (6.0±0.5 vs 6.3±0.8, p>0.05) or MVO/SVC ratio (0.83±0.02 vs 0.86±0.03, p>0.05) were observed for the non-VVS and VVS volunteers, respectively. There was a significant association between a higher MVO and SVC values and a larger decrease in diastolic blood pressure with standing, although correlations were weak (R^2=0.0582 and 0.0681, respectively).

In conclusion, at baseline, VC and VR are not impaired in healthy volunteers with a history of VVS. It remains unknown if similar results would be found in patients with cardiovascular comorbidities. Also, the sensitivity of VC and VR evaluations to identify a predisposition for VVS following physiological provocations merits further study.

Significance of this study

What is already known about this subject?

- Neurally mediated syncope is a common medical condition that may recur and be associated with severe complications.
- Decreased venous capacitance (VC) and venous return (VR) seem to mediate vasovagal syncope (VVS).

What are the new findings?

- No significant differences in maximum venous outflow (MVO), segmental venous capacitance (SVC) or MVO/SVC ratio were observed for the non-VVS and VVS participants.
- There was a significant association between higher MVO and SVC,and a larger decrease in diastolic blood pressure following standing, although correlations were weak (R^2=0.0582 and 0.0681, respectively).
- The most suitable provocation for uncovering abnormalities in VC and VR, to identify individuals predisposed to recurrent VVS and to evaluate the sensitivity of these diagnostic measures remain to be determined.

How might these results change the focus of research or clinical practice?

- The present study highlights the complexity of identifying patients who are prone to VVS.
- Resting VC and VR may provide promise in recognising causes of syncope other than VVS, and hence may help improve the diagnostic workup for syncope.

INTRODUCTION

Vasovagal syncope (VVS) is a subtype of neurally mediated syncope, an event driven by a sudden increase in parasympathetic tone with an accompanying decrease in sympathetic tone.[1] Reflex responses decrease cerebral perfusion, sometimes causing transient loss of consciousness (TLOC). In typical VVS, these responses may be triggered by strong emotions such as fear, pain or nervousness, or by disturbing sensory stimuli.[1] VVS may be preceded by prodromal symptoms, including diaphoresis, hyperventilation, nausea, profound sweating and palpitations.[1] Atypical VVS is a diagnosis of exclusion, describing patients with TLOC that lack any clear trigger or etiology and a positive response to head-up tilt test (HUTT).[2] Research suggests that syncope can occasionally be aborted by counterpressure maneuvers (CPM), which increase venous return (VR), counteracting the effects of vasodilation.[3] VVS is the most common cause of recurrent syncope,

and its prevalence may be as high as 69% in certain populations.[4] It has been estimated that nearly one-third of a population of syncopal patients experienced injury, with 4.7% classified as severe.[5] The economic burden is approximately US$2.4 billion per year in the US alone.[6] Better identification of patients at high risk for single or recurrent VVS episodes could substantially lessen these financial and healthcare burdens.

The mechanisms behind VVS are not clear.[7] It has been hypothesised that decreased VR results in inadequate ventricular filling, which leads to bradycardia, peripheral vasodilation and hypotension.[8] VR is mainly affected by central venous pressure and mean circulatory filling pressure,[9] which is related to the elastic recoil of peripheral veins and venules. It increases with fluid administration and with shifts of blood from splanchnic to systemic circulation. The latter occurs in the presence of increased levels of exogenous and endogenous sympathetic mediators,[9] which cause venoconstriction, predominantly of the splanchnic veins, thereby raising VR via decreased venous capacitance.[10] In contrast, central venous pressure depends predominantly on the pressure-volume relationship in the right side of the heart.[9]

Various physiological markers have been investigated to identify patients who are prone to developing VVS. Although scintigraphy using (123)I-metaiodobenzylguanidine (MIBG), a norepinephrine analog, was reported to be abnormal in VVS, this test is impractical for screening.[11] Altered autonomic response to HUTT has previously been demonstrated,[12–14] but this finding was not consistent in all studies.[15] Moreover, the test is difficult to perform and interpret, and may occasionally be associated with life-threatening complications.[16] While some studies have suggested that patients with VVS have abnormal autonomic nervous system (ANS) function at baseline,[12 17–20] this was not found in other studies.[11 12] Although increased nerve firing and norepinephrine (NA) levels were seen in VVS patients with low blood pressure (BP) at baseline,[21] monitoring these parameters is impractical as a screening modality.

Despite the seemingly central role of VR in the pathogenesis of VVS and the importance of using CPM to increase VR, when prodromal symptoms develop, there is a paucity of data on baseline VR in VVS patients. Older studies indicate that VVS patients have a proportionally greater increases in calf volume during HUTT, indicating a greater volume of blood pooling in the venous system.[22] More recent findings suggest no difference in volumes pooled, and instead indicate a prolonged rate of venous blood pooling in VVS, at least among female patients.[23] Previous studies on lower limb VR have typically focused on conditions in which vascular damage has occurred[24] or there is known or suspected venous obstruction,[25] leaving the subject of VC and VR in VVS at baseline unaddressed. Also, HUTT is contraindicated in many clinical conditions, such as carotid artery stenosis, significant coronary artery stenosis, hypertrophic cardiomyopathy, severe anemia and unstable conditions,[26] and may yield high rates of false positive responses.[27] Therefore, it is important to determine whether physiological markers for VVS are disturbed at baseline.

Accordingly, the purpose of this study was to investigate whether decreased VC and VR are more prominent at baseline in a population of patients who experienced VVS in the absence of external provocations. If identified, this impairment could represent an important diagnostic indicator for predicting the emergence or recurrence of syncope, or possibly be used as a therapeutic target for predisposed individuals.

METHODS

Participants and setting

Volunteers aged 18–65 were recruited from hospital staff and family members. They were questioned about family history of ischemic heart disease and personal history of syncope. Those with syncopal history were asked about triggers for the event and symptoms experienced prior to LOC. Volunteers were classified as typical VVS if they experienced at least one episode of typical VVS, characterized by short-duration LOC, amnesia for the duration of unconsciousness, loss of motor control, unresponsiveness to stimuli and an antecedent trigger (ie, strong emotion, pain or disturbing stimuli). Lightheadedness, fainting with prolonged sitting or standing, sweating or feel warm before fainting and lightheadedness or fainting from pain or in medical settings were considered strong supportive indicators for neurally mediated syncope, in accordance with established criteria.[28] Participants who had experienced postural presyncope (PPS) at least once under conditions other than dehydration, fever or blood loss and with no TLOC were included. Persons who experienced syncope due to any cause other than vasovagal (ie, epilepsy, psychogenic or situational syncope) were excluded, as were atypical VVS participants. Other exclusion criteria were conditions affecting sympathetic tone, including diabetes mellitus, hypertension, dysautonomia, Parkinson's disease, Lewy body dementia, multiple system atrophy, cardiovascular pathology and medications affecting the ANS. Thyroid abnormalities and conditions with altered VR due to deep venous thrombosis or pulmonary embolism, congestive heart failure, pregnancy, anemia, an intra-abdominal or intrathoracic space-occupying lesionand peripheral venous insufficiency were additional exclusion criteria.[29–31] Finally, volunteers were excluded if they were diagnosed with postural orthostatic tachycardia syndrome or postural hypotension, which were diagnosed using established criteria,[32] and if clinical data were limited or missing. Volunteers were not excluded if they had been diagnosed with mild dyslipidemia, balanced with dietary change.

Hemoglobin A1c levels were measured prior to inclusion via blood draw. Participants with levels above 5.7% were excluded. All volunteers underwent a thorough physical exam, including high-resolution ECG (PC-ECG 1200HR, Norav Medical, Yokne'am, Israel) to rule out structural heart disease and cardiac conduction disorder.

Procedure

Participants did not smoke, drink caffeinated beverages or take other stimulants at least 3 hours before the study and avoided strenuous exercise for 24 hours prior. All measurements were conducted between 09:00 and 12:00 hours. Room temperature was maintained at ~23°C. Participants

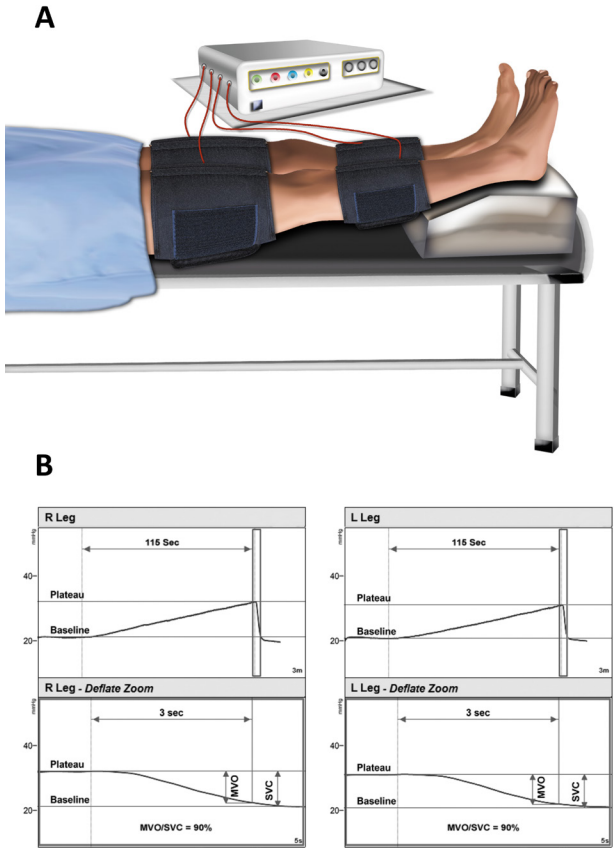

Figure 1 (A) Experimental settings used to study VC. (B) Typical blood pressure tracing in a patient without VVS. The baseline represents the blood pressure before proximal cuff inflation. The proximal cuff is then inflated to 75 mmHg and pressure increase in distal blood pressure cuffs reaches a plateau. The difference between baseline and plateau is the sSVC. The cuff is rapidly deflated and the blood pressure drop over the ensuing 3 s is measured. This blood pressure drop is the MVO. In this specific example, MVO/SVC ratio was computed to be 0.90 in each limb.

lay quietly for 10 min before the exam. They then underwent a 5 min ECG which was processed with PC-ECG, HRV V.5.514 commercial software (Norav Medical, Israel) to determine an average baseline heart rate.

MVO/SVC measurements were conducted using the Falcon Quad platform (V.1.6.0, Viasonix, Raanana, Israel). Participants had BP cuffs attached to their left and right legs at calf-level. The legs were elevated approximately 25 cm using a supporting pillow in accordance with accepted standards.[33] Additional cuffs were attached at the level of the thigh on both legs (figure 1A). The proximal cuffs were then inflated to 75 mmHg, blocking VR and the distal cuffs were inflated to 20 mmHg. Consequently, the pressure in the distal cuffs increased to a steady-state 'plateau', followed by abrupt deflation of the proximal cuffs. The subsequent drop in pressure over the ensuing 3 s was measured (figure 1B). This pressure drop constituted the MVO. The baseline was subtracted from the plateau, yielding the SVC. The MVO/SVC ratio was calculated by the software and was obtained separately for the left and right calf in each patient. These results were averaged to yield the MVO, SVC and the MVO/SVC ratio, reflecting the overall mean VC indices. Measurements were reviewed for error in the automatic detection of baseline pressures and any inaccuracies were corrected manually. Participants whose studies lacked the typical pattern of increase on cuff inflation and/or decrease on cuff deflation due to technical issues were excluded.

Following the test, arterial BPs were measured with an automatic sphygmomanometer (4200B-E1, Welch Allyn, New York, USA). The participants first sat for 5 min, after which BP was measured twice (results were averaged). They then stood for 5 min, followed by repeat BP measurement. After standing 2 min, a continuous electrocardiographic study was performed to determine the mean heart rate during the 3 min of ECG measurement. Weight and height were measured. Overweight was defined as body mass index (BMI) >25 kg/m^2.

Sample size calculations

The minimum sample size for each group for detecting a true difference in MVO/SVC mean values was determined with the assumption that an abnormal MVO/SVC ratio of ≤0.6[34] was found in 40% of the VVS group, and 3% of the control group. To achieve a power of 80% and 5% significance (two-sided), for detecting a true difference in means between the measures, the minimum sample size was calculated to be 19 patients for each group, separately.

Statistical analysis

The data were analyzed using JMP V.15.0 (SAS Institute, Cary, North Carolina, USA) and MedCalc V.19.1.5 (MedCalc Software, Ostend, Belgium; https://www.medcalc.org). Results are presented as mean and SEM. Abnormal results were defined as >2 SD from the normal range. Findings in participants with and without VVS were compared using Kruskal-Wallis one-way analysis and Fisher's exact test. A p value <0.05 was considered statistically significant. Regression analyses were estimated according to the proportion of the variance in the dependent variable that was predictable from the independent variable. Specifically, variance was estimated between age, height, BMI, sitting systolic blood pressure (SBP) and diastolic blood pressure (DBP), supine heart rate, change in BP and heart rate in response to standing, and between MVO, SVC and their ratio. The strength of the association was evaluated with coefficient of determination (R^2). Regression analyses of MVO and SVC in both the non-VVS and VVS groups were performed.

RESULTS

A total of 122 healthy volunteers were recruited. None had abnormal ECG patterns. Fourteen were excluded due to uncertainty about whether their TLOC should be diagnosed as VVS. Subsequent analysis of plethysmography data indicated 13 participants' measurements did not show the typical pattern of BP rise in the distal sensors with proximal cuff inflation. Their results were attributed to technical issues associated with limb mobilization, leg muscle spasm and inappropriate increased intrathoracic or abdominal pressures. Seven participants diagnosed with conditions that might have affected the test (anemia, hypothyroidism, impaired fasting glucose, etc) were excluded from the cohort. Of the remaining 88 participants, 26 (29.5%)

Table 1 Demographic and clinical and characteristics, and venous capacitance markers of the studied patient population

Parameter	No vasovagal syncope (n=62)	Vasovagal syncope (n=26)	P value
Age (years)	35.3±1.5	34.9±2.7	NS
M/F	34/28	10/16	NS
Height (m)	1.71±0.01	1.69±0.02	NS
BMI (kg/m^2)	24.8±0.4	24.2±0.5	NS
Overweight, n (%)*	27 (43.6)	10 (38.5)	NS
Active smoking, n (%)	9 (14.5)	5 (19.2)	NS
Past smoking, n (%)	10 (16.1)	1 (3.8)	NS
Dyslipidemia, n (%)	6 (9.7)	1 (3.8)	NS
Family history IHD, n (%)	27 (43.5)	11 (42.3)	NS
Hypertension, n (%)	0 (0)	0 (0)	NS
Diabetes mellitus, n (%)	0 (0)	0 (0)	NS
Sitting SBP (mmHg)	120.0±1.4	120.8±1.7	NS
Sitting DBP (mmHg)	74.3±1.1	75.5±1.5	NS
Supine heart rate (bpm)	63.7±1.5	59.3±2.0	NS
Standing SBP (mmHg)	120.6±1.5	120.0±2.3	NS
Standing DBP (mmHg)	77.3±1.1	76.2±1.8	NS
Standing heart rate (bpm)	77.7±1.8	73.8±2.5	NS
History of PPS, n (%)	5 (8.1)	4 (15.4)	NS
SBP difference (mmHg)	1.1±1.0	−1.3±1.4	NS
DBP difference (mmHg)	3.7±1.0	0.6±1.1	NS
Heart rate difference (bpm)	14.3±1.0	14.6±1.6	NS
MVO (mmHg)	5.0±0.5	5.6±0.8	NS
SVC (mmHg)	6.0±0.5	6.3±0.8	NS
MVO/SVC	0.83±0.02	0.86±0.03	NS

*Overweight was defined as BMI >25 kg/m^2.
BMI, body mass index; DBP, diastolic blood pressure; IHD, ischemic heart disease; MVO, maximum venous outflow; NS, not significant; PPS, symptoms suggestive of postural presyncope with no loss of consciousness; SBP, systolic blood pressure; SVC, segmental venous capacitance.

experienced typical VVS syncope and 62 (70.5%) did not. The percentage of participants in our study who had experienced VVS was similar to VVS rates reported by others.[35]

Demographics and clinical characteristics of the study groups are presented in table 1. All participants experienced their first TLOC before age 35 years. The mean age of the non-VVS group was 35.3±1.5 years, while the mean age of participants with VVS was 34.9±2.7 years (p>0.05). Among the participants, 44 were male, 10 of whom (22.7%) experienced VVS. Of 44 female participants, 16 (36.4%) experienced VVS. Rates of active smoking were similar in the non-VVS compared with the VVS group (14.3% vs 19.2%, respectively, p>0.05). Percentages of overweight participants were similar in the non-VVS and VVS groups (43.6% vs 38.5%, p>0.05), as were those of mild dyslipidemia (9.6% vs 3.8%, p>0.05) and family history of heart disease (43.5% vs 42.3%, p>0.05). Height (1.71±0.01 m vs 1.69±0.02 m, p>0.05) and BMI (24.8±0.4 kg/m^2 vs 24.2±0.5 kg/m^2, p>0.05) were also similar between the groups.

One person with VVS and five without did not undergo upright BP and heart rate measurements due to lack of cooperation or technical error. Seated SBP (120.0±1.4 mmHg vs 120.8±1.7 mmHg, p>0.05) and DBP (74.3±1.1 mmHg vs 75.5±1.5 mmHg, p>0.05) readings were similar in non-VVS and VVS participants, as were standing SBP (120.6±1.5 mmHg vs 120.0±2.3 mmHg, p>0.05) and DBP readings (77.3±1.5 mmHg vs 76.2±1.8 mmHg, p>0.05). SBP changes (standing minus sitting positions) were similar in both groups (1.1±1.0 mmHg vs −1.3±1.4 mmHg, p>0.05), as were change in DBP (3.7±1.0 mmHg vs 0.6±1.1 mmHg, p>0.05) and heart rate (14.3±1.0 bpm vs 14.6±1.6 bpm, p>0.05). There were no significant differences in supine heart rate (63.7±1.5 bpm vs 59.3±2.0 bpm, p>0.05), or heart rate following standing (78.5±1.8 bpm vs 76.6±2.7 bpm, p>0.05). Persons with VVS had similar rates of history of presyncope relative to non-VVS (15.4% vs 8.1%, respectively, p>0.05). None of the participants developed presyncopal symptoms during the study.

The results showed no significant differences between MVO (5.0±0.5 mmHg vs 5.6±0.8 mmHg, p>0.05) and SVC (6.0±0.5 mmHg vs 6.3±0.8 mmHg, p>0.05) in non-VVS and VVS participants, respectively. The MVO/SVC ratios were similar between non-VVS (0.83±0.02) and VVS (0.86±0.03, p>0.05). Male and female participants had similar MVO (5.1±0.6 mmHg vs 5.3±0.5 mmHg, p>0.05), SVC (5.9±0.6 mmHg vs 6.2±0.6 mmHg, p>0.05) and MVO/SVC (0.83±0.02 vs 0.82±0.02, p>0.05) results, respectively, regardless of VVS status. A separate analysis of MVO/SVC ratio for females did not reveal a significant difference between the non-VVS group (0.83±0.03) and the VVS group (0.84±0.05, p>0.05). Participants with a reported history of PPS had lower MVO/SVC ratio compared with those who did not (0.80±0.05 vs 0.84±0.02, respectively), but the results did not reach statistical significance (p>0.05).

There was a significant association between a larger decrease in DBP after standing and higher MVO and SVC, although correlations were weak (R^2 of 0.0582 and 0.0681, respectively). All other correlations between MVO, SVC and MVO/SVC ratio and clinical or hemodynamic parameters (age, height, BMI, sitting SBP and DBP, supine heart rate, change in SBP and heart rate in response to standing) were low and non-significant (table 2). Significant correlations (p<0.001) were found between MVO and SVC in patients with and without VVS with an excellent linear fit (R^2=0.928 in the non-VVS (figure 2A) and R^2=0.965 in the VVS group (figure 2B)).

DISCUSSION

VVS carries a substantial risk of serious injury and has a high rate of recurrence. It also imposes a substantial economic burden associated with hospitalization due to trauma.[4–6] The diagnostic yield of emergency room visits for syncope is often poor; patients receive minimal care and 39%–50% are discharged from the hospital without a diagnosis.[36] One aim of this study was to develop a tool that could help identify characteristics of high-risk individual, so they could be taught management techniques, such as CPM, to minimize the possibility of traumatic injury should symptoms of impending VVS develop; thereby, decreasing the financial and healthcare burdens.

Attempts to identify at-risk patients are ongoing. Previously identified clinical risk factors for recurrent VVS include the number of prior VVS episodes, female sex and bronchial asthma.[37] Interestingly, clinical response to HUTT does not significantly predict recurrence, according to some

Table 2 Regression analysis between clinical characteristic and venous capacitance and return parameters

Parameters	β1	R^2	P value
MVO-age (mmHg/years)	0.0324	0.0120	0.3120
MVO-height (mmHg/m)	−1.8587	0.0024	0.6486
MVO-BMI (mmHg/kg/m^2)	0.1052	0.0076	0.4198
MVO-sitting SBP (mmHg/mm Hg)	0.0589	0.0256	0.1408
MVO-sitting DBP (mmHg/mm Hg)	0.0892	0.0374	0.0741
MVO-supine heart rate (mmHg/bpm)	−0.0565	0.0293	0.1148
MVO-SBP difference (mmHg/mm Hg)	−0.0672	0.0161	0.2620
MVO-DBP difference (mmHg/mm Hg)	−0.1348	0.0582	0.0311*
MVO-heart rate difference (mmHg/bpm)	0.0208	0.0019	0.6968
SVC-age (mmHg/years)	0.0190	0.0034	0.5871
SVC-height (mmHg/m)	−1.9265	0.0022	0.6661
SVC-BMI (mmHg/kg/m^2)	0.0039	0.0009	0.7825
SVC-sitting SBP (mmHg/mmHg)	0.0055	0.0191	0.2037
SVC-sitting DBP (mmHg/mmHg)	0.1038	0.0424	0.0571
SVC-supine heart rate (mmHg/bpm)	−0.0463	0.0162	0.2421
SVC-SBP difference (mmHg/mmHg)	0.0695	0.0150	0.2788
SVC-DBP difference (mmHg/mmHg)	−0.1563	0.0681	0.0193*
SVC-heart rate difference (mmHg/bpm)	0.0163	0.0010	0.7766
MVO/SVC-age ($years^{-1}$)	0.0021	0.0312	0.1013
MVO/SVC-height (m^{-1})	−0.0471	0.0009	0.7801
MVO/SVC-BMI (m^2/kg)	0.0006	0.0196	0.2299
MVO/SVC-sitting SBP ($mmHg^{-1}$)	0.0014	0.0081	0.4097
MVO/SVC-sitting DBP ($mmHg^{-1}$)	0.0003	0.0003	0.8723
MVO/SVC-supine heart rate (bpm^{-1})	−0.0028	0.0437	0.0546
MVO/SVC-SBP difference ($mmHg^{-1}$)	−0.0027	0.0154	0.2722
MVO/SVC-DBP difference ($mmHg^{-1}$)	−0.0019	0.0065	0.4751
MVO/SVC-heart rate difference (bpm^{-1})	0.0024	0.0149	0.2735

*P<0.05.
BMI, body mass index; DBP, diastolic blood pressure; MVO, maximum venous outflow; NS, not significant; SBP, systolic blood pressure; SVC, segmental venous capacitance.

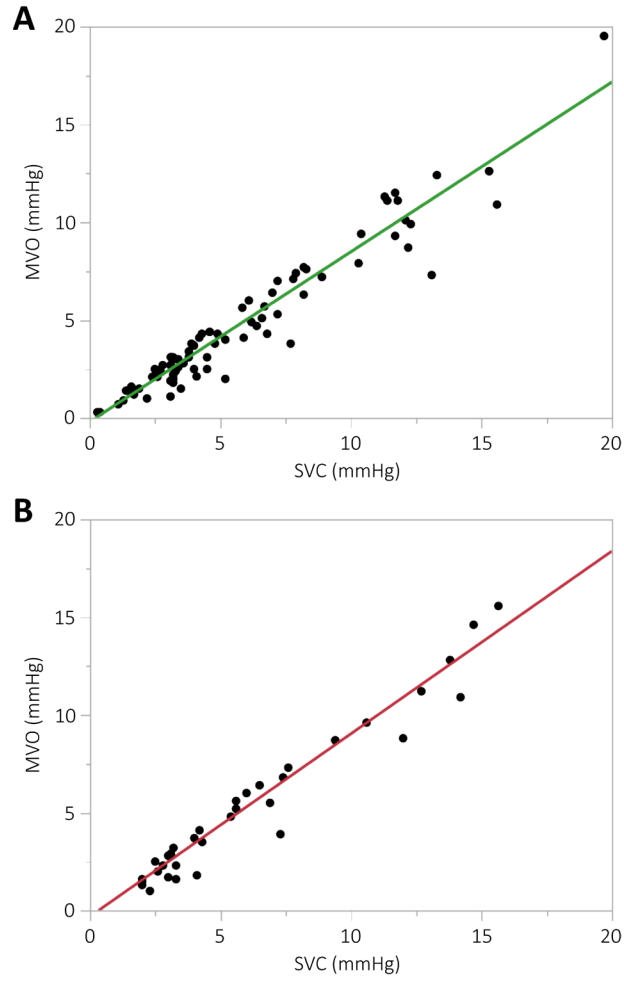

Figure 2 Correlations between maximum venous outflow (MVO) and segmental venous capacitance (SVC) in patients without vasovagal syncope (VVS) (A) and with VVS (B).

reports,[37] and false positive response rates may be as high as 52%.[27] Measurements of sympathetic markers, including muscle sympathetic nerve activity (MSNA) have shown conflicting results, with some studies suggesting decreased MSNA at baseline and during tilt testing in VVS patients, while others found normal MSNA.[38] However, studies of other markers, such as whole body NA spillover, found blunted NA levels in VVS patients, both at baseline and during HUTT.[38] Further support for decreased NA function is provided by the results of MIBG scintigraphy. MIBG shows an affinity for tissues with high NA activity.[39] VVS patients were reported to have decreased uptake of MIBG in the heart,[11] although a different study suggested the association did not reach statistical significance.[40] Moreover, the requirement to fast for 6 hours before MIBG intake and the need for complex multi-angle heart imaging and radiopharmaceuticals[11] make MIBG scintigraphy impractical as a clinical screening tool.

Most studies examining cardiac markers have shown that heart rate and autonomic responses are altered in VVS during HUTT.[12–14] Studies of sympathetic tone at baseline have shown mixed results,[11–13 15–17] but sympathetic tone and NA spillover increase in VVS patients with low BP at baseline.[21] This would seem to indicate that ANS screening during HUTT is a useful marker for VVS, as are NA levels in low BP patients. However, the cost and required expertise make this technique impractical for wide-scale screening efforts.

Our study found statistically similar values of VC and VR parameters among patients with and without VVS, suggesting that there is no specific predisposition to VVS related to these parameters at baseline. No significant differences in BP and heart rate were observed between patients with or without VVS both at baseline and in the upright position. As VC may be influenced by sympathetic tone,[9 10] our results seem to be in accord with findings of normal sympathetic activity at baseline, and to contradict studies that noted sympathetic impairment at baseline in persons with VVS. Another consideration is whether other vascular beds in VVS patients have impaired VR, while lower limb VR is maintained, as our study indicated. It is known that the concentration of sympathetic receptors is far higher in splanchnic and cutaneous veins than in peripheral veins. Thus, these venous beds are more susceptible to variations in levels of sympathetic mediators.[10] This could have important implications for VR in the setting of decreased sympathetic activity, and is worthy of additional study. Further research assessing VC and VR during HUTT and in the presence of provocative agents known to illicit

VVS in predisposed individuals is needed to verify the likely conclusion that VC and VR are impaired shortly prior to TLOC in VVS patients, but not at baseline.

Limitations

This study distinguished between people with or without VVS and did not further distinguish between subcategories of VVS. It has been argued[7] that neurally mediated syncope is a common presentation of several different pathophysiological processes rather than a single disease process. VVS in particular may represent several underlying pathophysiological conditions. The finding that variations in certain physiological markers among VVS patients have been shown to correlate with differences in underlying pathophysiology supports this. For example, one study[38] subdivided VVS into normal and low BP phenotypes, and showed that MSNA response varied according to these phenotypes. In addition, it has been suggested[41] that the mechanisms underlying syncope induced by tilt test and syncope in response to noxious stimuli may differ. This question requires further study with a larger cohort and longer follow-up to ascertain the correlations between baseline VC and VR, and syncope recurrence.

Our cohort included mainly young adults, as the prevalence of VVS is known to be highest among this population.[42] In this population, the pathophysiology of VVS seems to occur due to reduced cardiac output, systemic vascular resistance or both. The latter is predominantly associated with impaired splanchnic vasoconstriction.[43] Elderly and very young patients with VVS may exhibit VC characteristics and cardiovascular responses different than those observed here. Our study did not examine patients with atypical VVS or syncope due to orthostatic hypotension. As syncope associated with orthostatic hypotension is known to involve impaired venoconstriction and increased venous pooling,[44] these patients may be more likely to exhibit impairment in venous outflow relative to VVS. Only nine patients (10.2% of the cohort) reported PPS, suggesting the present study was underpowered to evaluate this question. Also, the mean MVO/SVC values in those patients were above the 0.6 cut-off recommended to identify patients with venous obstruction,[34] suggesting that in PPS, venous insufficiency is mild at baseline. Finally, VVS was diagnosed from medical history, because HUTT is not generally used when the presentation is typical, and the use of diagnostic questions to evaluate patients with TLOC is reportedly equivalent to HUTT.[28] Yet, we cannot predict whether the results would have been different if HUTT were used in the current study.

CONCLUSION

A tendency toward typical VVS cannot be identified based solely on abnormal basal VR and VC at rest. However, decreased DBP following standing was significantly associated with higher MVO and SVC values, although correlations were low. Future studies should focus on patients with orthostatic hypotension (whether systolic, diastolic or both), and on patients with atypical VVS. In addition, trials with longer follow-ups may determine whether VC and VR at baseline or during HUTT can predict recurrent syncope.

Acknowledgements We wish to thank Faye Schreiber, MS for editorial assistance, and Abdul Mannan for help with generating Figure 1A.

Contributors UN designed the study. IA, SBL, IS, EHK, HP and CC performed the experiments and analyzed the data. UN and EJF analyzed and interpreted the data, wrote the manuscript. UN revised the manuscript. All authors approved the submitted version.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This comparative cross-sectional case-control study was approved by the local Institutional Review Board (Meir Medical Center, #0074-18-MMC) and fulfilled the ethical guidelines of the most recent Declaration of Helsinki. All participants provided written informed consent.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

ORCID iD

Udi Nussinovitch http://orcid.org/0000-0002-3931-8003

REFERENCES

1 Freeman R. Syncope. In: Dennis L SLH, Kasper J, Jameson L, *et al*, eds. *Harrison's Principles of Internal Medicine*. McGraw Hill, 2015: 142–8.
2 Alboni P. The different clinical presentations of vasovagal syncope. *Heart* 2015;101:674–8.
3 Brignole M, Croci F, Menozzi C, *et al*. Isometric arm counter-pressure maneuvers to abort impending vasovagal syncope. *J Am Coll Cardiol* 2002;40:2053–9.
4 da Silva RMFL. The current indication for pacemaker in patients with cardioinhibitory vasovagal syncope. *Open Cardiovasc Med J* 2016;10:179–87.
5 Auer J. Syncope and trauma. are syncope-related traumatic injuries the key to find the specific cause of the symptom? *Eur Heart J* 2008;29:576–8.
6 McBride DW, Reis C, Frank E, *et al*. An experimental model of vasovagal syncope induces cerebral hypoperfusion and fainting-like behavior in awake rats. *PLoS One* 2016;11:e0163280.
7 Mosqueda-Garcia R, Furlan R, Tank J, *et al*. The elusive pathophysiology of neurally mediated syncope. *Circulation* 2000;102:2898–906.
8 Campagna JA, Carter C. Clinical relevance of the Bezold-Jarisch reflex. *Anesthesiology* 2003;98:1250–60.
9 Schroeder BMJ, Barbeito A, *et al*. Cardiovascular Monitoring. In: Gropper M, Eriksson L, Fleisher L, eds. *Miller's Anaesthesia*. 9th edition. Elsevier, 2019: 1145–93.
10 Gelman S. Venous function and central venous pressure: a physiologic story. *Anesthesiology* 2008;108:735–48.
11 Kochiadakis G, Marketou M, Koukouraki S, *et al*. Cardiac autonomic disturbances in patients with vasovagal syndrome: comparison between iodine-123-metaiodobenzylguanidine myocardial scintigraphy and heart rate variability. *Europace* 2012;14:1352–8.
12 Alehan D, Ayabakan C, Ozer S. Heart rate variability and autonomic nervous system changes in children with vasovagal syncope. *Pacing Clin Electrophysiol* 2002;25:1331–8.
13 Klemenc M, Štrumbelj E. Predicting the outcome of head-up tilt test using heart rate variability and baroreflex sensitivity parameters in patients with vasovagal syncope. *Clin Auton Res* 2015;25:391–8.
14 Folino AF, Russo G, Porta A, *et al*. Autonomic modulation and cardiac contractility in vasovagal syncope. *Int J Cardiol* 2010;139:248–53.
15 Miranda CM, Silva RMFLda. Analysis of heart rate variability before and during tilt test in patients with cardioinhibitory vasovagal syncope. *Arq Bras Cardiol* 2016;107:568–75.
16 Shenthar J, Pujar D, Aravind Prabhu M, *et al*. Ventricular fibrillation a rare complication during head-up tilt test. *HeartRhythm Case Rep* 2015;1:363–5.
17 Zygmunt A, Stanczyk J. Heart rate variability in children with neurocardiogenic syncope. *Clin Auton Res* 2004;14:99–106.
18 Khalil M, Hessling G, Bauch M, *et al*. Sympathovagal imbalance in pediatric patients with neurocardiogenic syncope during asymptomatic time periods. *J Electrocardiol* 2004;37 Suppl:166–70.
19 Cintra F, Poyares D, DO Amaral A, *et al*. Heart rate variability during sleep in patients with vasovagal syncope. *Pacing Clin Electrophysiol* 2005;28:1310–6.
20 Huang F, Xu C-F, Deng X-Y, *et al*. Deceleration capacity-a novel measure for autonomic nervous system in patients with vasovagal syncope on tilt-table testing. *J Huazhong Univ Sci Technolog Med Sci* 2017;37:326–31.

21 Vaddadi G, Guo L, Esler M, *et al*. Recurrent postural vasovagal syncope: sympathetic nervous system phenotypes. *Circ Arrhythm Electrophysiol* 2011;4:711–8.
22 Hargreaves AD, Muir AL. Lack of variation in venous tone potentiates vasovagal syncope. *Br Heart J* 1992;67:486–90.
23 Lindenberger M, Länne T. Slower lower limb blood pooling in young women with orthostatic intolerance. *Exp Physiol* 2015;100:2–11.
24 Vigilance JE, Reid HL. Venodynamic and hemorheological variables in patients with diabetes mellitus. *Arch Med Res* 2005;36:490–5.
25 Mcbride KJ, Odonnel TF, Pauker SG. Venous Volume Displacement Plethysmography - Its Diagnostic-Value in Deep Venous Thrombosis as Determined by Receiver Operator Characteristic Curves. *Cardiovasc Dis* 1981;8:499–508.
26 Zysko D, Jamil RT, Anilkumar AC. *Tilt table*. Treasure Island (FL): StatPearls, 2021.
27 Wu TC, Hachul D, Scanavacca M, *et al*. Diagnostic value of the tilt-table test for the assessment of syncope in children and adolescents. *Arq Bras Cardiol* 2001;77:501–8.
28 Sheldon R, Rose S, Connolly S, *et al*. Diagnostic criteria for vasovagal syncope based on a quantitative history. *Eur Heart J* 2006;27:344–50.
29 Kumar V, Abbas AK, Aster JC. Hemodynamic disorders, thromboembolic disease, and shock. In: *Robbins and Cotran pathologic basis of disease*. Saunders, 2015: 113–35.
30 Birklein F, Dimova Vand . Complex regional pain syndrome-up-to-date. *Pain Rep* 2017;2:e624.
31 Coon EA, Singer W. Synucleinopathies. *Continuum* 2020;26:72–92.
32 Raj SR. The Postural Tachycardia Syndrome (POTS): pathophysiology, diagnosis & management. *Indian Pacing Electrophysiol J* 2006;6:84–99.
33 Wang Z, Chen Q, Ye M, *et al*. Active ankle movement may prevent deep vein thrombosis in patients undergoing lower limb surgery. *Ann Vasc Surg* 2016;32:65–72.
34 McBride KJ, O'Donnell TF, Pauker SG, *et al*. Venous volume displacement plethysmography: its diagnostic value in deep venous thrombosis as determined by receiver operator characteristic curves. *Cardiovasc Dis* 1981;8:499–508.
35 Serletis A, Rose S, Sheldon AG, *et al*. Vasovagal syncope in medical students and their first-degree relatives. *Eur Heart J* 2006;27:1965–70.
36 Sun BC, Emond JA, Camargo CA. Direct medical costs of syncope-related hospitalizations in the United States. *Am J Cardiol* 2005;95:668–71.
37 Aydin MA, Maas R, Mortensen K, *et al*. Predicting recurrence of vasovagal syncope: a simple risk score for the clinical routine. *J Cardiovasc Electrophysiol* 2009;20:416–21.
38 Lambert E, Lambert GW. Sympathetic dysfunction in vasovagal syncope and the postural orthostatic tachycardia syndrome. *Front Physiol* 2014;5:280.
39 Wieland DM, Wu J, Brown LE, *et al*. Radiolabeled adrenergi neuron-blocking agents: adrenomedullary imaging with [131I]iodobenzylguanidine. *J Nucl Med* 1980;21:349–53.
40 Shinohara T, Ebata Y, Ayabe R, *et al*. Cardiac autonomic dysfunction in patients with head-up tilt test-induced vasovagal syncope. *Pacing Clin Electrophysiol* 2014;37:1694–701.
41 Epstein SE, Stampfer M, Beiser GD. Role of the capacitance and resistance vessels in vasovagal syncope. *Circulation* 1968;37:524–33.
42 Colman N, Nahm K, Ganzeboom KS, *et al*. Epidemiology of reflex syncope. *Clin Auton Res* 2004;14 Suppl 1:i9–17.
43 Stewart JM, Medow MS, Sutton R, *et al*. Mechanisms of vasovagal syncope in the young: reduced systemic vascular resistance versus reduced cardiac output. *J Am Heart Assoc* 2017;6.
44 Anderson BR, John AS. Syncope. In: *Netter's Pediatrics*. Saunders, 2011: 294–9.