Br Heart J 1992;67:486–90

Lack of variation in venous tone potentiates vasovagal syncope

Allister D Hargreaves, Alexander L Muir

Abstract

***Objective*—To investigate the peripheral venous response to head up tilting in malignant vasovagal syndrome.**

***Patients*—31 Patients with unexplained syncope or dizziness referred from the cardiology department.**

***Methods*—Changes in calf venous volume were studied by a radionuclide technique during 45° head up tilt testing.**

***Results*—During tilt testing six patients became syncopal but 25 were symptom free. The syncopal group had greater increases in calf venous volume after the change in posture and perhaps more importantly considerably less variability in the venous volume during the tilted period.**

***Conclusions*—The venous response was different in the syncopal patients. The lack of response of the peripheral venous circulation to changes in the central circulation may be responsible for triggering the Bezold-Jarisch reflex and malignant vasovagal syncope.**

Vasovagal syncope is a heterogenous condition. In a simple faint an external sensory stimulus—for example, sight of blood or venepuncture—causes the vagal response. Other forms of vasovagal syncope exist that result from stimulation of the Bezold-Jarisch reflex.[1] In these patients very low ventricular volumes result in a relatively empty ventricle contracting against itself and so generating very high intraventricular pressures. It is these high pressures that stimulate the Bezold-Jarisch reflex that causes parasympathetic activation and sympathetic withdrawal. This culminates in syncope due to hypotension and bradycardia. Several different circumstances can cause a very low central venous pressure and so provoke this chain of events. These include the administration of venodilator drugs—for example, glyceryl trinitate and amyl nitrite—and massive rapid haemorrhage.[2–4] Also the same reflex is thought to be responsible for the condition called either malignant vasovagal syndrome or neurally mediated syncope in which patients have recurrent syncope both without warning and without precipitating stimuli.[5,6] It is not understood why this occurs. Is it that they have a low threshold to initiation of the Bezold-Jarisch reflex or do they have an abnormality in their venous compartment that predisposes them to very low central pressures and this "empty heart syndrome"?

In this study we examined the changes in the peripheral venous blood volume during a head up tilt test and made correlations with the haemodynamic changes found. We used a radionuclide technique to monitor the changes in peripheral venous volume minute by minute after the change in posture.[7,8] We describe abnormalities that were associated with syncope and blood pressure changes.

Patients and methods

PATIENTS

All 31 patients (19 men, 12 women; age range 18–79) were referred for head up tilt testing as part of our investigation of unexplained syncope or dizziness. They included eight people with ischaemic heart disease (three with previous myocardial infarcts) and eight who were taking vasoactive medication—namely, β blockers, calcium antagonists, or nitrates. Earlier investigation was limited but all patients had undergone 24 hour Holter electrocardiographic monitoring and carotid sinus massage before referral and these tests had not explained the subject's episodes of syncope. No patient was assessed by electrophysiological study. Before participating in the study all patients gave informed consent.

MEASUREMENTS

The heart rate and rhythm were recorded continuously with a four channel electrocardiograph (Mingograf 34, Sweden) and monitor (Rigel DM721, Rigel Research, Surrey). Blood pressure was measured by a semiautomatic sphygmomanometer (Copal UA-251 digital, Japan) placed on the left arm. A radionuclide labelled blood pool was established by a semi in vitro technique.[9] Red blood cells labelled with 50 MBq technetium-99m were reinjected into the left arm and were allowed to reach equilibrium (10 minutes). Activity was detected by a caesium iodide crystal (John Caunt Scientific Ltd, Oxon), which was placed 5 cm from the skin of the right calf and was supported by a foam pad. Patients were asked not to move their legs during the study. Also, the crystal was clamped to the tilt table to prevent movement of the probe on tilting. The left leg was shielded with lead to prevent activity from this side contaminating the recordings from the right leg. The detector output was recorded and processed by a custom made nucleonics system con-

Department of Medicine, Edinburgh University, Royal Infirmary of Edinburgh
A D Hargreaves
A L Muir

Correspondence to
Dr A D Hargreaves, Department of Medicine, Royal Infirmary, Edinburgh EH3 9YW

Accepted for publication
8 October 1991

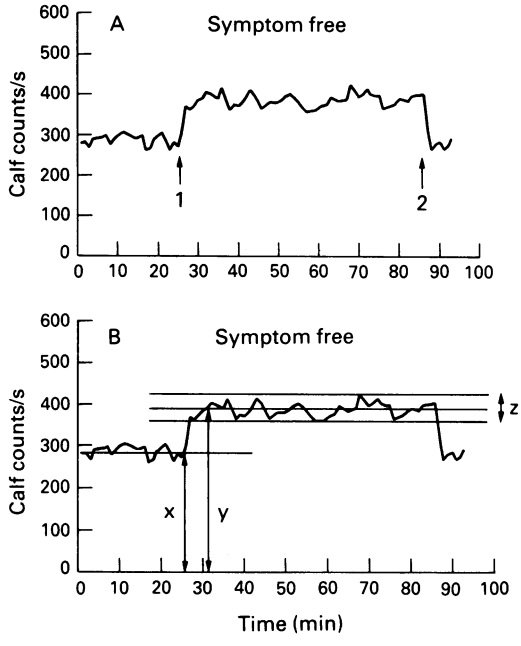

Figure 1 (A) Time activity curve from a symptom free patient. At time 1 the table was tilted and at time 2 it was returned to horizontal. (B) Same time activity curve with construction lines added. Percentage increase in venous volume $= \frac{y-x}{x} \times 100$. *Venous variability (%)* $- \frac{z}{y} \times 100$.

trolled by a microprocessor. Time activity curves were drawn and variables were derived after drawing construction lines (fig 1). The increase in venous volume (%) was derived by the formula: $(y - x)/x \times 100$ and the venous variability (%) was calculated by $z/y \times 100$. The time to plateau response is the time between lines x and y.

PROTOCOL

The patients had a light breakfast on the morning of the study. They were asked to continue their usual medication. The patient was positioned on the table and the measuring devices were set in place. Baseline recordings were made every five minutes over a 20 minute period with the table horizontal. The table was then tilted by a hand driven mechanism to 45° and maintained in this position for one hour or until the subject developed symptoms. When syncope or near syncope developed the table was returned to horizontal. Over the first five minutes of tilting haemodynamic recordings were made every minute, and between five and 10 minutes the rate was decreased to every two minutes. After 10 minutes of tilting, heart rate and blood pressure were documented every three minutes. If symptoms developed the recordings were repeated immediately.

STATISTICS AND ANALYSIS

The baseline haemodynamic measurements were the average of the recordings at five, 10, and 15 minutes when the patient was horizontal. The haemodynamic and venous response data in the two groups were compared by the non-parametric Mann-Whitney U test (Minitab 6.1 release, Minitab Inc). Correlation coefficients (Pearson moment product) were derived to assess associations between variables (Minitab 6.1 release, Minitab Inc).

Baseline characteristics, mean (SD)

	Symptom free		*With symptoms*
	All n=25	*Over 55 n=13*	*n=6*
Sex (M:W)	15:10	8:5	4:2
Age (y)	56 (17)	70 (7)	66 (6)
Ischaemic heart disease	7	6	1
Vasoactive treatment	8	6	0
Baseline:			
Heart rate (beats/min)	66 (12)	65 (8)	64 (3)
Systolic blood pressure (mm Hg)	138 (27)	155 (21)	142 (15)
Diastolic blood pressure (mm Hg)	78 (11)	84 (9)	75 (8)

Results

Patients were divided into two groups on the basis of their response to the tilt test: those that experienced syncope or near syncope (tilt positive) (n = 6) and those that remained symptom free (tilt negative) (n = 25). The age range of the group with symptoms was 60 to 77 years. To eliminate some of the effects of age on the cardiovascular response to tilting, analysis was also performed to include only those over age 55 in the symptom free group (n = 13).

BASELINE CHARACTERISTICS

Despite the differing age ranges of the groups with and without symptoms there were no significant differences in the age, sex, or haemodynamic variables at baseline (table). More people had ischaemic heart disease and were taking vasoactive medication in the symptom free group than in the group with symptoms but this difference was not statistically significant.

HAEMODYNAMIC RECORDINGS DURING TILT

The lowest recorded systolic blood pressure during head up tilt was significantly less in the syncopal group (mean (SD) 75·5 (19) *v* 124 (23) mm Hg p = 0·001) and the maximum fall in systolic pressure from baseline to lowest level during the tilt test was significantly greater in the patients with symptoms (66 (23) *v* 14 (12) mm Hg p < 0·001).

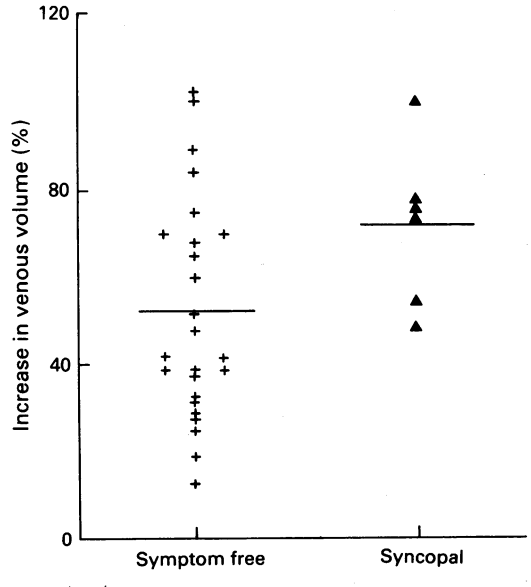

Figure 2 Comparison of percentage increase in venous volume during tilting in symptom free and syncopal patients (scattergram and means; p = 0·05 for difference between means).

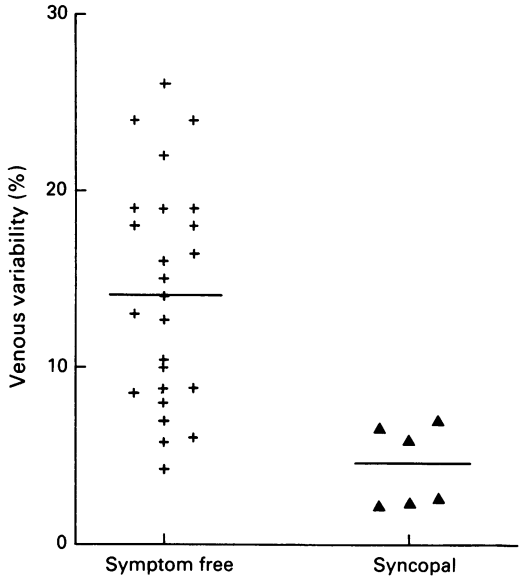

Figure 3 Comparison of variability of venous tone during the tilted period in symptom free and syncopal patients (scattergram and means; p = 0·001 for difference between means).

No significant difference in the mean heart rate was recorded at the time of the lowest blood pressure between those with and without symptoms (64 (23) *v* 72 (13) beats/min, NS). Only one patient in our syncopal group developed a profound bradycardia.

No sigificant difference was found in the time taken for the maximum fall in blood pressure to occur between those with and without symptoms (32 (21) *v* 33 (19) min, NS).

VENOUS RESPONSE

Patients with symptoms had a greater percentage increase in venous volume on tilting than symptom free patients (p = 0·05, fig 2) even when analysis was restricted to those of a similar age (with symptoms 72 (18)% *v* older symptom free 41 (17)%, p < 0·01). The variability of the venous reponse was significantly less in those that developed symptoms (p = 0·001, fig 3). The difference remained significant when those under 55 were excluded (with symptoms 4·4 (2·3)% *v* older symptom free 12·3 (6·4)%, p < 0·01. Fig 4 shows an example of a calf time activity curve in a syncopal patient. Patients who had syncope had a large increase in calf venous volume during the tilted phase; the volume varied little but tended to increase gradually. Some patients, however, had low variability but did not have symptoms or a significant fall in blood pressure (fig 3). The time taken for the venous volume to achieve the plateau phase after tilting was similar in the two groups (with symptoms 7 (3) *v* symptom free 5 (3) min, NS).

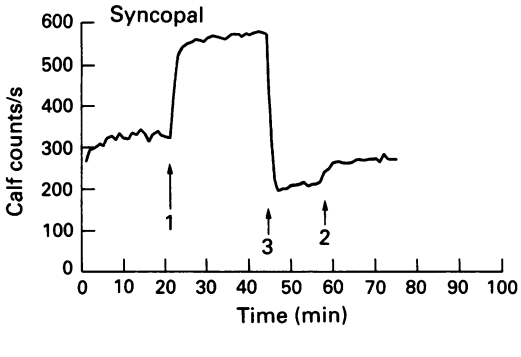

Figure 4 Time activity curve from a syncopal patient. Arrows 1 and 2 apply as for figure 1 and arrow 3 indicates head down tilt.

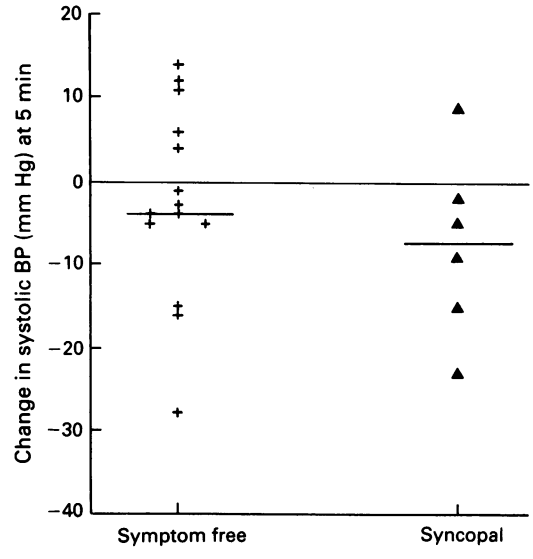

Figure 5 Comparison of fall in systolic blood pressure between horizontal values and recordings made five minutes after tilting in symptom free patients aged over 55 with those from patients with syncope (scattergram and means).

POSTURAL HYPOTENSION

Postural hypotension is judged by a fall in systolic pressure between horizontal and five minutes after tilting. The fall in blood pressure five minutes after tilting was significantly greater in the patients with symptoms, (− 7·5 (11) *v* 2·3 (11), p= 0·05). This difference, however, disappeared when the syncopal patients were compared with the older symptom free patients (fig 5). Of the older subjects tilted, two had a fall in systolic pressure of greater than 20 mm Hg (one symptom free and one with symptoms) and no patient had symptoms at this time.

Discussion

Our study has shown that patients who experience syncope during a head up tilt test have less variable venous tone and tend to have a larger increase in the volume of blood in their calf during tilting. This group of patients, identified by the tilt test, are thought to have malignant vasovagal syndrome. Symptoms induced by postural hypotension were not a problem in these patients. Also, none of the syncopal patients showed autonomic dysfunction when non-invasively tested by the methods of Ewing.[10]

Our evidence suggests that at least some of the pathology in malignant vasovagal syndrome lies in the peripheral veins. During head up tilt roughly 600 ml of blood shifts from the central circulation to the legs.[11] The body normally responds to this movement of blood by activating the sympathetic nervous system. This causes an increase in venous tone that tends to increase the venous return to the heart and maintain the cardiac output when standing. This increase in tone is seen even in an arm vein segment that has been isolated from the circulation by a tourniquet.[12] Other evidence for activation of the sympathetic nervous system lies in the increase in heart rate, peripheral

vascular resistance, and plasma noradrenaline concentrations that occur during head up tilt.[13] It is not known if this sympathetic stimulation is set at a constant level or whether it is variable.

Our patients who did not experience syncope had more obvious variability in the volume of calf venous blood, possibly as a result of variable sympathetic stimulation. Perhaps it is important for the calf veins to behave in an active manner with periods of constriction increasing the venous return in response to falling central venous pressure. Indeed we found an inverse correlation between variability of venous tone and the fall in systolic blood pressure during tilting ($r = -0{\cdot}57$, $p < 0{\cdot}01$). It is known that venoconstriction occurs in the arm veins of normal young men when syncope is induced by either head up tilt or negative lower body pressure.[14] When the stimulus became too great for venoconstriction to adequately increase venous return they became syncopal. If patients with malignant vasovagal syndrome have an impaired venous response during tilting this will predispose them to episodes with low central venous pressure and low cardiac volumes. If this occurs in assocation with increased sympathetic drive the conditions are right for stimulation of the Bezold-Jarisch reflex and vasovagal syncope. The importance of adequate sympathetic stimulation is underlined by the work of Almquist *et al* which shows a greatly increased rate of syncope in head up tilt testing when patients had a concomitant infusion of isoproterenol.[6] It is thought that high sympathetic outflow is required to generate the excessive intraventricular pressures that provoke the Bezold-Jarisch reflex.

In our study we found that only 19% of patients had syncope. This proportion is substantially lower than other groups looking at malignant vasovagal syndrome. Fitzpatrick and Sutton have reported that 74% of their patients experienced syncope.[5] Abi-Samra *et al* had a positive response in 42% and Strasberg *et al* detected syncope in 37·5% of their patients.[15,16] In interpreting these figures it is important to remember that the patients we studied had not already had intensive investigation and were relatively unselected. It is likely that these people had a range of conditions responsible for their initial symptoms. This had the advantage of allowing observation of the peripheral venous response in a population ranging from normal to severely abnormal. Our low rate of syncope is partly explained by the 45° of tilt that we used by contrast with the greater stress of 60° that has now become accepted as the optimal degree of tilt.[17] Our symptom free group may contain some people that would be syncopal in response to the greater stress. It was not our purpose to investigate the incidence of syncope but to examine the role of the veins in the pathogenesis.

As expected the fall in blood pressure during tilting was related to increasing age ($r = -0{\cdot}37$, $p < 0{\cdot}05$). This is thought to be due to a gradual functional impairment of the autonomic nervous system.[18] Consequently, it is perhaps predictable that malignant vasovagal syndrome tends to occur in older people.

Two pieces of work have stated that vasovagal syncope was associated in some instances with overactive cardiovascular reflexes.[19,20] This is not necessarily at variance with our findings. In one study the syncopal subjects were young and had no history of syncope. These results may simply reflect a group prone to fainting when under medical investigation and head up tilt. A second study also found evidence of exaggerated cardiovascular reflexes as judged by heart rate response both to tilting and to stimulation of the carotid sinus. Peripheral venous tone was not examined and the exaggerated heart rate response may reflect a normal reflex response to low cardiac filling pressures.

Our chosen method for assessment of calf venous volume has been validated against limb plethysmography.[7] Pharmacological studies suggest that calf venous volume is not influenced by changes in arterial volume. Hydralazine and felodipine cause noticeable decreases in systemic vascular resistance, but no change in venous volume.[8,21] By contrast, nitrates cause a 10% increase in venous volume without causing significant reductions in systemic vascular resistance.[8] Captopril, which acts on arterial and venous beds, decreases systemic vascular resistance and causes venous volume to increase.[22] Our extrapolation from calf measurements to venous volume is therefore not unreasonable, and this technique appears to be ideally suited to monitor changes in peripheral venous volume in response to posture.

We postulate that the abnormality in patients with malignant vasovagal syndrome may lie within the peripheral veins themselves, perhaps involving the smooth muscle or endothelium, and is not the result of generalised dysfunction of the autonomic nervous system. If the primary pathological defect is identified more satisfactory treatment may result—particularly for the vasodepressor type of malignant vasovagal syndrome.

We thank Miss Felice Taddei for technical assistance and to Mrs Venessa Campbell for the preparation of the manuscript.

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Br Heart J 1992 67: 486-490
doi: 10.1136/hrt.67.6.486

Notes