Haemodynamic changes early in prodromal symptoms of vasovagal syncope

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Aims Vasovagal syncope (VVS) is often preceded by prodromal symptoms. The haemodynamic changes occurring during the prodrome have not been systematically investigated. The aim of the present study was to investigate the behaviour of blood pressure (BP), heart rate (HR) and sympathetic activity at the beginning of the prodrome in patients with tilt-induced VVS.

Methods and Results Sixty-three patients with VVS underwent tilt testing. BP and HR were measured and blood samples for plasma catecholamine determination were obtained during the test.

Twenty-seven patients developed syncope of whom all had a prodrome. From the last scheduled measurement before prodromal symptoms to the beginning of the prodrome, both systolic and diastolic BP decreased in all patients (from 105 ± 16 to 74 ± 20 mmHg, \( P<0.001 \), and from 68 ± 13 to 51 ± 12 mmHg, \( P<0.001 \), respectively) and HR decreased in 18 (67%) (from 89 ± 22 to 80 ± 25 beats/min, \( P<0.02 \)). At the onset of loss of consciousness both BP and HR showed a further decrease (\( P<0.001 \)). Plasma adrenaline significantly increased from the last sample before prodromal symptoms to the beginning of the prodrome (\( P<0.01 \)) and showed a further increase during loss of consciousness (\( P<0.05 \)), whereas plasma noradrenaline did not increase, as an expression of inhibition of sympathetic neural outflow.

Conclusion These results demonstrate that in patients with tilt-induced VVS, BP is consistently decreased at the beginning of prodromal symptoms because of the withdrawal of sympathetic activity, and HR is often reduced, probably because of increased vagal activity. We may infer that similar haemodynamic features also occur during spontaneous VVS.

Introduction Vasovagal syncope (VVS) is often preceded by prodromal symptoms and signs. The haemodynamic changes occurring during the prodrome have not been systematically investigated in patients with this type of syncope. Tilt testing is believed to be able to reproduce the haemodynamic features of a spontaneous vasovagal attack.

The purpose of the present study was to investigate the behaviour of blood pressure (BP), heart rate (HR) and sympathetic activity at the beginning of prodrome in patients with tilt-induced VVS.

Methods Patients referred for evaluation of syncope were considered candidates for the present study if they: (1) were
aged >18 years; (2) had prodromal symptoms or signs suggestive of VVS (sweating, nausea, abdominal discomfort, pallor, feeling of cold); (3) did not show any sign of cardiological or neurological disease. The study was approved by the Review Board of Cento’ Hospital. Sixty-three consecutive patients who met eligibility criteria underwent tilt testing, which was performed according to the Westminster protocol (60° for 45 min)[1]. The test was always performed in the morning in a quiet room, after overnight fasting. Subjects were informed in detail about the nature and purpose of the experiments before consenting to participate in the study. The procedure was carried out by means of an electronically controlled tilt table with a foot-board for weight-bearing. BP and HR were measured by means of an Ohmeda Finapress and an ECG. Subjects remained supine for 1 h before the test, which was attended by a nurse and a physician. An antecubital venous cannula inserted 1 h before the test allowed the blood samples to be taken. Normal saline was infused to maintain the patency of the lines.

BP and HR were measured before the start of the tilt test (0 min) and then every 3 min. If syncope started to develop, these variables were measured at the beginning of prodromal signs (pallor, sweating, sighing and yawning) and symptoms (patients were asked to report instantly the perception of light-headedness, visual field changes, nausea, feeling of cold, abdominal discomfort) and at the beginning of the loss of consciousness.

Collection of blood and laboratory procedures

Blood samples for determination of plasma catecholamines were obtained before the start of the tilt test and then after 3, 10, 15, 30 and 45 min in the 60° position. If syncope started to develop, blood samples were obtained at the beginning of the prodrome and at loss of consciousness. The volume of samples withdrawn was replaced with a similar volume of intravenous normal saline.

Blood samples were drawn into precooled glass tubes containing glutathione (1-2 mg/ml) and ethylene glycol-bis (β-aminoethyl ether) N,N,N',N'-tetracetic acid (1-9 mg/ml). Specimens for determinatin of catecholamines were promptly centrifuged at 3000 × g for 15 min at 4°C, and the plasma was frozen at −80°C until analysis.

Plasma adrenaline and noradrenaline were measured by high-performance liquid chromatography (HPLC) with an electrochemical coulometric detector (Model 5011, ESA, Chelmsford, MA, U.S.A.), using materials supplied by ESA Laboratories. The intra- and inter-assay coefficients of variation for adrenaline were 4 and 5.3%, respectively at concentrations of 0.1–0.2 nmol/l in plasma. The intra- and inter-assay coefficients of variation for noradrenaline were 4.1 and 6.0%, respectively, at concentrations of 1–2 nmol/l in plasma. Detection limits for adrenaline and noradrenaline were 0.054 and 0.147 nmol/l, respectively.

Definitions

Syncope was defined as transient loss of consciousness with inability to maintain postural tone and with spontaneous recovery. A positive response to tilt testing was defined as reproduction of syncope in association with hypotension, bradycardia or both. A positive response in which syncope occurred in association with an asystolic pause >3 s was defined as asystolic.

Statistical analysis

Statistical evaluation of the data was achieved by using paired and unpaired Student’s t-test and chi-squared test, as appropriate. Results were expressed as mean ± standard deviation.

Results

Of the 63 patients, 27 (43%) developed syncope during tilt testing. The age of these 27 patients was 43 ± 20 years; 13 were males. The number of syncopes in the last year was 2 ± 1. During the tilt test, prodromal symptoms occurred in all 27 patients after 15 ± 12 min and loss of consciousness after 16 ± 13 min. The behaviour of BP and HR is shown in Fig. 1. Systolic BP had not significantly changed after 3 min of tilt, but had decreased slightly but significantly (P<0.005) by the last scheduled measurement before the prodrome (14 ± 19 min). Diastolic BP had significantly increased (P<0.005) after 3 min of tilt but was significantly decreased (P<0.005) at the last measurement before the prodrome. HR had significantly increased (P<0.001) after 3 min of tilt and then did not show significant changes at the last measurement before the prodrome.

Blood pressure and heart rate at the beginning of the prodrome

From the last scheduled measurement before prodromal symptoms to the beginning of the prodrome, both systolic and diastolic BP decreased in all patients (from 105±16 to 74±20 mmHg, P<0.01, and from 68±13 to 51±12 mmHg, P<0.001, respectively). HR significantly decreased at the beginning of the prodrome from 89±22 to 80±25 (P<0.02). The behaviour of HR in each patient is shown in Fig. 2. It decreased in 18 patients, increased in 8 and remained unchanged in 1. The interval between the beginning of the prodrome and the beginning of loss of consciousness was 48±36 s (range from 10 to 125).
At the beginning of loss of consciousness systolic and diastolic BP and HR showed a further significant decrease ($P<0.001$).

**Patients with asystole during loss of consciousness**

During loss of consciousness 6 of the 27 patients (22%) showed asystole. At the last scheduled measurement before the prodrome HR did not significantly differ between the 6 patients showing asystole (81 ± 15 beats/min) and the remaining 21 patients (92 ± 22 beats/min). At the beginning of prodromal symptoms HR was significantly lower in the 6 patients showing asystolic response than in the remaining 21 (58 ± 9 vs 87 ± 25 beats/min, $P<0.05$). The change in HR from the last measurement before prodromal symptoms to the beginning of prodrome was observed in 4 of the 6 patients (67%) with asystole and in 4 of the 21 patients (19%) without this response ($P<0.05$).

**Catecholamine changes**

Plasma adrenaline and noradrenaline were measured during tilt testing in 15 patients, 10 of whom developed syncope (age 32 ± 17 years, 4 males, number of syncopes in the last year 3 ± 1). The behaviour of catecholamines in these 10 patients is shown in Fig. 3. Both adrenaline and noradrenaline increased from the supine position to the 60° head-up position (3 min), but only the rise in noradrenaline was statistically significant ($P<0.001$). Noradrenaline did not change from the last scheduled sample before prodromal symptoms to beginning of the prodrome or from the prodrome to the loss of consciousness, whereas adrenaline significantly rose at the beginning of the prodrome ($P<0.001$), with a further increase during loss of consciousness ($P<0.05$).
Discussion

In the present study, we investigated patients with syncopal spells preceded by prodromal symptoms and with a positive response to tilt testing. The syncopal episodes of our patients can therefore be attributed to vasovagal cause.

The main finding of the present study is that systolic and diastolic BP are markedly and consistently reduced at the beginning of the prodrome, and HR is decreased in most patients. Therefore, these features can be considered to play a role in the genesis of prodromal symptoms.

There is strong evidence that the decrease in BP is secondary to inhibition of muscle sympathetic activity. First, in muscle sympathetic nerve recordings, sympathetic silence has consistently been observed at the moment of the actual faint, indicating complete cessation of sympathetic drive to skeletal muscle vessels[2–8]. Second, the disappearance of 0·1 Hz BP oscillations preceding the loss of consciousness indicates an inhibition of sympathetic vasomotor activity[9,10]. Third during the loss of consciousness, adrenaline increases markedly, whereas noradrenaline remains practically unchanged[11–14]. This behaviour has been interpreted as an expression of lack of sympathetic nervous activity that is responsible for severe hypotension. The results of the present study confirm that noradrenaline does not increase during loss of consciousness. Moreover, we have demonstrated that sympathetic inhibition is already present at the beginning of prodromal symptoms. Indeed, noradrenaline was increased, indicating a compensatory mechanism, whereas noradrenaline was unchanged, in spite of the decrease in BP.

The reduction in HR which can precede syncope is commonly attributed to increased vagal tone. The HF power of HR variability, which is mainly influenced by vagal activity, has been investigated during tilt testing, and the results appear contrasting[15–17]. Theodorakis et al.[15] and Morillo et al.[16] observed an increase in HF components before loss of consciousness, whereas Prinz-Zaiss et al.[17] did not find any significant change. These conflicting results can be attributed to the inter-individual variability of vagal activity during VVS. Our results suggest that an increase in vagal tone is present in most patients at the beginning of prodromal symptoms, even though vagal activity was investigated by the behaviour of HR, which constitutes an indirect index.
Indeed, HR significantly decreased from the last scheduled measurements to the beginning of the prodrome, and in some patients this decrease was marked (Fig. 2). We observed that, at the beginning of the prodrome, the reduction in HR was more marked in the patients who ultimately showed asystole. This suggests that in these patients the marked increase in vagal activity does not appear suddenly at the beginning of the loss of consciousness but precedes it.

Our results show that VVS is not a sudden-onset phenomenon, since a reduction in BP and often in HR is already present at the beginning of prodromal symptoms, and the interval between the prodrome and loss of consciousness, though variable from patient to patient (range 10–125 s), is not short (48 ± 36 s). A non-sudden onset of VVS has already been demonstrated by some authors, who investigated the behaviour of BP and HR during tilt testing in the minutes preceding loss of consciousness\(^{[8,12,17–21]}\). A reduction in BP starting 2–3 min before the actual faint\(^{[8,19–21]}\) and a decrease in HR starting 30–90 s before loss of consciousness\(^{[8,17,20]}\) were reported. Fitzpatrick et al\(^{[12]}\) showed, by using echocardiography, a decrease in left ventricular dimensions, which took place 15 ± 4 s before loss of consciousness simultaneously with the slowing of HR. A similar reduction in left ventricular dimensions has been reported by Shalev et al.\(^{[18]}\). However, in these studies the changes in BP, HR and the other variables were not correlated with the beginning of prodromal symptoms. To our knowledge, the only study in which the variations in BP and HR were correlated with the prodromal symptoms was carried out in young healthy subjects without history of syncope\(^{[22]}\). During tilt testing, BP decreased whereas HR did not. It is possible that healthy subjects without history of syncope who faint on tilt testing have different circulatory adjustments and, therefore, different haemodynamic changes. In this regard, Furlan et al.\(^{[23]}\) observed in healthy subjects without a history of syncope a consistent increase, instead of a decrease, in HR in the last minute of the tilt before loss of consciousness.

In conclusion, our results show that, in patients with VVS, systolic and diastolic BP are consistently decreased at the beginning of prodromal symptoms because of inhibition of sympathetic activity, and HR is often reduced, probably because of increased vagal activity. The reduction in HR is more marked in the patients who ultimately show asystole. The same haemodynamic changes are expected to occur during spontaneous VVS, but that remains to be assessed.

**References**


