Autonomic control of vasovagal syncope

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Jardine, David L., Hamid Ikram, Christopher M. Frampton, Rachell Frethey, Sinclair I. Bennett, and Ian G. Crozier. Autonomic control of vasovagal syncope. Am. J. Physiol. 274 (Heart Circ. Physiol. 43): H2110–H2115, 1998.—In the pathophysiological study of vasovagal syncope, the nature of the interaction between baroreceptor sensitivity (BS), sympathetic withdrawal, and parasympathetic activity has yet to be ascertained. Altered BS may predispose toward abnormal sympathetic and parasympathetic responses to orthostasis, causing hypotension that may progress to syncope if there is sympathetic withdrawal. To examine this hypothesis, we monitored blood pressure (BP), heart rate (HR), BS, forearm blood flow, and muscle nerve sympathetic activity (MNSA) continuously in 18 vasovagal patients during 60° head-up tilt, syncope, and recovery. Results were compared with those of 17 patients who were able to tolerate tilt for 45 min. During early tilt, BP was maintained in both groups by an increase in HR and MNSA from baseline (P < 0.01), but BS decreased more in the syncopal group (P < 0.05). At the start of presyncope (mean 2.7 ± 0.2 min before syncope and 15.2 ± 12 min after tilt), when BP fell, HR and sympathetic activity remained increased from baseline (P < 0.01). Thereafter, BP and HR correlated directly with sympathetic activity and regressed in linear fashion until syncope (P < 0.001), whereas BS increased to baseline. At syncope, BP, HR, and sympathetic activity fell below baseline (P < 0.01, P < 0.05, and P < 0.01, respectively), but BS did not increase. During recovery, sympathetic activity increased to baseline and BS increased (P < 0.05), whereas HR and BP remained low (P < 0.01 and P < 0.05, respectively). The mechanism for the initiation of hypotension during presyncope remains unknown, but BS may contribute. Vasodilatation and bradycardia during presyncope appear to be more closely related to withdrawal of sympathetic activity than to increased parasympathetic cardiac activity.

Vasovagal syncope refers to vasodilatation and inappropriate bradycardia leading to hypotension and loss of consciousness (37). Although the condition is common and may give rise to significant morbidity (8, 23), its mechanism remains obscure (16). The vasovagal response may be activated via inhibition of the brain stem by the higher centers (27) or the heart when central blood volume is reduced and mechanoreceptors fire paradoxically (1, 35). It is generally believed that the vasodilatation is a passive process mediated by sympathetic withdrawal, whereas the bradycardia is active, secondary to increased parasympathetic activity (37). During presyncope, vasodilatation usually occurs before bradycardia and is thought to be the dominant mechanism of the response (18).

Using tilt-induced syncope as a model for the vasovagal reaction, we aimed to compare the hemodynamics of syncopal patients with those of tilt-tolerant patients.

We also undertook detailed autonomic monitoring of both groups to see how the hemodynamic changes were controlled. In particular, we looked at autonomic tone before and during early tilt to determine whether certain patients were somehow predisposed to syncope. We also looked at autonomic activity immediately before and during presyncope to determine whether sympathetic withdrawal initiated the vasovagal response.

To our knowledge, the direct monitoring of parasympathetic cardiac activity in the intact human is not possible, so repeated measures of baroreceptor sensitivity and high-frequency heart rate variability were used for this purpose. Sympathetic withdrawal at the time of syncope has been demonstrated by measuring venous norepinephrine, although sampling times and pharmacokinetics of norepinephrine during hypotension may limit the accuracy of these studies (9, 11, 29). The measurement of whole body and regional norepinephrine spillover is more physiological but is invasive, and repeated sampling during syncope would be limited by the mixing of the tritiated infusion with plasma (3, 7). Heart rate variability has been used to monitor cardiac sympathetic activity during head-up body tilt and tilt-induced syncope (2, 17, 21), but this method is also limited by the sampling interval and only measures composite autonomic action on the sinus node (14).

Continuous microneurographic recording from the superficial peroneal nerve in the leg is thought to be representative of all limb muscle sympathetic activity and is therefore ideal for monitoring beat-to-beat changes during transient hypotension (5, 34). Previous work has demonstrated sympathetic withdrawal at the time of syncope with the use of vasodilator infusions and lower body negative pressure (30, 39), but only recently have patients with recurrent vasovagal syncope been studied (24, 25). To simplify the interpretation of our autonomic data, we used the head-up passive-tilt method to induce syncope without the use of any pharmaceutical agents. This method is generally believed to reproduce vasovagal syncope in the laboratory setting (4).

METHODS

Definitions

For the purposes of this study, presyncope was the interval between the onset of sustained hypotension (i.e., at least a 5-mmHg fall in mean blood pressure [MBP]) during tilt and syncope. Presyncope was usually associated with symptoms that included flushing, a feeling of impending loss of consciousness, nausea, yawning, sweating, abdominal discomfort, and altered vision.

Tilt-induced syncope consisted of loss of consciousness associated with a fall in MBP of at least 40 mmHg from baseline. A history of recurrent vasovagal syncope included at
least two episodes of loss of consciousness, preceded by some or all of the above symptoms during the 6 mo before tilt.

Patients

Fifty-one consecutive patients were retrospectively assigned to syncopal or nonsyncopal groups according to their responses to the tilt test. Sixteen patients in whom we were unable to obtain satisfactory microneurographic recordings were excluded. The demographic data for the remaining 35 patients are displayed in Table 1. All patients in the syncopal group (n = 18) and 13 of the patients in the nonsyncopal group (n = 17) were referred to our department for investigation of a history consistent with recurrent vasovagal syncope. Four patients in the nonsyncopal group had no history of syncyne. Patients with suspected autonomic neuropathy or cardiac syncope were not included in this study.

All patients gave consent before tilt, and the study design was approved by the Canterbury Health Enterprise ethics committee.

Methods

All patients were tilted at 10:00 AM after consuming a light, caffeine-free breakfast. Any vasoactive drugs were withdrawn 5 days previously. Permanent pacemakers were deactivated for the purposes of the study. The patients were positioned horizontally on a hydraulic tilt table, and cutaneous electrodes for electrocardiograms (ECG) were placed. A 3-Fr intra-arterial cannula was inserted in the right brachial artery for continuous BP monitoring. A 16-gauge venous catheter was inserted in the right antecubital fossa, and 200 ml of blood was withdrawn from 9 of the 35 patients 60 min before tilt to increase the chances of a subsequent syncopal reaction. Microneurography needles were inserted in the right superficial peroneal nerve for recording postganglionic sympathetic activity (MNSA). The left arm was placed in a sling at the same level as the heart for mercury-inrubber strain-gauge arterial plethysmography.

Blood pressure (BP), heart rate (HR), and MNSA were recorded continuously and averaged for 1 min at the following times: before tilt (−10, −5 min); baseline (0 min); early tilt (5 min); throughout tilt (16, 30, 45 min) or until syncope, and recovery (50, 55 min). Presyncopal recordings were taken from the onset of presyncope and 1 min before syncope. Forearm blood flow (FFB) was measured using strain-gauge plethysmography at 5-min intervals and at syncope (40).

Normalised low-frequency (0.06–0.1 Hz) and high-frequency (0.15–0.4 Hz) heart rate variability (LFHRV, HFHRV) were derived from spectral analysis of 256-beat samples using the fast Fourier transformation (2). MSNA was counted for each 1-min sample from the integrated voltage neurogram using burst frequency (time constant 0.1 s). Sympathetic bursts were recognized by their characteristic morphology and their relationship to ECG and BP (Fig. 1) (5). Baroreceptor sensitivity (BS) was calculated from the slope of the regression line between linearly related progressive increases and decreases in systolic BP and pulse interval. These sequences were selected for regression analysis, provided that systolic BP and pulse interval changes was linear (correlation coefficient > 0.85), the regression coefficient was accepted as a measure of the sensitivity of baroreflex control of HR (26). The baroreceptor and heart rate variability samples were 3–4 min in length and therefore included all the heart beats of the corresponding hemodynamic samples and those during the 2–3 min immediately beforehand.

In addition, six consecutive 30-s samples of BP, HR, and MNSA were analyzed during presyncope to ascertain correlation between these variables. MBP was derived from systolic and diastolic BP. Forearm resistance (FR) was calculated from MBP and FBF.

Statistics

Repeated-measures ANOVA was used to assess changes from baseline over time within the two groups. For the purpose of comparing the groups during early tilt, the three time points (−10, −5, and 0) were averaged. Comparisons between the groups before and during early tilt were made using independent t-tests.

The correlation analysis of MNSA with MBP and HR during presyncope was analyzed using a general linear-model approach. This method was used to assess the relationships between the variables within individuals.

RESULTS

Hemodynamics

Between-group changes. There were no differences in any of the parameters before tilt. FR decreased more in the syncopal group during early tilt (P < 0.05; Figs. 2 and 3).

Within-group changes. MBP was maintained in both groups during early tilt, and HR increased from baseline (P < 0.01). FBF decreased only in the syncopal group during early tilt (P < 0.01), and FR increased (P < 0.05). Presyncope occurred when MBP initially decreased from baseline (P < 0.05) at a mean time of 15.2 ± 12 min from tilt and 2.7 ± 7 min from syncope. HR was still increased from baseline (P < 0.01), whereas FR began to fall. One minute before syncope, MBP decreased further (P < 0.01) and HR fell to baseline. At syncope, MBP, HR, and FR were below baseline (P < 0.01, P < 0.05, and P < 0.01, respectively). During recovery, MBP and HR remained below baseline at 50 min (P < 0.01 and P < 0.05, respectively). HR increased to baseline at 55 min, but MBP remained low (P < 0.01). Total peripheral resistance and FR rapidly increased to baseline at 50 min.

<table>
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<tr>
<th>Table 1. Demographic data for tilt patients</th>
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<td>Nonsyncopal Group</td>
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<td>Age, yr</td>
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<td>BSA, m²</td>
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<td>Sex (M/F)</td>
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<td>Tilt time, min</td>
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<td>Presyncope time, min</td>
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<td>Atrial fibrillation</td>
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<td>Carotid sensitivity</td>
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<td>Coronary artery disease</td>
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<td>Hypertension</td>
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<td>LV hypertrophy</td>
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<td>Reduced ejection fraction</td>
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Values are means ± SD for age, body surface area (BSA), tilt time, and presyncope time (duration of presyncope). Values are number of patients in each group for remaining variables. LV, left ventricular.
Autonomic Activity

Between-group changes. There were no differences in any of the parameters before tilt (Figs. 4 and 5). BS decreased more in the syncopal group during early tilt.

Within-group changes. In both groups MNSA increased from baseline during early tilt (P < 0.01, P < 0.05) and HFHRV appeared to decrease. At the start of presyncope, MNSA remained above baseline (P < 0.01), even though MBP was already reduced (P < 0.05). HFHRV was below baseline (P < 0.05), and BS increased to baseline. One minute before syncope, MNSA began to fall but was still above baseline, whereas HFHRV and BS did not increase. During presyncope, MNSA correlated directly with both MBP and HFHRV.
and HR \((P < 0.001)\) (Figs. 6 and 7). At syncope, MNSA fell \((P < 0.01)\) and HFHRV remained below baseline \((P < 0.01)\), whereas BS did not increase. During the first 5 min of recovery, MNSA and HFHRV returned to baseline. BS increased beyond baseline levels and was maintained \((P < 0.05)\).

**DISCUSSION**

Muscle nerve sympathetic activity provides a direct beat-to-beat measurement of peripheral sympathetic tone, whereas heart rate variability and baroreceptor sensitivity are indirect indexes of autonomic activity. We used these methods to obtain a continuous assessment of autonomic activity before and during tilt-induced syncope to investigate the mechanisms involved in vasovagal syncope.

Before tilt, we found no evidence of altered autonomic tone in the syncopal group. The only predisposing factor for tilt-induced syncope identified in this
study was a greater reduction in arterial baroreceptor sensitivity, resulting in less parasympathetic activity during the first 5 min of tilt. This was consistent with the brisker forearm vasoconstriction and the fall in high-frequency heart rate variability seen in the syncopal group at this time (32). Current opinion is divided as to whether altered parasympathetic tone in the form of reduced baroreceptor sensitivity may predispose to vasovagal syncope (25, 31). An impaired sympathetic response to orthostasis has also been suggested as a possible mechanism (25), but our study showed that syncopal patients were initially able to maintain blood pressure by an increase in cardiac and muscle sympathetic activity similar to that in the nonsyncopal group. This would indicate that, although the parasympathetic reaction to orthostasis might be altered in syncopal patients, the efferent sympathetic response from both low- and high-pressure baroreceptor reflex arcs remains intact (20, 24, 36). The apparent increase in low-frequency heart rate variability during early tilt was consistent with this, but not with all of the previous studies (2, 15, 21).

When presyncope began and blood pressure decreased, muscle nerve sympathetic activity remained increased, suggesting that vasodilatory mechanisms other than sympathetic withdrawal were operative at this time. Possible mechanisms include: 1) active secretion of a circulating vasodilator under sympathetic control, e.g., nitric oxide, epinephrine (6, 13); 2) differential sympathetic control and early vasodilatation in other vascular beds, causing a fall in total peripheral resistance (12, 38); or 3) transient, sympathetically mediated, cholinergic vasodilation (10). The absence of increase in the measures of parasympathetic activity at this time would make a parasympathetic mechanism unlikely (33). This is consistent with previous studies on the secretion of pancreatic polypeptide during head-up tilt that showed only increased secretion at the time of syncope and not before (13, 28).

During presyncope, the fall in muscle nerve sympathetic activity correlated directly with mean blood pressure, whereas parasympathetic activity remained below baseline, suggesting that sympathetic control of total peripheral resistance was the predominant mechanism of vasovagal syncope (19). In addition, there was a linear correlation between sympathetic activity and heart rate that was consistent with the reduction of sympathetic cardiac activity rather than parasympathetic activation being the mechanism of the relative bradycardia (33).

The rapid decrease in muscle nerve sympathetic activity at syncope occurred despite the two groups having equivalent levels of activity at baseline and early tilt. There was no evidence of a preceding inadequate or exaggerated sympathetic response to tilt in the syncopal group (36). Furthermore, during early presyncope sympathetic activity was appropriately increased, and therefore the mechanism for the initiation of presyncope remains unclear.

Persistent hypotension and bradycardia were observed during the recovery phase of tilt-induced syncope similar to that occurring after vasovagal syncope. Although sympathetic activity recovered rapidly during this time to baseline values, it was not sufficient to normalize the blood pressure in the horizontal position within 10 min of a syncope episode. This would suggest that other factors may be involved in the control of blood pressure during recovery from vasovagal syncope, particularly parasympathetic activity because baroreceptor sensitivity was increased.

Limitations of Study

The autonomic mechanisms operating during tilt-induced syncope may be different from those that occur in vasovagal syncope. Because of the invasive nature of the test, we were unable to recruit a pure control group, and some patients in both groups were venesected before tilt. Although this may have affected the baseline comparisons between the two groups, we were concerned more with the response to early tilt and the pathophysiology of tilt-induced syncope. At present there is no beat-to-beat index of parasympathetic activity. The interpretation of heart rate variability analyses is made difficult by the sampling time, the composite nature of the different frequencies, and the distinction between absolute levels and changes in activity (22). Baroreflex sensitivity also is not a pure measure of efferent parasympathetic activity but involves central nervous system integration of multiple different pathways.

In summary, we found that during early tilt, arterial baroreceptor sensitivity was reduced in patients who were susceptible to tilt-induced syncope. Blood pressure was initially maintained by an appropriate increase in sympathetic activity. The mechanism for the onset of presyncope hypotension remains unknown, but it is not a reduction in muscle sympathetic activity or an increase cardiac parasympathetic activity. Presyncope and syncope appeared to be mediated by withdrawal of sympathetic activity, resulting in vasodilation and bradycardia with no evidence of a reciprocal increase in parasympathetic activity. However, in the recovery phase sympathetic activity was normalized, and the persisting hypotension may have been mediated by increased parasympathetic activity.

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REFERENCES

