Decrease in cardiac output and muscle sympathetic activity during vasovagal syncope

D. L. JARDINE,1 I. C. MELTON,2 I. G. CROZIER,2 S. ENGLISH,2 S. I. BENNETT, C. M. FRAMPTON,3 AND H. IKRAM2
Departments of 1General Medicine, 2Cardiology, and 3Medicine, Christchurch Hospital, Christchurch, New Zealand

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Jardine, D. L., I. C. Melton, I. G. Crozier, S. English, S. I. Bennett, C. M. Frampton, and H. Ikram. Decrease in cardiac output and muscle sympathetic activity during vasovagal syncope. Am J Physiol Heart Circ Physiol 282: H1804–H1809, 2002; 10.1152/ajpheart.00640.2001.—The importance of cardiac output (CO) to blood pressure level during vasovagal syncope is unknown. We measured thermoregulation CO, mean blood pressure (MBP), and leg muscle mean sympathetic nerve activity (MSNA) each minute during 60° head-up tilt in 26 patients with recurrent syncope. Eight patients tolerated tilt (TT) for 45 min (mean age 60 ± 5 yr) and 15 patients developed syncope during tilt (TS) (mean age 58 ± 2 yr, mean tilt time 15.4 ± 2 min). In TT patients, CO decreased during the first minute of tilt (from 3.2 ± 0.2 to 2.5 ± 0.3 l·min⁻¹·m⁻²; P = 0.001) and thereafter remained stable between 2.5 ± 0.3 (P = 0.001) and 2.4 ± 0.2 l·min⁻¹·m⁻² (P = 0.004) at 5 and 45 min, respectively. In TS patients, CO decreased during the first minute (from 3.3 ± 0.2 to 2.7 ± 0.1 l·min⁻¹·m⁻²; P = 0.02) and was stable until 7 min before syncope, falling to 2.0 ± 0.2 at syncope (P = 0.001). Regression slopes for CO versus time during tilt were −0.01 min⁻¹ in TT versus −0.1 l·min⁻¹·m⁻²·min⁻¹ in TS (P = 0.001). However, MBP was more closely correlated to total peripheral resistance (R = 0.56, P = 0.001) and MSNA (R = 0.58, P = 0.001) than CO (R = 0.32, P = 0.001). In vasovagal reactions, a progressive decline in CO may contribute to hypotension some minutes before syncope occurs.

vasodilatation. CO is dependent on heart rate (HR) and stroke volume (SV). Several tilt studies (8, 30) have shown that HR rate decreases after the onset of hypotension and artificially increasing the rate does not normalize the blood pressure. However, Weissler et al. (38) demonstrated in 1957 that increasing venous filling pressure was the most effective way of terminating a vasovagal reaction during orthostasis. Therefore, during tilt-induced syncope, venous filling pressure may be the main determinant of end-diastolic volume, SV, CO, and ultimately mean blood pressure (MBP) (26). We aimed to discern the importance of CO to MBP by measuring the rate of CO decay during the time between the onset of hypotension and syncope. Over the same time interval, we also correlated CO, TPR, and MSNA to MBP. We hypothesized that CO would decrease more rapidly in patients who developed syncope during tilt but that MBP pressure would be more closely correlated to TPR and MSNA than CO.

METHODS

Patients. Twenty-six consecutive patients underwent tilt testing after being screened for epilepsy, cardiac syncope, and autonomic disease. Demography and previous investigations are summarized in Table 1. All patients had a history suggestive of recurrent vasovagal syncope with at least two major episodes during the previous year. Patients with postural hypotension, heart failure, angina, or suspected cardiac syncope were excluded. No patients had carotid sinus hypersensitivity. Patients were divided into tilt-tolerant (TT; n = 8) and tilt-syncope groups (TS; n = 15) on the basis of their response to tilt. Syncope during tilt was defined as loss of consciousness and muscle tone associated with MBP <60 mmHg. The mean time to syncope was 15.4 ± 2 min, which is comparable to other studies (17, 22, 25) and included three patients who developed syncope after 20 min.

Only the 15 patients who developed syncope after at least 8 min of tilt were analyzed. Three patients who developed syncope before this time were rejected. We selected these patients to ensure that we could separate the hemodynamic adjustments during the first minute of tilt from those that occurred during the last 7 min before syncope. This time period was vital to the study because correlation analysis...
Thermodilution CO and SvO₂ were measured using a pulmonary artery fiberoptic oximetry catheter (Oximetrix III, Abbott Laboratories; North Chicago, IL) and CO computer (Critical Care System model 3300, Abbott). Ten milliliters of a room temperature (21–24°C) solution of 5% glucose water were injected in <4 s by the same operator. Injections were given at end expiration and the morphology of the thermodilution curve was checked. Baseline CO was averaged from three serial measurements taken during the 5 min immediately before tilt. If the variance was >10%, two additional measurements were made and the high and low values were rejected. During tilt, single measurements were made each minute for the duration of tilt so that the maximum total volume injected was 600 ml. CO was indexed to body surface area and TPR was calculated by dividing MBP by CO.

SvO₂ was measured by fiber-optic venous reflectance oximetry using the same catheter and computer system. Because oxygen consumption and arterial oxygen saturation were not measured, absolute values for CO were not calculated by this method, but assuming these variables remain constant, SvO₂ is directly related to CO with an estimated coefficient of variation of ≤10% (11). There is evidence to suggest that during tilt-induced syncope, hyperventilation occurs in some patients (38). This may increase oxygen consumption and so falsely increase CO calculated from the Fick equation (39).

Table 1. Demographic data for patients

<table>
<thead>
<tr>
<th></th>
<th>Tilt-Tolerant Group (n = 8)</th>
<th>Tilt-Syncope Group (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, men/women</td>
<td>3/5</td>
<td>10/5</td>
</tr>
<tr>
<td>Age, yr</td>
<td>60 ± 5 (53–73)</td>
<td>58 ± 4 (20–77)</td>
</tr>
<tr>
<td>Tilt time, min</td>
<td>45</td>
<td>15.4 ± 2 (8–38)</td>
</tr>
<tr>
<td>Duration of symptoms, yr</td>
<td>6 (1–15)</td>
<td>9 (1.5–40)</td>
</tr>
<tr>
<td>Minor cardiac disorders</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Vasoactive medications</td>
<td>3*</td>
<td>2*</td>
</tr>
<tr>
<td>Pacemakers</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.8 ± 0.04</td>
<td>1.8 ± 0.05</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of patients. BSA, body surface area. Minor cardiac disorders refers to patients with asymptomatic coronary artery disease. Numbers in parentheses refer to age ranges (in yr). Vasoactive medications in tilt-tolerant patients included enalapril in two and metoprolol in one. *In both groups, one patient was taking a β-blocker and another was taking a β-blocker-vasodilator combination. In the tilt-syncope group, one patient was on fludrocortisone.

Cardiac output. All methods of assessing CO may be unreliable during hemodynamic instability so two independent techniques were used. It was important to measure CO at 1-min intervals during tilt as accurately as possible. We used bolus thermodilution and mixed venous O₂ saturation (SvO₂) because both methods allowed rapid and repeated measurements using the same catheter. Extensive experience with these techniques from intensive care workers has been reported in a variety of patients (6, 11) and both are used as the gold standard for the assessment of noninvasive methods (16, 21).

The two groups had similar mean values for age, body surface area, and duration of symptoms, but there was a higher male-to-female ratio in TS patients. Minor coronary artery disease was present in four patients in each group.

Figures 1 and 2 show the hemodynamic and sympathetic responses to tilt in both groups. At baseline and after 1 min of tilt there were no differences between groups. The respective baseline values for TT and TS
CO, SvO₂ and PDBP remained decreased at 2.4 \pm 0.2 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}, 62 \pm 2\% and 5 \pm 1 \text{ mmHg}, respectively, after 45 min (P = 0.004, P = 0.002, and P = 0.003). MSNA levels remained increased at 48 \pm 5 \text{ bursts/min} after 45 min (P = 0.002). In TS patients, MBP progressively decreased during the 7 min before syncope from 104 \pm 4 to 47 \pm 3 \text{ mmHg} (P = 0.005, P = 0.001) whereas HR was maintained above baseline until syncope, when it decreased to 59 \pm 5 \text{ beats/min} (P = 0.06). PDBP remained decreased between 6 \pm 1 and 4 \pm 1 \text{ mmHg} (P = 0.001). Despite progressive hypotension, MSNA decreased to 41 \pm 6 \text{ bursts/min} 7 \text{ min before syncope} (P = 0.3), and further to 11 \pm 2 \text{ bursts/min} at syncope (P = 0.001). Over this time, CO and SvO₂ decreased linearly from 2.7 \pm 0.2 to 2.0 \pm 0.2 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2} (P = 0.001) and from 67 \pm 2\% to 61 \pm 2\%.

In TT patients, MBP initially increased during the duration of tilt and MBP did not fall below baseline levels until 20 min of tilt. In TS patients, MSNA increased for the remainder of tilt, but decreased to baseline levels at least 7 min before syncope. Values for MBP, HR, and MSNA from 7 min before syncope are plotted retrogradely from 15-min tilt time. bpm, Beats per minute; bs/min, bursts per minute. *Differences from baseline in TS group; #differences from baseline in TT group.

patients were as follows: MBP, 111 \pm 3 and 117 \pm 4 \text{ mmHg}; HR, 75 \pm 4 and 66 \pm 3 \text{ beats/min}; CO, 3.2 \pm 2 and 3.3 \pm 0.2 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}; \text{SvO}₂, 73 \pm 1 and 76 \pm 1\%; PDBP, 15 \pm 2 and 16 \pm 1 \text{ mmHg}; MSNA, 31 \pm 4 and 35 \pm 4 \text{ bursts/min}.

In TT patients after 1 min of tilt, MBP and HR were stable at 111 \pm 5 \text{ mmHg and 81 \pm 3 beats/min}. In the TS group, MBP decreased to 112 \pm 4 \text{ mmHg} (P = 0.05), whereas HR increased 75 \pm 4 \text{ beats/min} (P = 0.001). In the respective groups, CO decreased to 2.5 \pm 0.3 (P = 0.001) and 2.7 \pm 0.1 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2} (P = 0.02), \text{SvO}₂ to 69 \pm 1\% (P = 0.001) and 68 \pm 2\% (P = 0.001), and PDBP to 8 \pm 2 (P = 0.01) and 7 \pm 1 \text{ mmHg} (P = 0.001), whereas MSNA increased to 44 \pm 5 (P = 0.001) and 48 \pm 4 \text{ bursts/min} (P = 0.002).

In TT patients during the remainder of tilt, MBP gradually decreased to 101 \pm 5 \text{ mmHg after 20 min} (P = 0.03) and to 92 \pm 6 \text{ mmHg after 45 min} (P = 0.01). CO, \text{SvO}₂ and PDBP remained decreased at 2.4 \pm 0.2 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}, 62 \pm 2\% and 5 \pm 1 \text{ mmHg}, respectively.
were demonstrated ($P = 0.001$). Mean regression slopes for CO and $SvO_2$ versus time were greater in the TS group: $-0.01$ (TT) versus $-0.1 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2} \cdot \text{min}^{-1}$ (TS) ($P = 0.001$) and $-0.1$ versus $-0.8\%\text{min}$ ($P = 0.001$), respectively. The range of $R$ values for individual time versus CO slopes was $0.14–0.88$ in TT ($5/8$, $P < 0.05$) and $0.11–0.94$ in TS ($14/15$, $P < 0.05$). During the 7 min before syncope, closer correlations for MSNA and TPR versus MBP were demonstrated ($R = 0.58$, $P = 0.001$, and $R = 0.56$, $P = 0.001$) compared with CO versus MBP ($R = 0.32$, $P = 0.001$) (Fig. 3).

**DISCUSSION**

Although CO fell in all subjects during the first minute of tilt, the patients who became hypotensive were characterized by a further accelerated decline in CO, which began some minutes before syncope. During the progressive hypotension before syncope, MBP was correlated more closely to MSNA and TPR than CO.

**CO in vasovagal syncope.** Surprisingly little is known about temporal relationships between CO, ventricular filling pressures, MBP, and MSNA during the minutes immediately preceding syncope. This is due to the following: 1) vasovagal reactions may be of rapid onset and CO is difficult to measure quickly, 2) in laboratory studies, syncopal reactions occur at different times from the onset of the stimulus, which makes collective analysis difficult, 3) the use of vasodilators during tilt tests to increase the likelihood of syncope may falsely affect CO, and 4) until recently, the emphasis has been on absolute rather than the rate of change in CO. Previous studies (4, 5, 13) using dye and thermodilution demonstrated a similar decrease in CO to what we measured ($-25\%$) but sampling intervals were long and control data were few. The significance of this finding was uncertain after the demonstration of a 30\% decrease during tilt and lower body suction in normotensive subjects (5, 24). Furthermore, Stevens et al. (31) showed no exaggerated decrease in CO during early tilt in subjects who developed syncope between 10 and 18 min later. Wahbha et al. (36) measured CO indirectly using the single-breath method at 5-min intervals and found that CO progressively decreased during tilt, irrespective of the outcome. Although CO decreased, it was uncertain when and how rapidly this occurred during syncope. Closer monitoring during the period immediately before syncope was required. In a recent study (18), beat-to-beat SV was measured during tilt using pressure wave analysis and a gradual decrease was observed in seven normal subjects. However, SV decay appeared to be accelerated in three subjects who became hypotensive or symptomatic. Echocardiographic estimation of SV during tilt also suggested a more rapid decay before syncope (12, 40). With the use of two independent methods, we have demonstrated that CO decreases more rapidly in those patients who develop syncope during tilt. CO decreased to similar levels irrespective of the response to tilt but over a much shorter time in the TS group. We conclude that the absolute decrease may not be as important as the linear rate of decrease. HR was relatively maintained before syncope; therefore, the decrease in CO was secondary to a decrease in SV. Patients who developed syncope failed to maintain CO despite similar left ventricular filling pressures and lower TPR. This would suggest that venous filling pressure was decreased in syncope patients. We are aware that PDBP is only an indirect indicator of left ventricular function and venous filling (26). Even right atrial pressure may be difficult to interpret as an index of venous return because of venous compliance, which allows large changes in central blood volume with relatively small pressure changes. There is no evidence for left ventricular systolic dysfunction before syncope in echocardiographic studies (12, 19, 29, 40). There is other evidence for impaired venoconstriction in vasovagal patients.

![Graphs A, B, and C](http://ajpheart.physiology.org/)

Fig. 3. A: correlation between MSNA and MBP during the 7 min before syncope ($R = 0.58$, $P = 0.001$). B: correlation between total peripheral resistance (TPR) and MBP during the 7 min before syncope ($R = 0.56$, $P = 0.001$). C: correlation between CO and MBP during the 7 min before syncope ($R = 0.32$, $P = 0.001$).
and this may make SV measurement inaccurate (37). The impedance waveform becomes harder to analyze during tilt (21). We have observed that the upstroke of the impedance may not always be a reliable measure of CO last 5 min before syncope (25). However, thoracic impedance in 25 tilted patients showed no change in SV during the return. Against this, a study using thoracic impedance rapidly before syncope because of impaired venous return. Therefore, we suspect that CO decreases more rapidly than orthostatic stress (3). The invasive techniques which can be triggered by a variety of stimuli other than orthostatic stress (3). The physiological equivalent of vasovagal syncope.

MBP, TPR, and MSNA. Although CO decreased more rapidly in syncope patients, MBP was more closely correlated to TPR and MSNA. It has been suggested that the dominant hypotensive mechanism in vasovagal syncope is withdrawal of MSNA and arterial vasodilation (7, 17, 28). We found that, although MSNA increased initially, it decreased back to baseline as early as 7 min before syncope, despite progressive hypotension. If this attenuated MSNA response affected only the arterial resistance vessels, CO would be expected to increase. As we have demonstrated, both CO and TPR decreased before syncope. We postulate that partial MSNA withdrawal mediates venodilatation resulting in decreased CO and mild hypotension early in the vasovagal reaction, whereas total MSNA withdrawal mediates arteriolar vasodilation, resulting in severe hypotension and syncope. Finally, cardiac sympathetic withdrawal occurs later, resulting in bradycardia. This implies that the venous circulation may be more sensitive to changes in MSNA than the arterial resistance vessels (2). It is important to remember that MSNA in skeletal muscle may be different to that in other venous capacitance beds and there may be other factors involved in venous return besides active compliance, including passive recoil, central blood volume, and even arterial blood pressure (1, 9, 10, 27). For example, during the first minute of tilt, when blood is rapidly pooled in the legs, resulting in decreased venous return and central blood volume, CO decreased, despite a rapid increase in MSNA.

Study limitations. Tilt-induced syncope may not be the physiological equivalent of vasovagal syncope, which can be triggered by a variety of stimuli other than orthostatic stress (3). The invasive techniques used in this study may have affected autonomic reflexes and precluded the use of normal controls. However, we were concerned more with the physiology of vasovagal reactions than comparisons with normal controls. To achieve satisfactory regression slopes, we were only able to study patients monitored for at least 8 min of tilt; therefore, we cannot comment on patients who develop syncope before this time or who are extremely sensitive to tilt (23). In three patients whose tilt reactions occurred after 20 min, it could be argued that our regression slopes were not representative of total tilt time. However, individual analysis of these patients showed uniform CO decay slopes throughout tilt. Finally, both methods of CO estimation can be criticized on several points. First, thermodilution and venous oxygen may overestimate CO when there is increased venous pooling and hyperventilation. Second, individual dilution measurements take at least 30 s, which limits duplication during tilt. Third, the total injected volume may have hemodynamic effects in some patients and Svo₂ may be misleading in patients with respiratory insufficiency (39). We emphasize that trends in CO were analyzed, not absolute values, and that most of the above factors would result in falsely decreasing the CO decay slopes.

We conclude that an important mechanism in vasovagal syncope may be an exaggerated rate of decline in CO secondary to venodilatation and possibly sympathetic withdrawal. This is consistent with laboratory studies showing that orthostatic syncope can be prevented by inflating an antigravity suit, or simply crossing the legs (34, 38), and the clinical maxim that vasovagal syncope is reversed most rapidly by lying the patient down and raising the legs.

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REFERENCES
