

Predisposition to Vasovagal Syncope in Subjects With Blood/Injury Phobia

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Background—Most subjects with blood/injury phobia experience syncope or presyncope as part of the phobic response. We tested the hypothesis that these subjects have a constitutional autonomic dysregulation that predisposes them to vasovagal syncope during head-up tilt.

Methods and Results—We studied 11 subjects (9 females, 2 males) who had a history of syncope or presyncope only in response to a blood or injury stimulus and 11 healthy matched controls (10 females, 1 male) without a history of syncope. Blood pressure (BP) and heart rate (HR) were measured during a 15-minute baseline period with subjects in the supine position and then during 45 minutes of head-up tilt to 70°. Measurements at rest did not differ between the blood phobic and control subjects. During tilt, 9 (82%) of the 11 blood phobic subjects experienced presyncope or syncope, leading to termination of the study after 22±17 minutes of tilt. Only 1 (9%) of the 11 control subjects experienced presyncope ($\chi^2=11.7$, $P=0.001$). Hemodynamic responses to tilt were consistent with a vasovagal mechanism in the blood phobic subjects, with simultaneous decreases in BP and HR during tilt. During tilt, systolic BP fell by 21±15 mm Hg ($P=0.001$), and HR fell by 22±25 bpm ($P=0.01$). By contrast, BP and HR were very stable in the control group.

Conclusions—Subjects with syncope related to blood/injury phobia have an underlying autonomic dysregulation predisposing them to neurally mediated syncope, even in the absence of any blood or injury stimulus. Fainting related to these stimuli may in large part be due to dysfunction in neural circulatory control, which may secondarily lead to the phobia because of repeated syncopal events. (*Circulation*. 2001;104:903-907.)

Key Words: syncope ■ nervous system, autonomic ■ blood pressure ■ heart rate

Blood/injury phobia is a common psychiatric disorder, with an estimated prevalence of 3% to 4% in the general population.^{1,2} It is classified as one of the specific phobias and is defined as a marked and persistent fear of clearly discernible, circumscribed objects or situations.³ The fear can be triggered by seeing blood, by sustaining an injury, or by receiving an injection or some other invasive medical procedure.³ In ≈80% of the cases,^{4,5} the phobic response is characterized by syncope or presyncope. This response is peculiar to blood phobia and is not a characteristic of other specific phobias. The mechanism underlying the syncope/presyncope associated with blood phobia is poorly understood.

There is a lack of agreement between the various different hypotheses directed at explaining the unique response patterns of subjects with blood phobia.⁵ Several studies suggest complex interactions between psychological and physiological mechanisms as a basis for the fainting, such as parasympathetic conditioning from fear reactions or an innate idiosyncratic physiological circuitry.^{6,7} Although it is believed

that vasovagal mechanisms may contribute to the syncope, this has not been well characterized. Furthermore, it is not known whether there is an underlying predisposition to vasovagal syncope, even in the absence of the blood phobia emotional response. In other words, do these individuals have an abnormality in autonomic circulatory control, with the blood phobia syncopal response being a manifestation of the susceptible substrate? Alternatively, do they faint only because of the profound nature of the emotional response to blood or injury, being otherwise resistant to fainting by any other provocation?

Tilt table testing is widely recognized as an effective technique for providing direct evidence of susceptibility to vasovagal syncope. Symptomatic hypotension and bradycardia during head-up tilt is consistent with neurally mediated vasovagal syncope.⁸ To our knowledge, there have been no previous studies of the response to head-up tilt in patients with blood phobic syncopal responses. We tested the hypothesis that subjects who experience fainting only in response to blood or injury stimuli have a constitutional autonomic

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TABLE 1. Demographic Characteristics and Baseline Hemodynamic Values in Blood Phobic and Control Subjects

	Blood Phobic Subjects (n=11)	Control Subjects (n=11)	P
Age, y	29±8	31±6	NS
Height, cm	166±11	164±8	NS
Weight, kg	65±15	63±17	NS
BMI, kg/m ²	24±5	23±6	NS
Sex (female/male), n	9/2	10/1	NS
Baseline			
SBP, mm Hg	108±9	108±7	NS
DBP, mm Hg	64±8	66±7	NS
HR, bpm	70±11	69±12	NS

BMI indicates body mass index; DBP, diastolic BP; and NS, not significant. Values are mean±SD.

substrate that predisposes them to vasovagal syncope during head-up tilt, even in the absence of a blood or injury stimulus. Therefore, we evaluated the responses to tilt in blood or injury phobic subjects compared with responses to tilt in control subjects.

Methods

Subjects

We studied a total of 22 subjects. Eleven subjects (9 females, 2 males) met the diagnostic criteria for blood/injury phobia according to the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-IV (nonpatient version for specific phobia).⁹ These 11 subjects also had a history of syncope or presyncope only in response to a blood or injury stimulus and did not have a history of syncope in association with other nonphobic situations. Eleven healthy volunteers (10 females, 1 male) without a history of syncope were studied as the control group. The blood phobic subjects and the normal control subjects were matched for age (29±8 versus 31±6 years [mean±SD]), height (166±11 versus 164±8 cm), weight (65±15 versus 63±17 kg), and body mass index (24±5 versus 23±6 kg/m²) (Table 1). All subjects were free of any known cardiovascular, neurological, or other chronic disease. None of the subjects was taking medication. The study was approved by the Institutional Human Subjects Review Committee. All subjects gave informed consent.

Protocol and Measurements

All studies were performed in the late morning or early afternoon in subjects after a 3-hour fast. No other dietary or fluid restrictions were imposed on the subjects. Body straps and a foot rest were used to provide support during the tilt and to minimize muscle contraction. Blood pressure (BP) was measured by use of a Dinamap automatic sphygmomanometer. Heart rate (HR) was monitored by ECG. Measurements were obtained during a 15-minute baseline period with the subjects in the supine position and then during 45 minutes

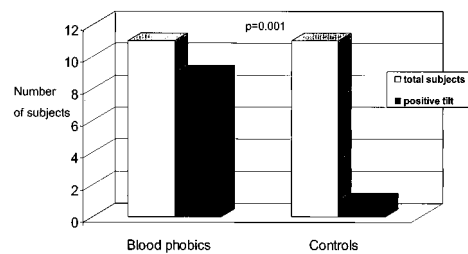


Figure 1. Prevalence of positive tilt tests (syncope or presyncope) in blood phobic and control subjects.

of head-up tilt to 70°, followed by a 15-minute period of recovery, again with subjects in the supine position. Subjects did not undergo any needle sticks or any other form of invasive or noxious measurements or instrumentation. Studies were discontinued early if syncope occurred. Furthermore, in the event of presyncopal symptoms (such as lightheadedness, blurred vision, or severe anxiety), all subjects were free to request discontinuation of the tilt test.

Data Analysis

Baseline data were the mean measurements during the 5 minutes preceding tilt. Mean data were calculated for the first 3 minutes of tilt (start tilt) and during the last minute of tilt (end tilt) before termination. For the symptomatic subjects, the test was terminated at 22±17 minutes after starting the tilt. Therefore, for the purposes of hemodynamic measurements in the asymptomatic subjects, the end tilt was also established as the 22nd minute of the tilt (the same as the average end-tilt timing in the symptomatic subjects), so that comparable durations of tilt could be used for both symptomatic and asymptomatic groups.

HR was calculated as the mean for each minute, except for the end-tilt period in the symptomatic subjects (syncopal and presyncopal), when it was calculated over ≈15 seconds at the end of the tilt.

Statistical Analysis

A χ^2 analysis was used to compare categorical variables with the Fisher exact test. The differences in the hemodynamic variables within the same group in different periods and the differences between groups in the same time period were assessed by paired or unpaired Student *t* test, where appropriate. Anthropometric data were expressed as mean±SD; the other data were expressed as mean±SE. Data were further analyzed as repeated-measures ANOVA, with time as within factor and group as between factor. Values were adjusted for sex, age, and body mass index. A value of $P<0.05$ was considered significant.

Results

Hemodynamic measurements at rest did not differ between the blood phobic subjects and the control subjects (Table 1).

During the tilt test, 9 (82%) of the 11 blood phobic subjects experienced presyncopal or syncopal symptoms, which led to termination of the study at the subjects' request. Only 1 (9%) of the 11 control subjects experienced presyncope. Ten of the

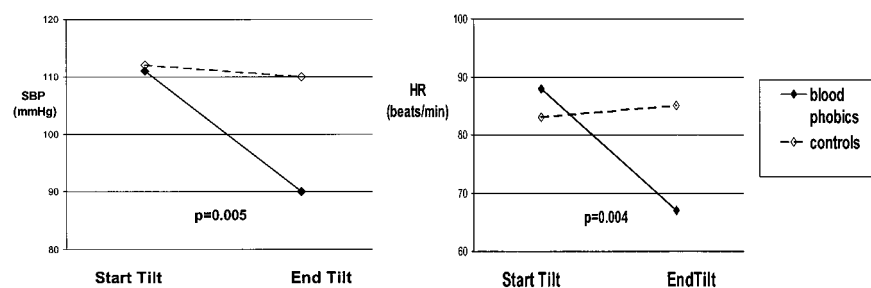


Figure 2. Changes in SBP and HR from start tilt to end tilt in blood phobic subjects and control subjects. In blood phobic subjects, SBP and HR decreased by the end of the tilt, whereas both these measures were stable in control subjects.

TABLE 2. Hemodynamic Comparisons in Blood Phobic and Control Subjects

	Tilt Studies					HR Studies				
	Blood Phobic Subjects (n=11)		Control Subjects (n=11)		ANOVA Trend, P	Blood Phobic Subjects		Control Subjects		ANOVA Trend, P
	Start Tilt	End Tilt	Start Tilt	End Tilt		Baseline	Max HR	Baseline	Max HR	
SBP, mm Hg	111±12	90±20*	112±9	110±15§	0.005	108±9	108±12	108±7	115±16	NS
DBP, mm Hg	70±7	61±15†	74±7	65±14†	NS	64±8	61±11	66±7	68±11	NS
MBP, mm Hg	83±8	70±16‡	87±7	80±14	NS	79±8	77±10	80±6	84±11	NS
HR, bpm	88±13	67±25‡	83±14	85±10§	0.004	70±11	103±14*	69±12	94±13*	0.05

Max indicates maximum; DBP, diastolic BP; and MBP, mean BP. Values are mean±SD.

*P=0.005, †P<0.05, and ‡P=0.01 vs start-tilt or baseline measurements; §P<0.05 for blood phobic vs control subjects.

11 control subjects completed the 45 minutes of tilt without symptoms or significant hemodynamic changes ($\chi^2=11.7$, $P=0.001$) (Figure 1). Tilt duration averaged 43 ± 7 minutes in the control subjects and 22 ± 17 minutes in the blood phobic subjects ($P=0.001$).

In comparing the peak HR and BP levels during tilt, the blood phobic subjects had an enhanced HR response and an attenuated BP response compared with respective responses in control subjects. Compared with the baseline period, during tilt, HR increased more in the blood phobic subjects than in the control subjects (by 33 ± 12 versus 25 ± 10 bpm, respectively; $F=4.30$, $P=0.05$). In contrast, the blood phobic subjects, compared with the control subjects, had a significantly blunted increase in systolic BP (SBP; 11 ± 6 versus 17 ± 7 mm Hg, respectively; $F=7.12$, $P=0.016$).

Comparing the start-tilt and end-tilt periods, SBP and HR dropped significantly in the blood phobic group. SBP fell by 21 ± 15 mm Hg ($P=0.001$), and HR fell by 22 ± 25 bpm ($P=0.01$) (Figures 2, 3, and 4; Table 2). In contrast SBP and HR were very stable in the control group: comparing start tilt with end tilt in control subjects, SBP fell by 2 ± 13 mm Hg ($P=NS$), and HR increased by 2 ± 10 bpm ($P=NS$) (Figure 2, Table 2).

SBP and HR were also significantly different between blood phobic subjects and control subjects at end tilt (SBP 90 ± 20 versus 110 ± 15 mm Hg, respectively [$P=0.02$]; HR 67 ± 25 versus 85 ± 10 bpm, respectively [$P=0.03$]).

Thus, even though baseline hemodynamic measures were not significantly different, the difference in response during tilt and at the end of tilt in blood phobic subjects versus

control subjects was significant for both HR and BP in the multivariate analysis of ANOVA (Figure 2, Table 2).

Discussion

The novel finding in the present study is that subjects who experience fainting episodes only in association with a blood or injury stimulus demonstrate a clear and striking predisposition to vasovagal syncope even during head-up tilt. This syncopal response occurs in the absence of the blood or injury stimulus. Thus, these subjects have an autonomic substrate that predisposes them to vasovagal syncope, and fainting during the blood phobic response is a manifestation of this underlying circulatory dysfunction.

Blood/injury phobia is very different from the other categories of the specific phobias. It is highly familial^{3,6,10} and is usually not associated with other psychiatric disorders, such as agoraphobia, social phobia, anxiety, panic, or depression. Furthermore, the association with fainting is not common to the other phobias.^{6,10} Previous studies of the syncopal event during a phobic stimulus have described a biphasic cardiovascular response. When first confronted with the phobic stimulus, these individuals exhibit increased BP and HR. This response is common to all the specific phobias. Soon after, there is bradycardia and hypotension, with consequent reduced blood supply to the brain, which leads to syncope.^{4,5,11,12} Thus, there is a precedent to suggest that fainting during blood exposure is vasovagally mediated.

Humans have a natural fear of blood and injury. Discomfort, nausea, HR changes, lightheadedness, and feeling faint are not unusual in the normal population when they are confronted with these situations.⁶ Typical examples encoun-

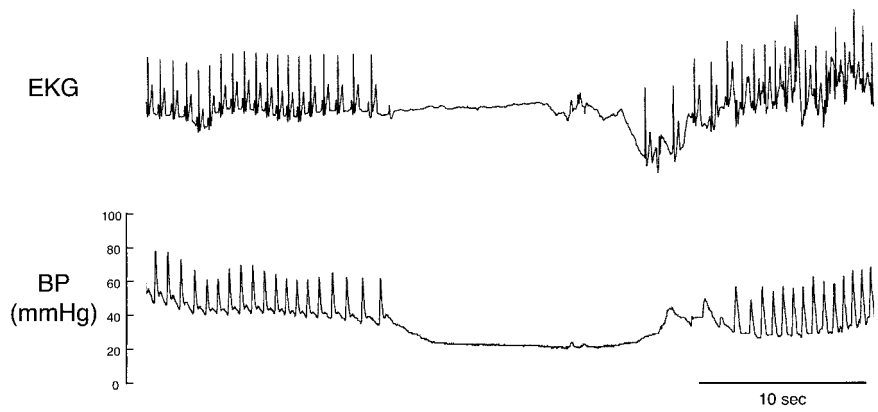


Figure 3. Example of predominant cardioinhibitory syncope occurring in a blood phobic subject after only 12 minutes of head-up tilt.

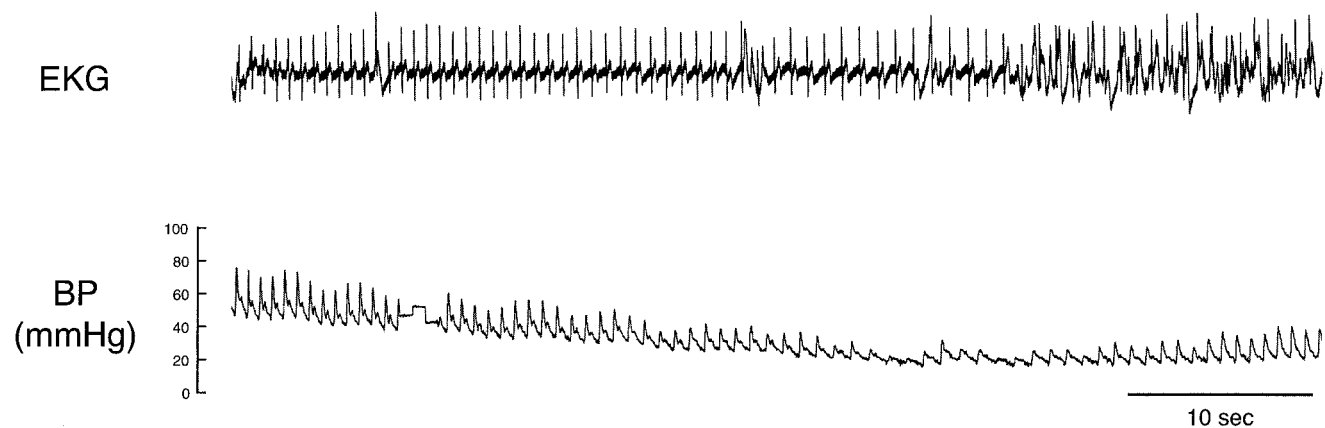


Figure 4. Example of a predominant vasodepressor syncope occurring in a blood phobic subject after only 10 minutes of head-up tilt. Marked hypotension is evident on beat-to-beat BP monitoring. Although profound bradycardia does not occur, the HR is nevertheless inappropriately slow for the severity of the hypotension.

tered in the clinical setting include the fainting of medical students at the sight of blood or autopsies. Vasovagal syncope is also widely described among blood donors (an incidence of 1% to 15%),^{4,13,14} especially during their first experience, and also among dental patients. Bradycardia has also been reported in normal subjects and in medical audiences on viewing violent films.¹⁵ The origins of these reactions have been addressed in an evolutionary context.^{16,17} Human fainting in response to blood/injury stimuli may be a trait evolved from the tonic immobility or “playing dead” observed in many animal species when confronted with specific fears. During this reaction, bradycardia and vasodilatation have been observed.^{16–18} This “emotional fainting” could be a physiological activation of a specific evolutionary reflex rather than an acquired cultural phenomenon.⁶

What is it that differentiates the blood phobic subjects from the normal population, in whom the fear of blood or injury also occurs? In other words, why should a natural fear evolve into a phobia? It has been hypothesized that fainting in association with the fear accompanying blood or injury exposure may occur in people who easily faint and that these subjects become more afraid of fainting and will avoid the blood or injury situation so as to avoid fainting.⁶ The strong familial component and the absence of other psychiatric conditions in these patients, and the usual absence of blood or injury phobia in patients with other psychiatric pathologies, further support the concept that a specific autonomic pattern of response, as a constitutional individual characteristic, is the basis for this fainting. Our results are consistent with this hypothesis, showing that compared with normal subjects, subjects with blood or injury phobia have an abnormal hemodynamic response during head-up tilt and are strikingly prone to vasovagal reactions. Fainting related to blood or injury stimuli may not be primarily due to a psychiatric condition but rather due to dysfunction in the autonomic nervous system, which may secondarily lead to the phobia because of repeated syncopal events.

Our data showing susceptibility to vasovagal syncope in patients with syncope accompanying blood phobia suggest that in addition to behavioral therapy, these individuals may benefit from pharmacological interventions that are effective

in the treatment of vasovagal syncope. We speculate that pharmacologically induced attenuation of syncopal episodes may even contribute to amelioration of the phobia itself.

Our data further imply that blood phobic subjects would be predisposed to vasovagal syncope in normal life and in other nonphobic situations. We are not aware that the natural history of the blood phobic syncope response has been evaluated to address this question. Monitoring any possible changes in the clinical history of these subjects, such as an increased tendency to develop neurally mediated syncope, could help in the general understanding of syncope mechanisms and contribute to understanding the continuum of disorders of orthostatic tolerance.^{19,20}

Limitations of the present study include the following: First, we permitted subjects to interrupt the tilt test as their symptoms developed. This approach, which was followed to minimize any anxiety component, mitigated the development of overt syncope in some of our subjects. If the test had been continued further, it is clear that the hypotension and bradycardia evident in the blood phobic subjects would have been even more marked than is apparent in the results. Second, the absence of direct intraneural recordings of sympathetic nerve traffic further limits our ability to define, in our subjects, the presyncopal autonomic and hemodynamic profile, as has been described in other studies of vasovagal syncope.¹⁹ Third, our study subjects were mainly females. We cannot exclude sex-related differences in the responses that we observed.

In summary, we have shown that compared with normal control subjects, subjects with syncopal events related only to blood or injury phobia have a markedly higher prevalence of vasovagal responses to head-up tilt. Thus, these subjects have an abnormality in autonomic circulatory control that predisposes them to neurally mediated syncope, even in the absence of a blood or injury stimulus.

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