Published in final edited form as:

Heart Rhythm. 2018 June ; 15(6): 921–929. doi:10.1016/j.hrthm.2017.12.013.

Pathophysiology of the vasovagal response

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Abstract

In part I of this study, we found that the classical studies on vasovagal syncope, conducted in fit young subjects, overstated vasodilatation as the dominant hypotensive mechanism. Since 1980, blood pressure and cardiac output have been measured continuously using noninvasive methods during tilt, mainly in patients with recurrent syncope, including women and the elderly. This has allowed us to analyze in more detail the complex sequence of hemodynamic changes leading up to syncope in the laboratory. All tilt-sensitive patients appear to progress through 4 phases: (1) early stabilization, (2) circulatory instability, (3) terminal hypotension, and (4) recovery. The physiology responsible for each phase is discussed. Although the order of phases is consistent, the time spent in each phase may vary. In teenagers and young adults, progressive hypotension during phases 2 and 3 can be driven by vasodilatation or falling cardiac output. The fall in cardiac output is secondary to a progressive decrease in stroke volume because blood is pooled in the splanchnic veins. In adults a fall in cardiac output is the dominant hypotensive mechanism because systemic vascular resistance always remains above baseline levels.

Keywords

Neurocardiogenic syncope; Sympathetic nervous system; Tilt test; Vasovagal syncope; Venous capacitance

Introduction

The classical literature (1920–1980) on the mechanisms underlying vasovagal syncope was recently reviewed in *HeartRhythm*.¹ We concluded that interpretation of data from early

reports was severely hampered by the inability to record rapid hemodynamic changes and as a result vasodilatation was overstated as the dominant hypotensive mechanism.

After 1980, techniques became available to monitor rapid hemodynamic changes continuously and noninvasively. Wesseling and coworkers implemented the volume clamp method of Penaz in the Finapres device.² This allowed continuous noninvasive measurement of finger arterial pressure. The Modelflow algorithm has subsequently allowed the computation of stroke volume (SV) from the area under the systolic pulse curve and thereby calculation of cardiac output (CO) and systemic vascular resistance (SVR). These extraordinary scientific developments enabled clinicians and researchers to study *noninvasively* the *beat-to-beat* hemodynamics of laboratory-induced vasovagal syncope. Over the same period, impedance measurements have demonstrated directional changes in segmental blood volume during tilt and microneurography has allowed us to monitor efferent muscle vasoconstrictor sympathetic activity (MSNA).^{3,4} As a result of this approach, researchers have been able to “sequence” the hemodynamic changes during orthostasis in much greater detail, and so relationships between variables (eg, mean arterial pressure [MAP] and CO) have become clearer. We have also studied carefully how each variable changes, *with time*, as blood pressure (BP) falls before syncope. In this review, we propose that the combined results of tilt tests undertaken over the past 35 years suggest a universal pattern of hemodynamic change leading to tilt-induced syncope. We have called this pattern “the 4 phases of syncope,” and we attempt to provide a physiological explanation for each phase.

The 4 phases of the vasovagal response

Careful analysis of continuous BP recordings (and other derived variables) during orthostatic stress allowed us to divide the sequence of hemodynamic events leading to vasovagal syncope into 4 phases: phase 1: early stabilization; phase 2: circulatory instability (early presyncope); phase 3: terminal hypotension (late presyncope) and syncope; phase 4: recovery. Figure 1 provides an example of a normal subject progressing through the 4 phases during a 60° head-up tilt test. Normal subjects are relatively syncope resistant, and in this example, lower body negative pressure (LBNP) was applied during tilt in order to decrease central blood volume (CBV) and induce syncope in a controlled and reproducible way.⁵

Analysis of continuous electrocardiographic and BP tracings indicates that the timing and duration of the 4 phases differ between individuals. We have observed that the length of time spent in phases 1 and 2 is variable.^{5–12} In some elderly patients, phase 2 may be prolonged.¹³ In young patients, phase 2 may be “cut short” by the rapid onset of bradycardia or asystole.¹⁴ Nearly all patients and subjects normalize their BP during the first minute of recovery. On the basis of the authors’ inspections of individual patients’ tilt data, we suggest that despite the variations mentioned above, for the vast majority the *order* of the phases is consistent and generally accepted by researchers despite varying terminologies.^{5–12,15,16} A similar sequence has also been demonstrated during syncope induced by venesection or LBNP in humans^{1,5} and hemorrhage in animals.¹⁷

Phase 1: Early phase of stabilization during tilt/standing

A change to the upright posture induces a rapid and large gravitational shift of approximately 500–1000 mL of the CBV from the thorax into vessels below the diaphragm (Figure 2). The bulk of venous pooling occurs within the first 10 seconds and is almost complete within 2–3 minutes, although transcapillary filtration of fluid may further decrease the total blood volume (Figure 2).³

As CBV falls, CO is decreased by 10%–20%, because the increase in heart rate (HR) does not compensate for the fall in SV.¹⁸ At the same time, the change in systolic BP (SBP) is variable but diastolic BP increases, and so MAP is maintained. The increase in diastolic BP reflects the rapid increase in SVR over about 10 seconds secondary to baroreflex-mediated vasoconstriction in both skeletal muscle and splanchnic arterioles.^{19–21} This compensates for the fall in CO. Direct recordings from splanchnic nerves have confirmed this is under sympathetic control in conscious mammals.¹⁸ Several human studies have demonstrated vasoconstriction in skeletal muscle and approximate doubling of MSNA levels during phase 1 irrespective of tilt outcome.^{7–12}

In addition to increasing SVR, splanchnic vasoconstriction decreases filling of the downstream capacitance venules, which contain approximately 20% of blood volume.^{22–24} The decrease in transmural pressure allows them to retract, directing more blood back to the heart by passive venous recoil.²⁵ Although only demonstrated in anesthetized animals, this is thought to be the most important mechanism limiting the initial fall in CO during phase 1. In animal models, active venoconstriction, mediated by sympathetic nerves under baroreflex control, further limits splanchnic capacitance.^{22–25} Human and animal studies have demonstrated that innervated splanchnic venules contract simultaneously with their (upstream) arterioles in response to similar levels of sympathetic stimulation.^{26,27} By contrast, in mammalian skeletal muscle, sympathetic venous innervation is sparse and baroreflex-mediated venoconstriction is minimal.^{22–24} Venous filling here is totally controlled by arterial vasoconstriction, passive venous recoil, and, most importantly, the muscle pump.^{27,28}

Phase 2: Circulatory instability

After a variable period of stable adjustment to tilt, all tilt-positive adults enter into phase 2 characterized by a fall in SBP (~20 mm Hg) and CO and onset of increased BP variability (see Figures 1, 3, and 4).^{6–12,29} Adult studies have demonstrated that the progressive increase in SVR is mediated by sustained baroreflex-mediated vasoconstriction of splanchnic and skeletal muscle arterioles.^{19–21} Splanchnic capacitance also remains restricted by mechanisms already described.^{22–24}

The increase in BP variability (seen in Figures 1, 3, and 4) consists of regular oscillations at a frequency of 0.1 Hz, known as Mayer waves.²⁹ They have been quantified using spectral analysis and reflect bursts of MSNA firing at the same frequency.⁹ They are an indication of increased baroreflex-modulated vasoconstrictor activity in response to decreased CBV.⁹ Later in phase 2, there is a gradual fall in cerebral blood flow velocity, proportionate to a minor fall in MAP.³⁰ Some studies have reported limited cerebrovascular vasoconstriction as

early as 2 minutes before syncope (secondary to increased ventilation).³¹ However, most studies demonstrate that cerebral blood flow velocity is closely related to MAP throughout phase 2.³⁰ Consistent with this, a modest early fall in cerebral perfusion has also been demonstrated using near-infrared spectroscopy, a noninvasive measure of cerebral oxygenation.³²

Phase 3: Terminal hypotension and syncope

After another variable time interval (1–5 minutes), the patient enters phase 3 or “terminal hypotension,” marked by a rapid fall in SBP of about 50 mm Hg over the final 30–60 seconds before syncope. In addition, MAP, BP variability, and HR decrease.^{6–12} This coincides with symptoms of autonomic activation (eg, warmth and nausea) and cerebral hypoperfusion (eg, loss of concentration and vision). When absolute SBP falls below 60 mm Hg at heart level, syncope occurs.³³

At the start of this phase, continuous beat-to-beat CO measurement is required to assess the mechanism for the accelerated fall in BP, and this has only been achieved in noninvasive studies. From the tilt study literature, we selected only those studies that detailed the course of BP, HR, SV, CO, and SVR continuously using noninvasive pulse-wave analysis during syncope (n = 9).^{6,10,16,34–39} Collective analysis of the studies needs to take into account patient selection and study design; therefore, we have quoted ranges of hemodynamic data only. In adults, HR decreased at syncope but only after a pronounced fall in BP from baseline levels, consistent with other studies.^{6–12,40} Although the collective data suggest that bradycardia is preceded by a rapid fall in BP, this may be misleading. Some individuals may become asystolic early in phase 3 and merit consideration for pacemaker therapy.¹⁴ This will be discussed in our next article.

Late phase 3 was marked by a fall in CO (35%–48% from baseline) and a consistent increase in SVR (12%–44% from baseline). Therefore, in adults the fall in CO was the dominant hypotensive mechanism, because SVR always remained above baseline levels.

The data support our previous conclusion that in the classical Barcroft papers, major vasodilatation (~40%) was overstated as the dominant hypotensive mechanism of vasovagal syncope.¹ We emphasize that this is not the case for many younger patients (see later and Figures 4 and 5).^{10,16,34–37}

Phase 4: Recovery

Tilting the patient quickly back to the horizontal position results in a rapid increase in MAP and symptomatic improvement (phase 4, “recovery”).

In nearly all patients, BP recovers within 30 seconds of tilt back to the horizontal position. Recovery may even include transient “overshoot” of BP (see Figures 1 and 3).⁴¹ The mechanism for the rapid increase in BP is primarily cardiac. As the subject becomes supine, there is a rapid transfusion of blood from capacitance vessels below the diaphragm back into the central thoracic veins and right heart. Increased venous return results in rapid recovery of preload, SV, and CO, secondary to the Frank-Starling mechanism.⁴² Recovery of MSNA and

HR toward baseline levels is most likely secondary to the rapid reversal of phase 3, namely, restored brainstem perfusion and baroreflex function (see later and Figure 3).

Not all patients recover their BP rapidly, and some experience “prolonged postfaint hypotension” (PPFH). They remain pale, unwell, bradycardic (HR <60 beats/min), and hypotensive (SBP <80 mm Hg) for up to 5 minutes or even longer with gastrointestinal symptoms.⁴³ Pronounced bradycardia in combination with abdominal discomfort and nausea is consistent with increased vagal outflow from the nucleus ambiguus to the heart and from the dorsal nucleus to the stomach. Surprisingly, the mechanism for PPFH has been demonstrated (by continuous MSNA and left ventricular dP/dt recordings) to be delayed recovery of SV and CO because of decreased cardiac contractility, not vasodilatation mediated by vascular sympathetic withdrawal.^{43,44} These effects would not be expected from a surge of epinephrine or some other vasodilatory hormone. Decreased cardiac contractility has been attributed to a combination of excess vagal activity and decreased sympathetic neural outflow to the heart.⁴⁵ During PPFH, the arterial baroreflex is unloaded and the persistent inappropriately low HR and BP are consistent with sustained suppression of excitatory mechanisms. These patients may be unable to activate the central sympathetic pathways in order to overcome exaggerated vagal activity. This concept is supported by the observation that all the time-honored remedies for ameliorating a severe faint (including dynamic exercise, slapping the face, splashing the face with cold water, and administering smelling salts) are all stimulatory in nature.⁴⁶

Age factor: Children and young adults

As stated earlier, although the sequences of the phases are consistent, there is major variation between individuals in the length of the phases and the hemodynamic mechanisms responsible for progressive hypotension. The most important factor responsible for this is age. In children, teenagers, and some young adults, phase 1 looks quite different from what is seen in most adults.^{10,16,34–37} There is a pronounced postural tachycardia and an attenuated increase in SVR during the first minute of orthostasis. In phase 2, this pattern persists: HR is higher, and vasoconstriction remains attenuated (Figure 4).

The exaggerated increase in HR is baroreflex-mediated by cardiovagal withdrawal in response to the progressive decrease in CBV and transitory loss of vasoconstrictor tone. Presumably this reflects higher resting vagal tone in the young. With respect to loss of vasoconstrictor tone, MSNA levels are not clearly decreased in less vasoconstricted patients.¹⁰ Other possible mechanisms include active vasodilatation, increased epinephrine levels, or exaggerated nitric oxide activity.^{12,47–50} During phase 3, HR remains higher in the younger group (86–110 beats/min vs 73–93 beats/min in adults)^{6,16,34–37} and the fall in CO from baseline is much less than that in adults (13%–30% vs 35%–48%). Therefore, SVR is relatively lower in younger patients (28% to 115% vs 112% to 144% in adults). However, as stated earlier, collective analysis may hide variant hemodynamic profiles, and with this in mind researchers have divided their younger patients into groups on the basis of CO and SVR changes during presyncope.^{10,16,36} For example, 3 hemodynamic profiles were described by Stewart et al¹⁶ (Figure 5), showing marked hemodynamic differences during circulatory instability and terminal hypotension.

Possible mechanisms for phase 3: Neuroendocrine and baroreflex dysfunction

There is uncertainty about the mechanism for vasodilatation (or loss of vasoconstrictor tone) during phase 3. In humans, limited vasodilatation has been demonstrated in the upper limbs *during* syncope,^{11,12} but to date, not in the lower limbs or the splanchnic circulation.^{19–21,51} Some withdrawal of MSNA has been demonstrated in the lower limbs, but not in all studies.^{7–11,52} Loss of splanchnic sympathetic activity during severe hypotension has only been demonstrated in conscious animal models.¹⁷ By contrast, adrenal sympathetic activity is rapidly increased and epinephrine levels surge up to 10 times their baseline levels at syncope.^{12,49,53} Epinephrine is usually a powerful vasoconstrictor of splanchnic vessels (via alpha receptors), but at high levels it also has vasodilatory effects on skeletal muscle splanchnic arterioles and hepatic veins (via beta receptors).⁵⁴ The surge in epinephrine levels during phase 3 is higher in younger patients and may explain why vasodilatory responses are more common in this age group.^{50,53} In adults, it is uncertain if this surge is a cause or an effect of terminal hypotension.^{12,54} Transient baroreflex impairment is another possible hypotensive mechanism.^{55–57} Cardiovascular reflex control of HR starts to fail first during phase 2 and gets weaker as SBP declines and ventilation increases.^{55,56} The neural (central) limb of the sympathetic baroreflex is affected at the end of phase 2, resulting in loss of Mayer waves.^{9,29} The peripheral limb (the effect of MSNA bursts on vascular tone) is lost at syncope.⁵⁷ This is the pattern of progressive baroreflex impairment as MAP, cerebral blood flow, and brainstem perfusion fall. The tendency of younger adults to become asystolic during phase 3 is likely secondary to vagal stimulation via nonbaroreflex pathways (eg, the Bezold-Jarisch reflex),^{14,58} Alternatively, vagal tone may be “unleashed” during progressive baroreflex impairment (described above) when cerebral MAP falls below critical closing pressure and autoregulation is lost.^{30,31} This would explain why tilt studies have demonstrated that syncope consistently occurs only after SBP falls below the threshold level (60 mm Hg). When systemic BP falls to this level, cerebral blood flow is decreased by approximately 30% and is reliably reversed by tilting back to the horizontal level.^{5,30,33}

Conclusion

1. Laboratory studies performed since 1980 using noninvasive continuous monitoring technology have included normal subjects and patients over a much wider age range than did the classical studies. Detailed vasovagal responses to head-up tilt, standing, and LBNP have included continuous monitoring of BP, HR, sympathetic vasoconstrictor activity, cerebral blood flow, and regional blood volumes.
2. The use of continuous monitoring has allowed us to divide vasovagal syncope into 4 phases that are present in all subjects, although there is huge variation between individuals with regard to the duration of each phase and the mechanisms underlying circulatory adjustments.
3. Collective analysis of patients with syncope irrespective of age may be misleading. Forcing data into time intervals and fiducial markers may hide

individuals who do not fit the overall pattern. This is particularly important in phase 3 when considering the delay between the rapid fall in BP and the onset of bradycardia.

4. Vasovagal syncope is a complex reaction, and although much of the variation between individuals may relate to study methods, age is most important. For example, during phase 2, CO falls in nearly all adult patients whereas isolated loss of vasoconstrictor tone occurs only in younger patients.
5. The mechanism of circulatory instability in younger patients is variable: for example, some have splanchnic shunting with increased CO while others have splanchnic pooling with decreased CO. The second mechanism is thought to apply to all adults but has not been fully demonstrated.
6. In all patients, the mechanism for terminal hypotension is a fall in CO, with or without a fall in SVR.
7. The mechanism for recovery is more likely the effect of increased venous return on stroke volume (Frank-Starling relationship) than the reversal of a cardioinhibitory reflex.

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Figure 1.

The 4 phases of the vasovagal response. Vasovagal response monitored in a 48-year-old healthy man (author W.W.) without a fainting history using Finapres technology and thoracic impedance (TI). Fainting was induced by a head-up tilt with -20 mm Hg followed by -40 mm Hg of lower body negative pressure (LBNP), enabling a large shift of blood to the lower body from the thorax in a controlled and reproducible way. Four phases can be distinguished: Phase 1: Early stabilization—The adjustments from supine to head-up tilt at 0–2 minutes show a rapid increase in TI, indicating a decrease in central blood volume

(CBV), which results in decreases in stroke volume (SV) and cardiac output (CO) despite an increase in heart rate (HR). Although blood pressure (BP) becomes more variable, mean blood pressure (MAP) is maintained by an increase in systemic vascular resistance (SVR). This mechanism maintains MAP for over 20 minutes despite a progressive fall in CO. Phase 2: Circulatory instability (or early presyncope)—At 28–32 minutes, the addition of –20 mm Hg of LBNP to head-up tilt causes further decreases in CBV and CO. Systolic BP and pulse pressure decrease as BP variability and HR increase further. MAP is maintained by a further increase in SVR. Phase 3: Terminal hypotension (or late presyncope)—At 38–40 minutes, increasing LBNP further to –40 mm Hg induces a fall in HR and CO. Although SVR decreases, it remains far above supine control, BP variability virtually disappears (see below), and a classical vasovagal faint occurs. Phase 4: Recovery—After tilt-down and cessation of LBNP, there is a rapid recovery of BP to baseline levels followed by an overshoot. From Wieling, unpublished data.

Figure 2.

Impedance changes during head-up tilt. **Upper panels:** Representative changes in thoracic, splanchnic, pelvic, and leg impedances induced by head-up tilt (dotted lines) in a healthy adolescent. **Lower panels:** Impedance changes correspond to calculated fractional changes in regional blood volumes. Not all impedance scales are the same. Thoracic impedance increases (central blood volume decreases) while other segmental impedances decrease (regional blood volumes increase) with tilt up and revert toward control when tilted down. Revised from Stewart et al.³

Figure 3.

A: Blood pressure (BP), muscle vasoconstrictor sympathetic activity (MSNA), and cardiac output (CO) measurements during the 4 phases of syncope in a tilted patient. During phase 1, BP is maintained by a rapid increase in MSNA and vasoconstriction. CO falls despite a minor increase in heart rate (HR). During phase 2, there is a progressive gradual fall in SBP and CO despite further increases in HR and MSNA. During the last minute of phase 3, BP falls more rapidly whereas slowing of HR and MSNA burst frequency occur only seconds before syncope. During phase 4 (recovery), MSNA is maintained despite a rapid increase in

BP as the patient is tilted back to the horizontal. From Jardine, unpublished data. **B:** Mayer waves during head-up tilt. Magnified 45-second section from phase 1. Note the Mayer waves (marked with asterisks) in the BP tracing. They have a frequency of ~0.1 Hz and are synchronized to surges in MSNA.

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Figure 4.

Loss of vasoconstrictor tone during phases 1 and 2 in a young adult. From top to bottom: arterial blood pressure, (BP), mean arterial pressure (MAP), thoracic impedance (TI), heart rate (HR), stroke volume (SV), cardiac output (CO) estimated from the Modelflow algorithm, and systemic vascular resistance (SVR) estimated from MAP/CO are shown in an 18-year-old patient with vasovagal syncope during a 70° upright tilt test. There is a modest increase in TI associated with a decrease in SV and an increase in HR. SVR is initially similar to baseline, which is somewhat unusual, and then falls steadily throughout orthostasis in parallel with MAP and inversely to CO. The spike of SVR at the BP minimum reflects a precipitous fall in CO as fainting supervenes. From Stewart, unpublished data.

Figure 5.

Different hemodynamic patterns in tilt-induced syncope. Graphs showing heart rate (HR), mean arterial pressure (MAP), cardiac output (CO), and systemic vascular resistance (SVR) for representative subjects during head-up tilt table testing. From top to bottom: HR, MAP, CO, and SVR for healthy control subjects (Control, black filled circles), patients with vasovagal syncope (VVS) who have a decrease in CO (gray squares) but no decrease in SVR, patients with VVS syncope who have a decrease in CO and SVR during tilt designated (VVS-↓CO and ↓SVR, gray triangles), and patients with VVS syncope who have a decrease

in SVR during tilt but no decrease in CO designated (VVS-↓SVR, gray diamonds). There is an increase in HR rate with orthostasis in all subjects, which is largest in those with VVS-↓CO. MAP first gradually declines, followed by rapid hypotension and bradycardia in all patients with VVS. Patients with VVS-↓CO and YSVR have a decrease in CO and an initial increase in SVR, which then decreases for the remainder of tilt. CO in patients with VVS-↓SVR trends above baseline, while SVR declines monotonically. At the time of faint, all patients with VVS experienced hypotension rapidly followed by bradycardia while SVR and CO decreased. Revised from Stewart et al.¹⁶

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