When the heart is stopped for good: hypotension-bradycardia paradox revisited

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Prakash, E. S., and Madanmohan. When the heart is stopped for good: hypotension-bradycardia paradox revisited. Adv Physiol Educ 29: 15–20, 2005; doi:10.1152/advan.00027.2004.—In vasovagal syncope, occurrence of bradycardia/asystole in the wake of hypotension has often been considered paradoxical. The major objective of this teaching module is to critically examine the pathophysiological mechanism and significance of the hypotension-bradycardia paradox unique to this condition. We narrate here how we discussed the pathophysiology of vasovagal syncope in a large classroom session attended by 275 doctors and medical students. A case study was used to describe the typical clinical presentation of vasovagal syncope. The pathophysiological mechanisms involved were then discussed systematically using a series of open-ended questions. We made it clear 1) that the occurrence of bradycardia or asystole in the face of acute severe hypotension is a mechanism to possibly minimize further blood loss, prevent myocardial damage, and increase ventricular filling; and 2) that fainting, which occurs as a consequence of this, is a homeostatic mechanism that serves to restore venous return and cerebral blood flow before blood pressure is normalized by neural reflex mechanisms. Eighty-four percent of participants reported that they were satisfied with the session. The information contained herein could be used to explain to any suitable audience the neural regulation of blood pressure in the face of acute severe hypotension and the pathophysiology of vasovagal syncope.

asystole; case study; vasovagal syncope

VASOVAGAL SYNCOPE, a neurally mediated syncopal syndrome, is the commonest cause of recurrent unexplained syncope (24). Sudden and transient decline in cerebral perfusion in this condition is due to hypotension caused by abrupt vasodilatation, often accompanied by a vagally mediated reflex bradycardia (5, 26). Not surprisingly, the bradycardia that occurs in the wake of hypotension has been viewed as paradoxical by researchers in this field (2, 5, 20). Sometimes, the bradycardia is intense enough to result in asystole, but when recumbency is achieved, blood pressure (BP) and heart rate (HR) normalize, and consciousness is quickly regained with no residual neurological deficit. Thus the syncope is for the most part benign and has an excellent prognosis when there is no underlying evidence of structural heart disease (2, 24). The pathophysiological mechanism and significance of the hypotension-bradycardia paradox is the major theme of this paper. We describe here how we dealt with this in a large classroom session on cardiovascular physiology.

The session narrated here occurred during a cardiovascular physiology class. The participants (n = 275) included 215 doctors who had obtained a Bachelor of Medicine and Bachelor of Surgery degree within the last 5 yr and 60 undergraduate medical students who were within 6 mo of obtaining the same degree. All participants were training for entrance examinations to enter graduate programs in various specialties e.g., medicine, surgery, pediatrics, radiology, or anesthesiology. All had taken their undergraduate physiology course in medical college 5–10 yr ago. Among the 215 doctors, 105 had clinical medical practice exceeding 4 h per day. The classes, which over 250 students attend in preparation for these examinations, involve a systematic, topic-wise discussion of a series of multiple-choice questions in various basic and clinical medical sciences. Participants generally prefer a point-for-point explanation for each question, and they try to cram in lots of information in a quick time. However, there can be little doubt that they are at a great advantage in having the ability to think critically and integrate information obtained from the basic as well as clinical sciences, as many of the questions that have appeared in entrance examinations clearly suggest.

In the session narrated in this paper, we aimed to teach the participants how to think critically about the possible pathophysiological mechanism and significance of the hypotension-bradycardia paradox that is unique to vasovagal syncope. To place this question in context, we used a case study to introduce to our participants the typical clinical presentation of a patient with vasovagal syncope. We then briefly discussed how to differentiate vasovagal syncope from other causes of syncope. The pathophysiological mechanisms culminating in syncope and subsequent recovery of BP, HR, and consciousness in this condition were then discussed systematically using a series of open-ended questions. This also gave us the opportunity to examine the mechanism of the “paradoxical bradycardia/asystole” in this condition.

Classroom Management

In this particular class, several multiple choice questions in cardiovascular physiology were being discussed, and we also asked the following question. Could you tell me one clinical condition in which the heart stops (or more correctly, is stopped) for a possibly good reason? There were a number of attempts but no correct response. We then presented a case that gave them the clue to the correct answer. The case per se was used as a starter and was discussed only briefly. We then discussed the first question and relevant facts at length.

Case details. A 32-yr-old female presented to the Medicine Outpatient Service with a history of 6–8 episodes of loss of consciousness over the past 3 mo, with each episode lasting 1–2 min. Her husband had witnessed a few attacks. Typically, each episode was characterized by a prodrome of lightheadedness, nausea, and profound sweating, resulting in loss of postural tone and frank syncope followed by immediate recov-
Hypotension (this point is discussed later). We then recapitu-

lating the relationship between BP and HR in four different 
clinical situations, as set forth in Table 1.

At first sight, the occurrence of bradycardia in conjunction 
with hypotension appears paradoxical and counterproductive. 
However, the answer to this lies in understanding the mecha-
nisms triggering and leading to vasovagal syncope and the 
significance of syncope itself. We summarize here point-by-

point, the cascade of reactions that result in syncope in this 
condition and recovery of consciousness thereafter. Teaching 
points that we did not use in our presentation but may be 
appropriate for advanced learners are italicized.

Vasovagal Cascade

What characterizes the vasovagal attack? Vasovagal at-
tacks are due to abrupt severe vasodilation, which leads to 
a fall in total peripheral resistance (TPR) and BP (BP = stroke 
volume × HR × TPR). This occurs as a result of sudden 
withdrawal of sympathetic vasoconstrictor nerve activity to 
resistance vessels (16). Sometimes an acute increase in plasma 
epinephrine, which causes vasodilation in liver and skeletal 
muscle, has been demonstrated (21). The vasodilatation has 
also been shown to be mediated, at least in part, by acetylcho-
ine and nitric oxide (14). This leads to a fall in venous return, 
stroke volume, and BP.

What is the usual cardiovascular reflex response to 
abrupt vasodilation? In this case, the fall in BP is primarily 
due to a precipitous decline in TPR, and, hence, BP is defended 
by increasing HR. Vagal withdrawal and activation of sym-
pathetic outflow to the heart lead to an increase in HR and 
myocardial contractility. Normally, a fall in BP is also 
accompanied by a reflex increase in sympathetic vasoconstric-
tor discharge. In this case, transient “failure” of this reflex 
mechanism is what is responsible for the abrupt fall in BP in 
the first place. In fact, impairment in reflex vasoconstriction 
during exercise has been reported in patients with vasovagal 
syncope (25).

When a fall in BP is accompanied by an increase in HR, 
why does syncope occur at all? In vasovagal syncope, vaso-
dilation (the primary abnormality) is sustained and TPR con-
tinues to fall. Venous return greatly decreases. Reflex sympa-
thetic stimulation causes the heart to beat faster and vigorously 
while it is under filled. This is the origin of the term “empty 
heart syndrome” (19). Reflex increases in TPR do not occur 
promptly as they normally do and this is the primary abnor-
nality in this condition. Thus the arterial baroreflex mecha-
nism fails to rapidly normalize BP. Eventually, mean arterial
pressure (MAP) falls considerably to a value < 60 mmHg. Cerebral blood flow is autoregulated only when MAP is between 65 and 140 mmHg (9). Loss of cerebral autoregulation during acute severe hypotension leads to global cerebral hypoperfusion resulting in transient loss of postural tone and consciousness (syncope). This results in the faint, and recumbency is thus achieved.

Now have a look at the BP and the ECG records obtained from this patient during a drug-free 70° head-up tilt-table test. The HR falls precipitously from ~90 down to 36 beats/min in ~6 s. However, the beat-to-beat BP recording indicates that BP had fallen before HR started falling (at this time the patient lost consciousness) and then the heart stops (there is no electrical activity for nearly 6 s). This is followed by a few ventricular escape beats and restoration of normal sinus rhythm with a rate > 60 beats/min in ~30 s. By this time, the patient had regained consciousness.

What is the actual hemodynamic mechanism of syncope in this patient? Syncope can occur due to one of two reasons: a fall in cardiac output or a fall in TPR or both. In vasovagal syncope, the fall in BP usually precedes the fall in HR (21). Thus the fall in BP due to abrupt vasodilation is sufficient to cause intense presyncope or even frank syncope. This is called vasodepressor syncope. This is supported by the fact that at least in some patients with vasovagal syncope, pacemakers cannot prevent the occurrence of frank syncope (21). Lewis (15) demonstrated that while atropine could inhibit bradycardia, it did not prevent syncope, meaning that vasodilation rather than bradycardia is the cause of hypotension (15).

Why did this patient have asystole during the tilt-table test? Severe hypotension (MAP < 50 mmHg) is accompanied by hypoxemia (28). At this time the impulse traffic in the afferents from arterial baroreceptors is considerably reduced, and, consequently, tonic vasoconstrictor sympathetic discharge from the vasomotor center is disinhibited (8). The reduction in blood flow to the systemic arterial chemoreceptors in the aortic and carotid bodies reflexly augments sympathetic outflow to blood vessels. The cardiovascular response to chemoreceptor stimulation consists of peripheral vasoconstriction and bradycardia (8). In rats, hypoxia of the vasomotor center has been demonstrated to selectively excite vasomotor neurons of the rostral ventrolateral medulla (23). In the adult cat, rapid hemorrhage has been found to result in a paradoxical decrease in HR (18). Activation of vagal outflow to the heart results in bradycardia, but this may sometimes be intense enough to stop the heart for a few seconds in diastole (asystole). Vagally mediated bradycardia has often been suggested to be triggered by activation of ventricular mechanoreceptors in a forcibly contracting but hypovolemic heart (a vagovagal reflex). This reflex, often referred to as Bezold-Jarisch reflex, results in bradycardia and vasodilation (5, 13, 17). However, the vasovagal reaction has also been shown to occur in patients with transplanted hearts (6). Also, sinoaortic denervation has been shown to attenuate the bradycardic response to hypoxia in fetal sheep (27). This finding suggests that impulses from systemic arterial chemoreceptors play a part in the genesis of bradycardia (27). Thus multiple afferent mechanisms could trigger a vasovagal reaction (5, 13).

What is the effect of increased sympathetic outflow on BP? Which mechanisms normalize BP? Stimulation of the vasomotor center causes a gradual increase in TPR. In the context of acute hypotension and hypoxemia, the chemoreceptor reflex and the central nervous system (CNS) ischemic pressor response play an important role in selectively augmenting sympathetic outflow from the vasomotor center and normalizing BP (12).

If sympathetic stimulation could normalize BP after syncope has occurred, then why did syncope occur in the first place? In other words, what is the pathophysiological significance of vasovagal syncope? In the first place, occurrence of vasovagal syncope is clear evidence of an inability of the arterial baroreflex mechanism to defend a large, sudden fall in BP during upright posture without also resulting in fainting. However, after the faint, venous return and cerebral blood flow increase, and other adaptive reflex mechanisms, mainly the chemoreceptor reflex and the CNS ischemic response operate to normalize BP within 30 s to 1 min. Also, the CNS is able to withstand ischemia for a few seconds duration without permanent loss of function. Fainting, which occurs as a consequence of a profound reduction in cerebral blood flow, may thus be thought of as a homeostatic mechanism that enables venous return and cerebral blood flow to improve before BP is normalized by neural reflex mechanisms (10).

What is the pathophysiological mechanism and significance of bradycardia/asystole in vasovagal syncope? From what has been said above, it follows that hypotension accompanied by hypoxemia elicits a bradycardic response. The bradycardia is most likely triggered by hypoxic stimulation of arterial chemoreceptors because it is attenuated by sinoaortic denervation (27). It has been suggested that the vagally mediated bradycardia may have evolved as a mechanism to reduce further blood loss (10). The bradycardia/asystole may also be thought of as a mechanism that allows ventricles to fill adequately before they start contracting again (28). It would take at least 10 s before venous return increases significantly, because sympathetic modulation of vasomotor tone, which results in low-frequency BP oscillations (often called Mayer waves) occurs at a frequency of ~0.1 Hz (3). Furthermore, the myocardium would lose its ability to regulate its blood flow in the face of severe hypotension. If the heart were to continue beating fast, myocardial damage could result. Because consciousness and muscle tone are lost and recumbency achieved, the metabolic demand is so low that asystole for a short duration (5–10 s) would be inconsequential. This leads us to believe that in the context of vasovagal syncope, the heart is (transiently) stopped (by neural reflex mechanisms) for good.

In the normal course, what happens after the period of asystole? The sympathetic nervous system, which has already been activated, eventually increases TPR and BP is normalized in ~1 min. The increase in BP increases pulmonary blood flow, and hypoxemia is corrected. Once hypoxemia is corrected, reduction in cardiac vagal outflow follows and HR eventually normalizes. The BP quickly increases to a range in which the arterial baroreflex becomes the principal BP regulatory mechanism. This explains why vasovagal attacks are benign and self-limiting. In fact, the prognosis is excellent in the absence of structural heart disease, such as sinus node dysfunction or heart block (24). There is a risk of serious injury, however, depending on the prevailing circumstances. Full recovery of consciousness occurs in ~1 min without any residual neurological deficit. However, patients with structural heart disease may have prolonged asystole and hypotension.

Teaching with Problems and Cases

WHEN THE HEART IS STOPPED FOR GOOD

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Based on your knowledge of the mechanism of vasovagal syncope, could you suggest a means of identifying individuals with a susceptibility to vasovagal attacks? A typical history is sometimes obtained as in the case illustrated. However, sometimes the presentation is atypical and may include an associated history of convulsive movements. The basic idea of a test for identifying susceptible individuals would be to trigger a vasovagal reaction in the laboratory while monitoring BP and ECG. Think of factors that trigger vasovagal attacks and identify one or two provoking factors that could be used in the laboratory. A diagnosis of vasovagal syncope is ascertained by performing a tilt-table test (24). This is done by keeping the patient strapped onto a tilt table with footplate support and tilted 70° head upright for 45 min while ECG and BP are continuously monitored (24).

How does a tilt-table test help establish a diagnosis of vasovagal syncope? The underlying premise is that venous pooling that occurs during passive head-up tilt results in a significant fall in venous return, and the capacity of the arterial baroreflex and other neurohumoral mechanisms to defend decreases in BP during prolonged orthostatic stress is tested. Patients with vasovagal syncope are unable to maintain adaptive neurohumoral and neurocardiovascular mechanisms during prolonged periods of tilt (2). Typically, this test would reproduce the sequence of events leading to syncope in the natural course. The development of intense presyncope or syncope accompanied by hypotension and/or a relative bradycardia constitutes a positive test. Syncope occurring due to hypotension unaccompanied by a significant decrease in HR is termed vasodepressor syncope. More often, hypotension is accompanied by a decrease in HR to ~40 beats/min. This is the typical mixed form of the vasovagal syndrome. The bradycardia may sometimes be intense so as to result in transient asystole (this is called cardioinhibitory syncope). The patient we discussed had the cardioinhibitory form of vasovagal syncope. Absence of symptoms, even after 45 min of tilt, constitutes a negative test (24).

What should you do if you see a patient faint on the tilt table and the heart stops? “The table must be returned to the horizontal position quickly,” said a few participants telling us that they understood the homeostatic value of the faint. However, some said that they would administer atropine first. The value of the faint had to be emphasized once again.

We finally outlined the educational objectives we intended to achieve (this was also the carry-home message). The key points follow.

First, one must suspect neurally mediated syncope in a patient with recurrent unexplained syncope and no clinical evidence of a cardiac cause for symptoms.

Second, the occurrence of bradycardia or asystole in the face of acute severe hypotension is a mechanism to minimize further blood loss, prevent myocardial damage, and increase ventricular filling before the heart resumes beating. Fainting, which occurs as a consequence of this, is a homeostatic mechanism that serves to improve venous return and cerebral blood flow before BP is normalized by neural regulatory mechanisms.

It was appropriate to conclude by quoting George Von Bekesy, “Nothing has been more rewarding than to concentrate on the little discrepancies that I love to investigate and see them slowly disappear” (1a). At the end of the presentation, a very exciting question came from one of the participants: “Why does abrupt vasodilation occur in the first place? Isn’t that paradoxical anyway?” Indeed, this is the most fundamental question that remains to be answered with regard to vasovagal syncope. What exactly triggers the vasovagal reaction is still incompletely understood and is a subject of considerable research (13). Several stimuli including hypovolemia, severe pain, and emotion, which are known to trigger the vasovagal reaction, possibly converge on a final common pathway leading to profound sympathoinhibition and vagal activation. For example, vasovagal syncope triggered by pain or emotion (sometimes called “central type vasovagal syncope”) originates in corticohypothalamic centers (9, 22). It is worthwhile noting that an epinephrine surge precedes the vasovagal reaction (2, 22). Withdrawal of sympathetic vasoconstrictor tone (16) and active vasodilation triggered by acetylcholine and nitric oxide has been demonstrated (14). Epinephrine from adrenal medulla suddenly increases blood flow to skeletal muscle and liver (this may be one reason why β-adrenergic receptor blockers are effective in preventing vasovagal syncope in certain patients). Indeed, the prodromal symptoms in a vasovagal attack, which include palpitations, lightheadedness, and profuse sweating (24), are much like a fright-flight response. Engel (4) has suggested that under conditions of emotional arousal and psychophysiological uncertainty (situations that are conducive to vasovagal syncope as well as sudden cardiac death) there may be simultaneous activation of two emergency biological regulatory systems (the flight-flight and conservation) withdrawal systems (4). This sudden cardiac death due to lethal arrhythmias and the self-limiting emotional faint may represent the extremes of a spectrum of responses to unfamiliar psychophysiological stressors.

One must also explain why, occasionally, vasovagal reactions are observed in apparently normal individuals (7). It should be understood that the basic neural pathways that mediate the vasovagal reaction are probably present in all humans (26). However, the single most important factor that determines whether syncope will occur or not is the extent to which vasodilation occurs and the ability of the arterial baroreflex mechanism to buffer this rapidly. Thus individuals differ wildly in their susceptibility to attacks. For example, on a very hot day, one could get dehydrated quickly, the excess heat would tend to produce greater cutaneous vasodilation resulting in a profound fall in BP, and frank syncope would be very likely. Thus an aggregation of triggering factors would increase the likelihood of attacks and this has obvious implications for the management of this condition. This is why reassurance and avoidance of precipitating factors are all that is required in most situations to prevent these attacks (1, 24).

Participants’ Views

The session lasted ~50 min. After obtaining informed consent, participants were requested to complete a questionnaire in which they indicated whether they were satisfied with the session or not. Participants’ views regarding various aspects of the session are presented in Table 2. Written comments were
invited, and some are mentioned in Table 3. Only 240 of 275 participants responded to the questionnaire. Only 1,113 of a maximum of 1,200 responses were obtained, because some columns were left blank. Data are therefore expressed as number of responses.

Eighty-four percent of participants reported that they were satisfied with the session, 4.4% of participants reported that they were not satisfied, and 11.6% did not respond to this question. However, a small percentage (4%) of participants expressed concerns about imbalance between content coverage and time taken for discussion. One shortcoming was that a significant percentage of participants (11%) overtly stated that it was not easy to make notes during the session. This is perhaps only a minor concern, because all participants were provided with lecture notes immediately after the session concluded.

Limitations. In the first place, we did not aim to demonstrate that this represents an effective strategy to learn the pathophysiology of vasovagal syncope. However, a majority of the participants agreed strongly that the classroom presentation was clear and interesting as well as thought provoking. We believe, therefore, that this would be a valuable educational tool. By necessity, this was a large classroom session with a much lesser scope for teacher-learner interaction. As mentioned earlier, the participants included doctors and students with diverse interests, and therefore, it is reasonable to assume that they were not peculiarly concerned with pathophysiological mechanisms in vasovagal syncope. This could have possibly led to a slightly lower satisfaction rating. However, vasovagal syncope is an exceedingly common clinical entity, and we feel that all medical students and doctors (no matter what their specialty) should know and appreciate the pathophysiological mechanisms involved in this condition.

As teachers, we increasingly realize the importance of critical thinking skills and hold this as a course outcome. It is our responsibility to train our students to think critically. Obviously, discussions like the one narrated here are time consuming, and at least in the initial stages, we would expect a certain amount of resistance from learners with a surface approach. However, in the long run, it would set the stage for more meaningful learning. We suggest that the information contained herein be used to explain to any suitable audience, the neural regulation of BP in the face of acute severe hypotension. The content could be tailored to meet their course requirements. It would be more effective for a smaller group, especially if this discussion is held after the demonstration of a positive tilt-table test.

Activity. Readers could try answering the critical thinking questions given below.

- Why is prolonged head-up tilt preferred to standing for a comparable duration to assess an individual’s susceptibility to vasovagal syncope?
- How would you investigate the role of various mechanisms likely to cause vasodilatation leading to syncope?
- Emotion is a very well-known trigger for the vasovagal reaction. What are the possible physiological mechanisms involved in this case?
- What is the physiological basis for the use of beta-blockers in the treatment of vasovagal syncope?
- Could syncope occur when BP is in the normal range? Explain.
- On the basis of your knowledge of pathophysiology of vasovagal syncope, mention one or two maneuvers that could help abort an impending vasovagal attack and explain the mechanisms involved.
- Which subset of patients with vasovagal syncope would be expected to benefit most from pacemakers?

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References