

Vasovagal Syncope As A Manifestation Of An Evolutionary Selected Trait

Paolo Alboni¹, Marco Alboni²

¹Section of Cardiology and Syncope Unit, Ospedale Privato Quisisana, Ferrara, Italy. ²Department of Zoology and Anthropology, University of Sassari, Italy.

Abstract

Some observations suggest that typical (emotional or orthostatic) vasovagal syncope (VVS) is not a disease, but rather a manifestation of a non-pathological trait. We conducted an extensive bibliographic research on the vasovagal reactions in animals, including humans, in order to investigate the possible factors that may explain the origin and evolution of VVS. We found two processes which appear relevant for the investigation of VVS evolution: fear/threat bradycardia (alarm bradycardia) in animals, mainly during tonic immobility and vasovagal reflex during hemorrhagic shock (thoracic hypovolemia) both in animals and humans. The available data suggest that VVS in humans, alarm bradycardia in animals and the vasovagal reflex during hemorrhagic shock share the same physiological mechanisms and that is indicative of a common evolutionary root. However, during the vasovagal reflex loss of consciousness occurs in humans, but it is absent (or extremely rare) in animals. That can be explained as a by-product due to the erect position and the large brain evolved in our species. If the vasovagal reflex persisted for millions of years along the vertebrates evolutionary history, we can reasonably assume that it has a function and it is not harmful. It could be neutral or beneficial, but the available data suggest it is beneficial; likely, it evolved as an advantageous response to stressful and possibly dangerous heart conditions. Emotional or orthostatic vasovagal reflex is preceded by enhanced sympathetic activity, which is harmful and possibly dangerous. The transient inhibition of the sympathetic system, together with activation of the vagal tone, characterizes VVS. The consequent slowing of the heart rate induced by the vasovagal reflex may constitute a beneficial break of the cardiac pump, thereby reducing myocardial oxygen consumption. We suggest that typical VVS should be regarded as a selected response, which probably evolved in the ancient past as a defense mechanism of the organism within some ancestral group(s) of vertebrates.

Introduction

Vasovagal syncope (VVS) is a clinical manifestation of the vasovagal reflex, characterized by the occurrence of bradycardia and hypotension. VVS can be typical or non-typical. Typical VVS is diagnosed when loss of consciousness (LOC) is precipitated by triggers as strong emotion/fear or prolonged standing and is associated to autonomic prodromes (pallor, sweating, nausea, abdominal discomfort).¹ In about 80% of subjects with emotional VVS, LOC can be induced even during orthostatic stress (tilt testing).² Non-typical VVS includes episodes of LOC without any evident trigger and without (or only minimal) autonomic prodromes¹ and can be diagnosed when LOC is induced during tilt testing in the absence of other competing diagnosis. Typical VVS generally starts at young age and the natural

history is extremely variable.³ VVS is benign and very frequent in the general population. The mechanism of the hypotension/bradycardia reflex responsible for VVS is not completely understood. Very little is known about the afferent part of the vasovagal reflex (i.e., the step from trigger to autonomic control and central processing), whereas the efferent part of the reflex has been elucidated: hypotension appears to be secondary to transient withdrawal of the sympathetic system and bradycardia to a transient increase in vagal tone; both are generally preceded by an increase in sympathetic activity.⁴⁻⁹

Typical Vasovagal Syncope As An Evolutionary Selected Trait

In the medical community, VVS is often regarded as a disease. That is probably true for VVS starting in old age, which is generally non-typical (without trigger and autonomic prodromes) and frequently associated to other autonomic disturbances, mainly carotid sinus hypersensitivity.¹⁰⁻¹² In other words, VVS beginning in old people seems to be related to the emergence of a pathological process of the autonomic nervous system, not yet defined in nosology or, more in general, to aging,^{13,14} even if the efferent pathways leading to hypotension and bradycardia appear to be the same as in subjects with typical VVS. By contrast, we believe that typical VVS is not a disease but an evolutionary selected trait.¹⁴ Some observations support this view. First, the incidence of spontaneous VVS is very high. It has been reported that about 40% of young Duch students with mean age of 21 years experienced spontaneous VVS.¹⁵ Second, the neural

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Corresponding Author:
Dr. Paolo Alboni
Section of Cardiology
Ospedale Privato Quisisana
Viale Cavour 128
44121 Ferrara,
Italy.

pathways involved in the vasovagal response, though not completely elucidated, are probably present in all (or almost all) healthy humans. In fact, during diagnostic head-up tilt testing at 60°–70°, which induces thoracic hypovolemia through a venous pooling in the legs, 10–15% of adult subjects without a history of fainting experience syncope.^{16,17} Using stronger stressors, such as a tilting angle of 80° in conjunction with low-dose isoproterenol, the percentage of subjects without history of fainting experiencing VVS increases to 40–45%.^{18,19} Among children, the percentage of asymptomatic subjects developing vasovagal reactions during tilt testing is also very high, approaching 40% even when a mild stressor is applied.²⁰ Also astronauts, who are heavily selected on the basis of their great resistance to gravitational changes and cannot be regarded as sick, have a 20% of chances to experience presyncope or frank bradycardic syncope during upright posture on the day of landing after a short-duration space flight.²¹ In some studies, subtle alterations have been reported in subjects with VVS during orthostatic stress: impaired venoconstriction,^{22,23} lower increase in total peripheral resistance,²² higher increase in heart rate (HR)²⁴ and enhanced sympathetic activity;²⁵ impaired baroreflex sensitivity²⁵ and reduced blood volume²⁶ have also been described. However, other studies have failed to confirm these subtle alterations^{27–31} and their presence is currently uncertain in subjects with VVS. A multiplicity of mechanisms may contribute to these different observations. In any case, these subtle alterations cannot be regarded as pathological disorders. Moreover, a cause-effect relationship cannot be clearly established. All together, these data suggest that about 40% of young individuals experience spontaneous VVS and a large fraction of the others experience VVS under orthostatic stress. Considering that orthostatic stress is not the only stressor known to evoke VVS, it seems reasonable to assume that the vasovagal reflex is predisposed in all (or almost all) individuals. Third, subjects with typical VVS have generally normal blood pressure (BP) and a normal vagal tone outside the syncopal episodes.³² All these aspects of VVS are definitely not typical for a disease.

Since typical VVS is not a disease, but rather a manifestation of a non-pathological trait, we investigated the possible factors that can explain its origin and evolution.³³ To this end, we carried out an extensive bibliographic research in order to analyze published theories dealing with the evolution of VVS and to investigate the vasovagal reactions in animals, including humans.

Previous Theories On The Evolution Of Vasovagal Syncope

Two major theories have been put forward to explain the origin of VVS, the Human Violent Conflicts and the Clot Production hypotheses. Under the Human Violent Conflicts hypothesis, the VVS evolved during the Paleolithic era only in the human lineage.³⁴ In situations of inter-group attacks and killing, LOC triggered by fear-circuitry activation might have conferred a survival advantage to non-combatants, particularly children and women, when threats were inescapable. The second theory, the Clot Production hypothesis, suggests that the vasovagal reflex is a defense mechanism against hemorrhage in mammals.^{35,36} During bleeding traumas, the reduction of BP induced by the vasovagal reflex, would give to the coagulation system a higher chance to produce a clot, thus arresting the loss of blood.

In addition to these two theories, some authors have briefly mentioned two other hypotheses for the evolution of VVS. One of these hypotheses suggests that VVS is the human homologue of alarm bradycardia in animals, which is a decrease in HR documented in

several species during fear-induced tonic immobility.^{37,38} Under this hypothesis, the origin of VVS is therefore related to a selective advantage initially enjoyed by some ancestral groups when tonic immobility increased the survival during the interaction with predators. Finally, the heart defense hypothesis proposes that VVS evolved as an advantageous mechanism to reduce myocardial oxygen consumption when cardiac strain is excessive.^{38–40} Both alarm bradycardia and heart defense hypotheses imply that VVS is just a manifestation in humans of a general response present in several other vertebrates. Vasovagal syncope and similar responses in other vertebrates should therefore share the same or very similar physiological mechanisms.

Vasovagal Reflex In Animals

When investigating the literature dealing with the vasovagal reflex in animals, including humans,³³ we found two processes, which, in our opinion, are relevant for the investigation of VVS evolution: alarm bradycardia during tonic immobility in animals and vasovagal reflex during hemorrhagic shock both in animals and humans. We found reports of vasovagal reflex only in vertebrates and not in invertebrates.

Alarm Bradycardia In Animals

The most common animal response to fear or threat is active, the so called “fight-or-flight” response, which is characterized by increased physical activity and systolic BP, tachycardia and dilatation of muscle vessels. In contrast to this active response, many animals can show a passive response to fear/threat by remaining motionless, above all when attacked by predators from which there is not possibility of escape. A variety of names have been used to describe this phenomenon: tonic immobility, hypnosis, death-feint, fright-paralysis and playing dead. The most used name is tonic immobility.

During tonic immobility, which is a reflex and involuntary response, the animal typically assumes a recumbent posture to achieve the lowest body profile. Muscles are hypertonic, but a certain degree of relaxation is possible. Breathing is reduced in rate and amplitude. The animal is alert, as shown by electroencephalographic recording,⁴¹ but in a state of catatonic-like reduced responsiveness which simulates the death.

Two aspects of tonic immobility are relevant for this paper: the physiological modifications occurring during this behavior (alarm bradycardia) and its selective advantage. These physiological aspects are relevant because the alarm bradycardia hypothesis for the evolution of VVS suggests that alarm bradycardia during immobility behavior in animals and VVS in man are homologous. The selective advantage of tonic immobility is obviously relevant to explain its evolution. We will briefly analyse these two aspects in turn.

The prevalence in the various animal species of alarm bradycardia during tonic immobility is unknown; sometimes an acceleration of HR has been observed.^{42–45} Extensive evidence, however, suggests that transient episodes of this phenomenon, documented by using a telemetric system, are common in mammals as well as in lower vertebrates.

In white-tailed deer fawns, the sudden approach of an intruder induced in some animals tonic immobility associated with a decrease in HR up to 68%; the duration of bradycardia ranged from 5 seconds to about 2 min.⁴⁶ Similarly, when young red deers were threatened by an intruder, HR decreased in some animals up to 85%, and sinus pauses > 3 seconds were recorded during tonic immobility; the bradycardic episode generally lasted < 1 min in this case.⁴⁵ Alarm brad-

ycardia was more frequent in young than in adult individuals.^{45,46} In several other mammals (spotted ground squirrel, western chipmunk, and grasshopper mouse), the appearance of a predator, generally a snake, induced tonic immobility associated with a slowing of HR, episodes of sinus arrest and/or second or third degree atrioventricular block.⁴³ But the most extreme tonic immobility behavior is probably the “playing dead” reaction observed in the opossum.⁴⁷ During tactile stimulation by a dog, the opossum reacts with apparent death, prone position and marked stiffness of the body. Respiratory rate is reduced by about 30%. In some individuals “playing dead” is accompanied by a decrease in HR (about 50%), as well as the onset of other signs of vagal activation such as salivation, urination and defecation. The animal is conscious, though looking dead, and at this point the dog loses interest in the potential prey. The experiment was repeated after atropine administration. When the dog approached the opossum, the animal displayed tonic immobility, but alarm bradycardia was not observed. That means that tonic immobility and alarm bradycardia are two different reflexes and that alarm bradycardia is mediated by the vagal system.

Alarm bradycardia in response to threat has been documented not only in mammals but also in all classes of vertebrates. In birds (willow grouse), the HR of some individuals threatened by intruders markedly decreased from 120-140 beats/min to 30-40 beats/min.⁴⁴ Gaunt et al⁴⁸ reported that a reptile, a caiman, became motionless after the sudden approach of an investigator and the HR decreased from ~ 15 to ~ 5 beats/min. Similarly, an amphibian, the salamander, displayed tonic immobility associated with slowing of HR and cardiac pauses when threatened by a moving shadow.⁴² Various fish species stopped swimming and elicited cardiac pauses lasting up to 10-20 seconds when frightened by moving objects.⁴⁹

Tonic immobility is not commonly observed in primates or in carnivores. To this regard, Klemm⁴¹ suggested that the neocortex exerts an inhibiting influence on tonic immobility and that this behavior diminishes as the neocortex increases in size.

Adams et al⁵⁰ investigated the behavior and the cardiovascular changes in a carnivore, the cat, during an emotional situation, i.e., when preparing to fight in response to an attack of another cat. In addition to HR, they measured intra-arterial BP. Just before the attack, the cats were immobile, but tonic immobility was not displayed. Electrocardiographic recording showed in some individuals a marked slowing of HR associated to a sudden decrease in BP, as an expression of withdrawal of sympathetic system. This appears to be a clear demonstration of an emotional vasovagal reflex in animals, outside tonic immobility. It must be underlined that all the above mentioned animals did not lose consciousness during alarm bradycardia.

The evolution of tonic immobility as an anti-predator behavior alternative to “fight-or-flight” to increase the chances of survival was first suggested by Charles Darwin.⁵¹ For example, in situations where the animal has been caught by a predator, pretending to be dead can increase the possibilities to escape in an unguarded moment. Also, predators are usually adapted to react to a moving prey, and if escape is not possible, immobility can be an advantageous behavior for the prey by reducing the attention of the predator. Some experimental studies showed that the survival rate was indeed increased by this behaviour.⁵²⁻⁵⁴

Vasovagal Reflex During Hemorrhagic Shock In Animals

The vasovagal reflex during hemorrhagic shock has been observed in mammals such as rats, rabbits, cats, dogs and rhesus monkeys, as

well in humans⁵⁵⁻⁶² and it appears to be due to thoracic hypovolemia which triggers afferent stimuli from the cardiopulmonary system. The hemodynamic response to acute thoracic hypovolemia consists of two phases. During the first phase, BP is maintained in the face of falling cardiac output by baroreceptors-mediated activation of the sympathetic system, as shown in conscious rabbits and dogs by the progressive increase in renal sympathetic nerve activity and norepinephrine plasma level, which are responsible for vasoconstriction and tachycardia.^{57,59,61} During the second phase, a vasovagal reaction occurs in all the mammalian species studied,⁶³ but only when the blood volume is reduced by about 30%: BP suddenly falls and HR decreases. It has been shown during hemorrhagic shock in cats and rabbits that the decrease in BP is secondary to transient withdrawal of the sympathetic system, as evidenced by a dramatic decrease in renal sympathetic nerve activity.^{59,60,62,63}

The same response (bradycardia and hypotension) observed during hemorrhage has been reported in an experimental setting during reduction of the venous return by graded occlusion of inferior vena cava in conscious rabbits and rats.^{5,64} After a first phase characterized by vasoconstriction and tachycardia, a vasovagal reflex occurs. Even in this situation there is first a progressive rise and then a sudden decline in sympathetic nerve activity.⁶⁴

Comments

The major result of our analysis is that VVS in humans shares the same physiological mechanisms observed in the other vertebrates and this is indicative of a common evolutionary root.

The Clot Production theory suggests that the vasovagal reflex constitutes a protective mechanism against hemorrhage.^{35,36} This theory is based on the observation that hypertension worsens bleeding and that the normalization of BP by liquid infusion in patients with bleeding trauma can be harmful, impairing the formation of clots.⁶⁵ According with this theory, lowering the BP could reduce blood loss until stable blood clotting takes place. Moreover, Casonato et al⁶⁶ have reported an increase in von Willebrand factor and factor VIII, which facilitate coagulation, in two subjects who experienced VVS during venipuncture. These observations are interesting, but since vasovagal reflex occurs in humans and animals also during situations of fear or emotion, one should assume that two selective forces independently drove the evolution of the same physiological response; this is clearly an unlikely process.

The other theory, the Human Violent Conflicts hypothesis, suggests that VVS evolved in the human lineage in situations of inter-group attacks.³⁴ Even though VVS is really more frequent in adolescents and women, this theory implies that any resemblance between VVS in man and similar responses in non-human animals is the result of convergent evolution, that is an independent evolution of similar features in species of different lineages. As in most cases of convergent evolution, we would expect this similarity to be rather superficial, and probably based on different physiological mechanism. We will show in the next session that this is not the case. The remaining two hypotheses, the alarm bradycardia and the heart defense hypotheses, will be discussed in the context of our analysis of the contributions offered by the literature on the vasovagal reflex in animals.

Similarities Between Orthostatic Vasovagal Syncope In Man And Vasovagal Reflex During Hemorrhagic Shock In Animals

In these two situations the trigger appears to be the same, i.e.,

thoracic hypovolemia, which is responsible for the vasovagal reflex during prolonged standing or diagnostic tilt testing in humans and hemorrhagic shock in animals and humans. The efferent pathway also appears to be the same: an increase in sympathetic tone followed by withdrawal of the sympathetic system, as shown by the sudden decrease in BP and also by micro-neurographic recordings^{59,60,62,63} and then by an increase in vagal activity, as shown by the slowing of HR. Since the vasovagal reflex during hemorrhagic shock has been observed in many mammals as well as in humans with the same physiological mechanism,^{55-62,67} this means that the orthostatic vasovagal reflex is predisposed in primates and other mammals.

Similarities Between Emotional Vasovagal Syncope In Man And Alarm Bradycardia In Animals

Bradycardia appears in humans during emotional vasovagal VVS and in animals during fear/threat, both in the context of tonic immobility and in the absence of this behavior, as in carnivores.⁵⁰ We believe that there is a similarity in the physiological mechanism responsible for bradycardia in humans and animals, for the following reasons: 1) the same trigger evokes the same type of response (bradycardia); 2) both emotional VVS in humans and alarm bradycardia in animals are more frequent in the young individuals than in the older ones;^{3,45,46} 3) both emotional VVS in humans and alarm bradycardia in animals are generally preceded by acceleration of HR, as an expression of increased sympathetic activity.^{43-45,47,48,50} Unfortunately, BP has not been measured during alarm bradycardia in the context of tonic immobility, possibly because of limited availability of continuous BP measurements. This is a weak point in the analysis and interpretation of the vasovagal reflex. However, the only study in which both HR and BP were measured during fear-induced bradycardia, the slowing of HR was associated with a sudden decrease in BP;⁵⁰ these cardiovascular changes elicited by a trigger such as emotion/fear suggest that we are dealing with a vasovagal reflex.

The similarities of the triggers and of the efferent response in the various types of vasovagal reflex suggest a common evolutionary root. Accordingly, typical VVS would not have evolved in the modern human being, as suggested in the Human Violent Conflicts theory,³⁴ but it should be regarded as an advantageous response which originated in the ancient past within some ancestral groups of vertebrates.

If the vasovagal reflex is predisposed in all the vertebrates, from fishes to mammals, why is LOC present in humans, but absent (or extremely rare) in animals? Recently van Dijk⁶⁸ offered a possible explanation based on some anatomical or physiological traits evolved in the human lineage: 1) the metabolic demand for the brain is lower in animals than in humans; for example, in man about 20% of cardiac output is destined for the brain, while in apes (gorilla, chimpanzee) the proportion of cardiac output that needs to be pumped upwards is only 4-7%. As a consequence, a cerebral hypoperfusion severe enough to elicit LOC occurs rarely in animals or it does not occur; 2) human legs are relatively more robust than hind legs in other primates or other tall or long-necked mammals, and muscle pump appears less active in man; as a consequence, upon assuming the upright position, gravity causes more venous pooling in the human legs and, consequently, more orthostatic difficulties. In other words, the orthostatic vasovagal reflex appears to be predisposed in primates and other mammals. However, for the above mentioned reasons, and because and the quadruped or recumbent position, this reflex is most likely activated less often in animals. When activated,

it is unable to induce cerebral hypoperfusion severe enough to elicit LOC. Probably, for the same reasons, spontaneous emotional VVS is absent (or very rare) in primates and other mammals. In man, who recently assumed an erect position and developed a large brain, the vasovagal reflex can more easily induce severe cerebral hypoperfusion, and, consequently, LOC.

Another hypothesis has recently been postulated to explain the occurrence of LOC only in humans, "the brain self-preserving response" (Blanc JJ et al, Personal communication). According to this hypothesis, when the large human brain senses a decrease in blood supply, activates through an unknown mechanism the autonomic nervous system in order to drastically decrease BP and HR up to LOC, responsible for a fall. After the fall, BP and HR rapidly increase and the subject recovers consciousness without any damage of the brain. In other words, "the brain self-preserving response" should have developed during the evolution of human being to protect the large brain; however, the mechanism of this response remains to be elucidated.

Vasovagal Reflex As A "Defense Mechanism"

If the vasovagal reflex has persisted for millions of years along the vertebrates evolutionary history, we can reasonably assume that it has a function and it is not harmful. It could be neutral or beneficial, but some observations suggest that it could be beneficial. Since this phenotype is sporadically displayed, a possible role as a defense mechanism appears likely. The open question is "what is the advantage of the vasovagal reaction?" In other words, which hypothesis best explain its evolution? Did the vasovagal reflex evolve as an advantageous response to inescapable predators or to stressful and possibly dangerous heart conditions? Under the first hypothesis, emotional VVS might be an evolutionary relict or correlate of a prey-related behavior. Alarm bradycardia is not a constant response during tonic immobility.^{43,45,47} However, when it occurs associated with the reduction of respiratory rate, it may help to better simulate death by lessening the movements and/or sounds that accompany normal or increased heart and breathing rates that a predator can detect.⁴⁶ On the other hand, under the heart defense hypothesis, the inhibition of the sympathetic system, together with the activation of the vagal system and consequent slowing of HR, may 1) constitute a beneficial break of cardiac pump (thereby reducing myocardial oxygen consumption), 2) permit better diastolic filling and coronary perfusion, and probably 3) ameliorate the pumping efficiency of the heart even if BP decreases. Thus, both the alarm bradycardia and heart defense hypotheses seem to imply a selective advantage which could explain the evolution of the vasovagal reflex, and both advantages are possibly enjoyed today in several species. Only the heart defense hypothesis, however, naturally emerges as a unifying theory able to explain the occurrence of the vasovagal reflex and its associated selective advantage during both emotional and orthostatic stress. The hypothesis that alarm bradycardia during tonic immobility behavior improves survival is fascinating, but it does not directly explain the vasovagal reflex during orthostatic stress.

Conclusion:

In conclusion, our extensive analysis of the literature suggests that typical VVS in humans has the same origin as the fear and threat bradycardia observed in all classes of vertebrates and the vasovagal reflex during hemorrhagic shock (thoracic hypovolemia) observed in humans and other mammals. The major difference, LOC due to the

vasovagal reflex only in humans, might be explained as a by-product due to the erect position and the large brain evolved in our species. We also argue that VVS appears to be a defense mechanism evolved to protect the heart during stressful and possibly dangerous conditions. To this regard, it should be underlined that during the vasovagal reflex, the transient withdrawal of the sympathetic system is generally preceded by increase in sympathetic activity. The paradox of high adrenaline level followed by transient sympathetic inhibition seems to be characteristic of the vasovagal reflex both in humans and animals. That is, the sympathetic system, activated up to a certain level, likely different from individual to individual, inhibits itself. This unique mechanism appears to be highly suggestive for a defense mechanism because high sympathetic activity could be dangerous. As for other defense mechanisms, i.e., antibody production, we should not forget that the vasovagal reflex is a potential source of negative effects in man, mainly due to the occurrence of LOC. In fact, fainting, which often occurs during upright posture, may lead to traumas. In some subjects, VVS is very frequent and may be responsible for psychological affections. High recurrence rate of syncopal episodes and/or asystolic pauses, probably due to increased susceptibility, should be regarded as a harmful excess of the defense response. To date, the gene(s) responsible for the vasovagal reflex, and a possible genetic polymorphism responsible for enhanced susceptibility, have not been discovered.

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