Paolo Alboni
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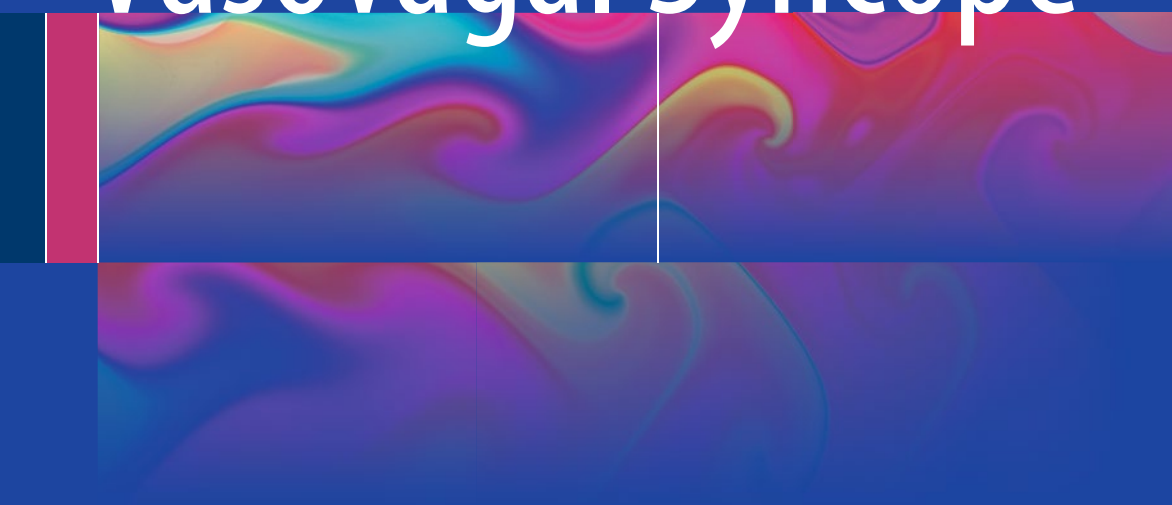
Editors

Vasovagal Syncope



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Foreword

The authors and editors of this text have produced a delight. Their great knowledge of the subject has permitted at once detailed exploration of the aetiology of vasovagal syncope and informative, didactic, conventional and contemporary sections on diagnosis and management of this fascinating clinical problem. For a reader who has some understanding of vasovagal syncope, the sophistication of thought and investigation into its causes will be the source of delight. For those relatively new to the subject, there is everything needed to address and treat a patient while the background of attempts to explain this physiological conundrum will be bound to excite. This will prove to be a thrilling book for all those who are and have struggled to understand vasovagal syncope.

London, UK

Richard Sutton, DSc

Preface

Syncope is a transient loss of consciousness leading to interruption of awareness of one's surroundings and falls with risk of injury. Syncope has been estimated to occur at least once in about half of all individuals during their life. Causes underlying syncope are different, and since the time of Hippocrates, physicians have struggled to understand the complex and diverse etiologies that may culminate in transient loss of consciousness. The most frequent cause of loss of consciousness is the vasovagal syncope (VVS), which gave the title to the present book.

VVS represents the clinical expression of an autonomic neural reflex, the vasovagal reflex, that is present not only in humans but also in the other mammals and very likely in all the vertebrates. The vasovagal reflex is responsible for hypotension and bradycardia with consequent cerebral hypoperfusion. Very likely, this reflex is a defense mechanism for the organism, but only in humans it induces loss of consciousness; that may be explained as a by-product due to the erect position and the large brain evolved in our species. Therefore, though benign in terms of mortality and cardiovascular events, VVS can be associated with traumas and, when recurrent, with psychological distress and impaired quality of life. In the elderly, recurrent VVS may result in significant loss of confidence and independence. Typical VVS was well described by Sir Thomas Lewis in 1932, who detailed dizziness, pallor, nausea, retching, weak slow pulse, and confusion followed by profound hypotension and unconsciousness. Since then, our knowledge on VVS has been markedly improved, above all after the introduction of the tilt test table in the clinical practice by Rose Anne Kenny and Richard Sutton in the 1980s. We have learned that VVS can have different clinical presentations as typical VVS, atypical VVS, sleep syncope, and unexplained fall. Moreover, in particular situations, even sudden death may be a clinical presentation when an emotional vasovagal reflex occurs simultaneously with the diving reflex. The diagnosis of typical VVS is usually easy, but in the absence of a trigger (emotional or orthostatic), the differential diagnosis with other types of loss of consciousness, mainly cardiac syncope, may be difficult, particularly in the elderly, in whom the activation of the autonomic nervous system is less pronounced. Implantable loop-recorder may be very useful for the differential diagnosis.

The mechanism of VVS has not been completely elucidated. The efferent part of the vasovagal reflex is quite certain: Hypotension and bradycardia are due to the inhibition of the sympathetic system and to an activation of the parasympathetic

system, respectively. On the contrary, the afferent part of the reflex (i.e., the step from trigger to autonomic control and central processing) is still a puzzle. The "ventricular theory" (vigorous contractions associated to a hypovolemic ventricle) gained wide acceptance, but recent observations have challenged the universality of this theory.

This book was aimed at bringing together, for the first time, epidemiology, pathophysiology, clinical presentations, differential diagnosis, prognosis, treatment, and implications on driving, working, and physical activity of a very common disorder such as the VVS. Moreover, apparently unrelated issues have been included such as VVS and orthostatic intolerance after space flight because the analysis of this relationship has shed some light into the complex mechanisms underlying VVS.

We do believe that VVS crosses the boundaries of the different medical and scientific disciplines. Accordingly, the authors of the present book tried to provide a thorough multidisciplinary review of this subject by a strict collaboration among cardiologists, internists, neurologists, emergentists, geriatricians, pediatricians, and physiologists. In each aspect, we have attempted to provide a useful and complete body of information that not only gives a summary of the published literature but also furnishes a personal insight based on the experiences of each author. In organizing the present book, there has been an attempt to optimize the "quantity" of information in order to make data easily usable by physicians. Each section was designed to stand alone while also being part of a coherent whole. When appropriate, different perspectives on the same issue have been presented. We made our best to keep the overall language accessible for nonspecialist doctors with the aim of being at their site with the present book during their daily clinical practice as well as helping them to better understand the complexity of VVS. Finally, the authors wish to thank their numerous friends and colleagues for their crucial inputs, valuable suggestions, and sometimes hard discussions over many years on this fascinating and elusive disorder.

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Part VI Special Issues

Part I

Introductory Aspects

Origin and Evolution of the Vasovagal Reflex

1

Paolo Alboni and Marco Alboni

Key Points

- Typical vasovagal syncope is not a disease, but rather a manifestation of a non-pathological trait.
- The vasovagal reflex appears to be predisposed in all classes of vertebrates.
- Typical vasovagal syncope (emotional or orthostatic) in humans, fear/threat bradycardia in animals, and vasovagal reflex during hemorrhagic shock (thoracic hypovolemia) in animals and humans share the same physiological mechanisms, and that is indicative of a common evolutionary root.
- During the vasovagal reflex, loss of consciousness occurs in humans, but it is absent (or extremely rare) in animals. Loss of consciousness is an acquired disadvantage which may be explained to be due to the erect posture and the large brain that evolved in our species.
- Typical vasovagal syncope should be regarded as a selected response, which evolved in the ancient past as a "defense mechanism" to protect the organism, very likely the heart, during a stressful and possibly dangerous condition as is the sympathetic overactivity.

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Vasovagal syncope (VVS) is a loss of consciousness (LOC) due to activation of the vasovagal reflex, characterized by the occurrence of bradycardia and hypotension. VVS can be typical or nontypical. Typical VVS is diagnosed when LOC is precipitated by triggers such as strong emotion/fear or prolonged standing and is associated to autonomic prodromes (pallor, sweating, nausea, and abdominal discomfort) [1]. In about 80 % of subjects with emotional VVS, LOC can be induced even during orthostatic stress (tilt testing) [2]. Nontypical VVS includes episodes of LOC without any evident trigger and without (or only minimal) autonomic prodromes [1]. Typical VVS generally starts at young age, and the natural history is extremely variable; some subjects experience only a single or a few episodes during their lives, whereas others have frequent episodes [3]. In the vast majority of subjects, typical VVS is not associated to cardiovascular, neurological, or other diseases, and therefore constitutes an isolated manifestation. 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 inhibition of the sympathetic system and bradycardia to a transient increase in vagal tone together with cardiac sympathetic inhibition; this autonomic pattern is generally preceded by an increase in sympathetic activity [1, 4–13]. In humans hypotension and/or bradycardia are responsible for LOC through a global cerebral hypoperfusion.

1.1 Typical Vasovagal Syncope Is not a Disease

VVS is often regarded as a disease. That is probably true for VVS starting in old age, which is generally nontypical (without trigger and autonomic prodromes) and frequently associated not only to cardiovascular or neurological diseases, but also to other autonomic disturbances, mainly carotid sinus hypersensitivity [14–16]. In other words, VVS in elderly seems to be related to the emergence of a pathological process involving the autonomic nervous system, not yet defined in nosology or, more in general, to aging processes [17, 18]. However, the efferent pathways leading to hypotension and bradycardia appear to be the same as in subjects with typical VVS.

We do believe that typical VVS is not a disease but an evolutionary selected trait [18]. Three major lines of evidence support this view. *First*, the incidence of spontaneous VVS is exceedingly high. It has been reported that about 40 % of young Dutch students with mean age of 21 years experienced spontaneous VVS [19], indicating that VVS is very common. *Second*, the neural pathways involved in the vasovagal response, though not completely elucidated, are probably present in all (or almost all) healthy humans. Indeed, during diagnostic head-up tilt testing at 60–70°, which induces thoracic hypovolemia through a venous pooling in the inferior part of the body, 10–15 % of adult subjects without a history of fainting experience

syncope (false positives) [20, 21]. 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 % [22, 23]. 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 [24]. Also astronauts, who are heavily selected on the basis of their great resistance to gravitational changes and cannot be regarded as sick individuals, have a 20 % chance to experience presyncope or bradycardic syncope during upright posture on the day of landing, after a short-duration space flight [25]. In some studies, subtle alterations have been reported in subjects with VVS during orthostatic stress: impaired venoconstriction [26, 27], blunted increase in total peripheral resistance [26], higher increase in heart rate (HR) [28], and enhanced sympathetic activity [29]. Impaired baroreflex sensitivity [29] and reduced blood volume [30] have also been described. However, other studies have failed to confirm these subtle alterations [31–35], and their presence is currently uncertain in subjects with VVS. A multiplicity of mechanisms may contribute to these discordant findings. In any case, these subtle alterations cannot be regarded as pathological disorders; at worst, they are an expression of susceptibility to VVS. Moreover, a cause–effect relationship cannot be 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 almost all individuals. *Third*, subjects with typical VVS are generally normotensive and do not have increased vagal tone during daily life [36]. 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 [37]. To this end, we conducted 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.

1.2 Evolution of Vasovagal Syncope

Two major theories have been put forward to explain the origin of VVS, here referred to as the Human Violent Conflicts (Conflict) and the Clot Production (Clotting) hypotheses. According to the Conflict hypothesis, the VVS evolved during the Paleolithic era only in the human lineage [38]. In situations of intergroup attacks and killing, LOC triggered by fear-circuitry activation might have conferred a survival advantage to noncombatants, particularly children and women, when threats were inescapable. The second theory, the Clotting hypothesis, suggests that the vasovagal reflex is a defense mechanism against hemorrhage in mammals [39, 40]. During bleeding traumas, the reduction of BP in the context of 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 Conflict and Clotting theories, some authors have briefly mentioned two other hypotheses for the evolution of VVS. One of these hypotheses suggests that VVS is the human homolog of alarm bradycardia in animals, which is a decrease in HR documented in several species during fear-induced tonic immobility [41, 42]. In keeping with this hypothesis, the origin of VVS is therefore related to a selective advantage initially used 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 [42–44]. 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 [37], 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.

Before discussing these two processes, we briefly mention an additional mechanism, the "attentional" response, which has been related, sometimes, to vasovagal reflex in humans and animals.

Attentional Response

In humans, the general response to emotion or fear usually involves an increase in HR and BP. A sudden loud noise consistently evokes an acceleration in HR, whereas low-intensity auditory stimuli, or visual stimuli such as unpleasant pictures, can induce a reduction in HR [45–47]. In a subsequent study, however, a slowing of HR was observed in several subjects, regardless of the type of picture shown (pleasant, unpleasant, or neutral) [48]. In all cases, the reduction in HR was very limited (2–3 beats/min). It has been suggested that HR decreases in response to stimuli which require particular attention and detailed visual inspection ("attentional" or "alerting" response). Similar responses have been observed in animals [49, 50]. In rabbits, a small reduction in HR has also been observed after low-intensity acoustic stimuli, sometimes associated with a slight decrease in blood pressure (−4 mmHg) [51]. The relationship between the attentional response and the vasovagal reflex has not yet been clarified, though recent data suggest that the physiological mechanism of the attentional response involves "vagal" and not "vasovagal activation" [51].

Recently, attentional response was investigated during visual stimuli in two groups of subjects, one with and the other without history of VVS [52]; this response

Fig. 1.1 Young deer during tonic immobility, after the sudden approach of a dog. The animal assumes a recumbent posture to achieve the lowest body profile, in order to simulate the death

showed similar characteristics in the two groups of subjects. This suggests that the attentional response and the vasovagal reflex should involve different mechanisms.

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, dilatation of muscle vessels, and tachycardia. 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 no 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 term 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 (Fig. 1.1). 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 [53], but in a state of catatonic-like reduced responsiveness which simulates the death.

Two aspects of tonic immobility are relevant for our investigation: 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 analyze 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 [54–57]. Even the reproducibility of alarm bradycardia has not been investigated. 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.

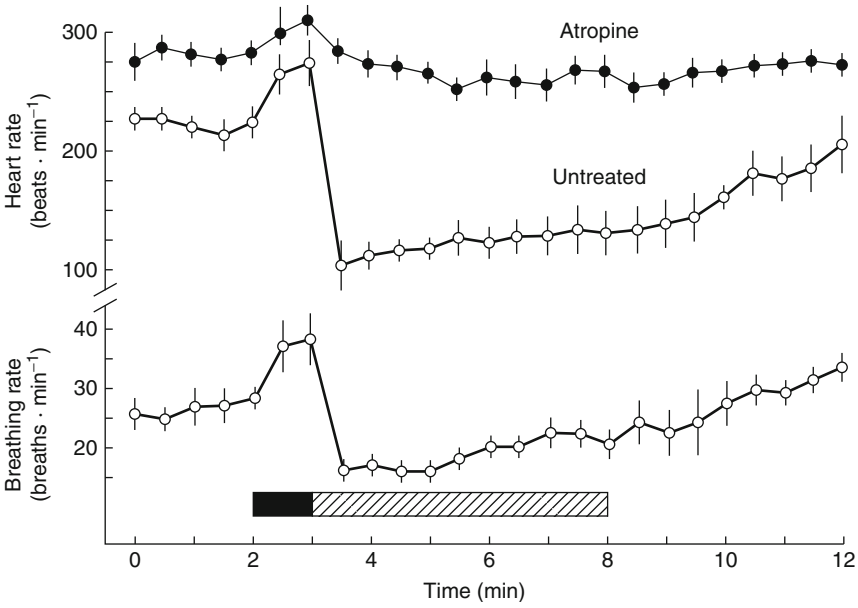

Fig. 1.2 Alarm bradycardia in a mammal, the opossum. The opossum was approached by a dog. The heart rate (HR) first increased, then the animal displayed tonic immobility and HR decreased from 250 to 100 beats/min. Even the breathing rate markedly decreased. When the animal was approached by a dog after atropine administration, it displayed tonic immobility, but alarm bradycardia did not occur (From Gabrielsen et al. [59], with permission)

In white-tailed deer fawns, the sudden approach of an unfamiliar person, with or without a dog, induced in some animals tonic immobility associated with a decrease in HR up to 68 %; the duration of bradycardia ranged from 5 s to about 2 min [58]. Similarly, when young red deer were threatened by a man approaching from a hidden position, HR decreased in some animals up to 85 %, and sinus pauses >3 s were recorded during tonic immobility; the bradycardic episode generally lasted for <1 min in this case [57]. Alarm bradycardia was more frequent in young than in adult individuals [57, 58]. 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 [55]. But the most extreme tonic immobility behavior is probably the "playing dead" reaction observed in the opossum [59]. 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 %, and body temperature is decreased by 4°. 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, defecation, and erection of the penis. The animal is conscious, though looking dead. 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 (Fig. 1.2). That means that tonic immobility and alarm bradycardia are two different reflexes and that alarm bradycardia is mediated by the vagal efferent activity.

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 to 140 beats/min to 30–40 beats/min [56]. Gaunt et al. [60] reported that HR decreased from ~20 to ~15 beats/min after diving (the so-called diving reflex) in a reptile, the caiman, and the animal became motionless after the sudden approach of an investigator, with its HR reduced to only 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 [54]. Various fish species stopped swimming and elicited cardiac pauses lasting up to 10–20 s when frightened by moving objects [61].

Tonic immobility is not commonly observed in primates or in carnivores. To this regard, Klemm [53] suggested that the neocortex exerts an inhibiting influence on tonic immobility and that this behavior diminishes as the neocortex increases in size.

Adams et al. [62] investigated the behavior and the cardiovascular changes in a carnivore, the cat, during an emotional situation, for example, 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 a typical tonic immobility was not observed. 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 abovementioned animals did not lose consciousness during alarm bradycardia.

The evolution of tonic immobility as an antipredator behavior alternative to "fight-or-flight" to increase the chances of survival was first suggested by Charles Darwin [63]. 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, reducing the attention of the predator. Some experimental studies suggest that the survival rate is indeed increased by this behavior [64–66].

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 as in humans [67–74]. 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 reflex 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 in turn are responsible for vasoconstriction and tachycardia [69, 71, 73]. During the second phase, a vasovagal reaction occurs in all the mammalians [75], but only when the blood volume is reduced by about 30 %. At this point 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 inhibition of the sympathetic system, as evidenced by a dramatic decrease in renal sympathetic nerve activity [71, 72, 74, 75].

The same response (bradycardia and hypotension) observed during hemorrhage has been reported in an experimental setting during reduction of the venous return to the thorax by graded occlusion of inferior vena cava in conscious rabbits and rats [5, 76]. 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 [76].

Few studies have analyzed the hemodynamic responses to hemorrhage in other vertebrates. Vasoconstriction during graded loss of blood has been observed in a snake and an iguana, and in two bird species [77–80]. Baroreflexes are therefore active not only in mammals, but also in lower vertebrates, but a vasovagal reflex, although not specifically investigated, has never been reported.

1.3 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.

Previous Theories

The Clotting theory suggests that the vasovagal reflex constitutes a protective mechanism against hemorrhage [39, 40]. This theory is based on the observation that hypertension worsens bleeding and that the normalization of BP by liquid infusion in bleeding patients after trauma can be harmful, potentially impairing the formation of clots [81]. According to this theory, lowering the BP could reduce blood loss until stable blood clotting takes place. Moreover, Casonato et al. [82] 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 Conflict hypothesis, suggests that VVS evolved in the modern human lineage in situations of intergroup attacks [38]. 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 animals is the result of convergent evolution. 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 section 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 reactions 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, that is, 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 drive to the heart and vessels, as shown by the sudden decrease in BP and by micro-neurographic recordings [71, 72, 74, 75], followed by an increase in vagal activity, as shown by the slowing of HR. Since the vasovagal reflex during hemorrhagic shock has been observed in rats, rabbits, cats, dogs, and apes as well as in humans with the same physiological mechanism [67–74, 83], 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 occurs 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 [62]. 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, 57, 58]; (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 [55–57, 59, 60, 62]. 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, in the only study in which both HR and BP were measured during fear-induced bradycardia, the slowing of HR was associated in some individuals with a sudden decrease in BP [62]; 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 lineage, as suggested in the Conflict theory [38], 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 Dijk [84] 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 rarely occurs in animals or it does not occur at all; (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 posture, 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 abovementioned reasons, and because of the quadruped or recumbent position [85], this reflex is less likely activated in animals. When activated, the reflex cannot 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 posture and developed a large brain, the vasovagal reflex can more easily induce severe cerebral hypoperfusion and, consequently, LOC. On the other hand, emotional VVS in humans appears to be extremely rare in the supine position. It is likely that, in this position, the vasovagal reflex-induced cardiovascular changes are not sufficient to elicit severe cerebral hypoperfusion.

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, the autonomic nervous system is activated by an unknown mechanism in order to drastically decrease BP and HR up to LOC, which in turn results in a fall. Because of the new clinostatic position, BP and HR rapidly increase and the subject recovers consciousness without any damage to the brain. In other words, "the brain self-preserving response" should have developed during the evolution of human beings 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 such as a defense mechanism appears likely. The open question is "what is the advantage of the vasovagal reaction?" In other words, which hypothesis best explains 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 [55, 57, 59]. However, when it occurs associated with the reduction of respiratory rate, it may help to better simulate death by lessening the movements and/or body sounds that a predator can detect [58]. On the other hand, under the

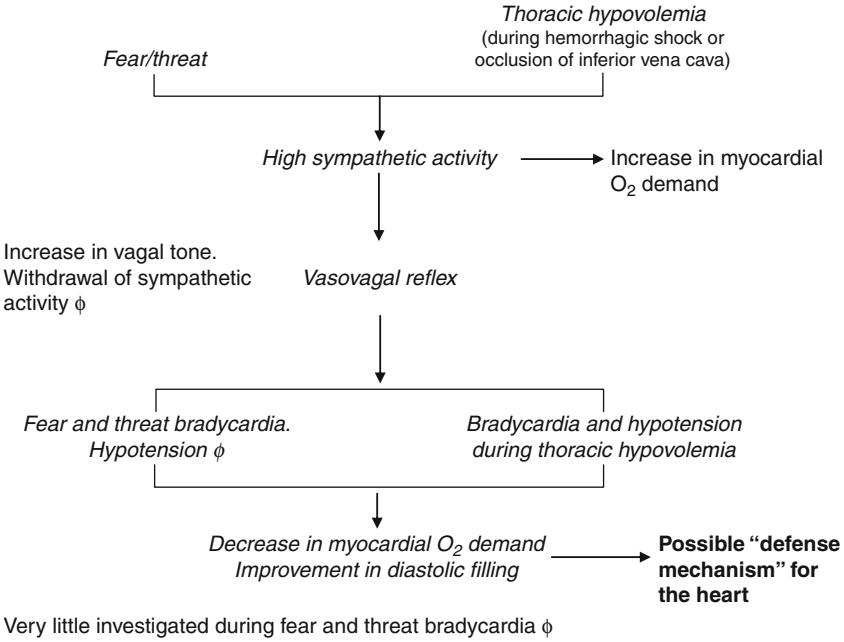

Fig. 1.3 Vasovagal reflex as a possible defense mechanism for the heart

heart defense hypothesis, the transient 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 O_2 consumption), (2) permit better diastolic filling and coronary perfusion, and probably (3) ameliorate the pumping efficiency of the heart even if BP decreases (Fig. 1.3). Thus, both the alarm bradycardia and heart defense hypotheses seem to imply a selective advantage which could explain the evolution of the vasovagal reflex. Presently, both advantages are possibly shared by 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.

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. LOC due to the vasovagal reflex characterizes only humans and might be explained to be due to the erect posture and the large brain that 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 apparent 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, that is, 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 may be frequent and responsible for psychological disorders. 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. Our analysis suggests that the bradycardia/hypotension reflex occurs in animals under triggers such as fear/threat or orthostatic stress (thoracic hypovolemia). Other triggers did not emerge, even if it is not possible to exclude other triggers under some pathological situations. Therefore, only the emotional or orthostatic vasovagal reflex, which occurs under high sympathetic activity, appears to be a physiological reflex; that should be relevant for the classification and perspective of reflex syncope in man (see Chap. 3).

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Vasovagal Syncope in the Divine Comedy and the Holy Bible: Suggestions and Interpretations

2

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Key Points

- Episodes of possible vasovagal events found in the Divine Comedy and in the Holy Bible have been discussed, and the clinical aspects and differential diagnosis presented.
- An emotional vasovagal syncope identified in the Inferno Canto III has been discussed in relation to potential seizures and catecholaminergic ventricular tachycardia.
- A second typical orthostatic vasovagal syncope occurring in the Inferno Canto V has been analyzed in relation to the potential underlying pathophysiological mechanisms.
- The third loss of consciousness observed in the Divine Comedy has been analyzed, focusing on the potential differences between vasovagal episodes and conversion disorders.
- For the case of loss of consciousness found in the Holy Bible, the problem of vasovagal syncope relapse has been addressed.

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2.1 Syncope in the Divine Comedy

The Divine Comedy [1] is Dante Alighieri's masterwork, written in vulgar language instead of Latin. It represents an allegoric work: Lost in a dark wood (understood as sin), he is unable to find the "straight way," wandering in an imaginary journey through Hell, Purgatory, and Heaven that represents the human soul's journey towards God. During this journey he encounters historical and mythological creatures, each symbolic of a particular fault or virtue. Virgil guides Dante through Hell and Purgatory; Beatrice, Dante's great love, whom he regarded as a manifestation of the divine, is his guide through Paradise.

In the Divine Comedy, Dante *faints* three times. Besides Dante's efficacious description of fainting, we will try to give a *medical interpretation* of those three episodes of transient loss of consciousness.

The first fainting occurs in Inferno Canto III. It is the night between 8th and 9th of April, the Holy Saturday (or 25th and 26th of March, in keeping with other annotators), Dante and Virgil are first entering the "vestibule" of Hell. Here, they see the damned who are punished because they spent their life in a state of apathy and indifference both to good and evil. Then, Dante and Virgil approach the river Acheron, where they find the old ferryman Caronte, who takes the spirits over to the opposite shore and....

> This being finished, all the dusk champaign
> Trembled so violently, that of that terror
> The recollection bathes me still sweat.
> The land of tears gave forth a blast of wind
> And fulminated a vermilion light,
> Which overmastered in me every sense,
> And as a man whom sleep hath seized I fell

The loss of consciousness allows Dante to solve the "problem" of passing through the Acheronte without taking Caronte's ferry. Indeed, there is an unexpressed divine law stating that only damned souls can board that ferry. Dante passed out because of the earthquake, and when he resumes consciousness he is already in the first circle of Hell. He describes the fainting as a sudden very short sleep, from which a thunder woke him soon, and he resumes consciousness promptly.

From the clinical standpoint, to understand the causes of this episode of loss of consciousness we may consider three hypotheses: *seizure*, *arrhythmia*, and *vasovagal syncope*.

Flushing lights may trigger seizures [2, 3]. In particular, the so-called reflex or triggered epileptic seizures denote seizures which are consistently elicited by a specific stimulus. Reflex seizures have a prevalence of 4–7 % among patients with epilepsy [2]. Most of them are genetic in origin.

Patients suffering from *reflex seizure* may be sensitive to flickering lights. Many artificial or natural light sources such as video games, television, computer visual display units, discotheques, and natural flickering light can provoke epileptic seizures acting as triggers. This photosensitivity may result from functional abnormalities in the cortical mechanisms that control the response to strong visual stimulation [3].

The hypothesis of a seizure as a cause of Dante's loss of consciousness is unlikely. Indeed, the episode was too brief and the recovery prompt and complete without any post-critical phase.

Coming to the arrhythmia hypothesis, it is well known that a violent stress can induce potentially life-threatening arrhythmias.

For example, *catecholaminergic polymorphic ventricular tachycardia* [4] (CPVT) is a bidirectional or polymorphic ventricular tachycardia characterized by episodic syncope occurring during exercise or acute emotions, in subjects without structural heart disease. The episode may be self-terminating and well tolerated, or may degenerate into ventricular fibrillation and cause sudden death. The onset of symptoms (usually a syncopal episode) is in the first decade of age, but onset as late as the fourth decade of life has been described.

One more time a correct case history may help to define a correct diagnosis [5]. It is possible, but unlikely, that the first manifestation of CPVT occurs after the first decade of life, and we know that Dante was "halfway along our life's path" (Inferno, Canto I), which means around 35 years of age.

More convincingly, Dante was sweating while standing. These two conditions, together with *central neural mechanism* activated by the violent emotion because of the earthquake, may have triggered an emotional *typical vasovagal episode*.

The most famous syncope of the Divine Comedy occurs in the Canto V: Dante and Virgil are now descending into the Second Circle of Hell, smaller in size than the First Circle but greater in punishment. Here are the Lustful, those who committed sins of the flesh. Dante asks Virgil to identify some of the individual souls for him. They include many of great renown. Dante immediately feels sympathy for these souls, essentially for they are damned by love.

Francesca da Rimini relates how love was her ominous. Bound in marriage to an old and deformed man, she eventually fell in love with Paolo da Rimini, her husband's younger brother. Francesca's husband quickly discovered their transgression and had the young lovers killed. Now Paolo and Francesca are doomed to spend eternity in the Second Circle of Hell. Overcome with emotion and pity for the two suffering souls, Dante faints.

> And all the while one spirit uttered this,
> The other one did weep so, that, for pity,
> I swooned away as if I had been dying,
> And fell, even as a dead body falls.

During Francesca's narration, Dante's emotional involvement becomes higher and higher, and it is likely that this is paralleled by a concomitant exaggerated rise in the neural *sympathetic activity* to the heart. Therefore, an abnormal peripheral neural input might have originated from the heart similarly to what described in animals by Oberg and Thoren [6]. These authors reported that the final *reflex bradycardia* could be observed as a result of the mechanical activation of unmyelinated ventricular vagal afferents produced by the left ventricle exaggerated squeeze, in the presence of a relative hypovolemic state, because of an exceeding cardiac sympathetic activation. In humans, this hypothesis has been referred to as ventricular

hypothesis [7] and proved to be effective particularly in *nontypical vasovagal syncope* reproduced by tilt, a benign condition characterized by the absence of prodromal symptoms. In keeping with this hypothesis, in a study based on power spectrum analysis of RR variability, in young subjects who fainted during a tilt maneuver [8], the period preceding the loss of consciousness was characterized by progressive rise of the spectral marker of cardiac sympathetic activity LF_{RR}, until a sudden drop which was concomitant with the onset of reflex bradycardia. In these subjects presyncope symptoms were elusive. Dante indeed faints without warnings, suddenly, like a dead body.

This fainting has been interpreted by Dante's annotators as a metaphorical, liberating mystical decease.

At the same time, this is an effective way in which the Canto V closes and the scene changes.

The third syncope occurs in the Purgatorio Canto XXXI (the Earthly Paradise). Dante's Purgatory is a lofty island-mountain, the only land in the southern Hemisphere, at the antipodes of Jerusalem. On the lower irregular slopes are the souls whose penitence has, for some reason, been delayed in life and whose purgation is now delayed.

As in the preceding Canto, *Beatrice* continues to press *Dante* to face up how his life has been sinful. Dante appears completely stunned, unable to speak. He would like to give voice to his agreement but in vain. Beatrice is unmerciful; she continues in a close questioning to Dante about the causes that made him leave "the right way." Finally, Dante is forced to look at her. The sight of her beauty and his great shame overwhelm him so that he faints.

> Than I upraised at her command my chin;
> And when she by the beard the face demanded,
> Well I perceived the venom of her meaning.
> So pricked me then the thorn of penitence,
> That of all other things the one which turned me
> Most to its love became the most my foe.
> Such self-conviction stung me at the heart
> O'erpowered I fell, and what I then became
> She knoweth who had furnished me the cause.

At first sight, this loss of consciousness may resemble another typical vasovagal syncope triggered by a passionate emotion. However, in the context of a vehement discussion and conflictual relationship between the two actors, being Dante the frailest, a different interpretation may raise.

Nothing could be more far away from our mind than the idea of considering Dante a subject with psychiatric problems. Nonetheless, considering the violence and hardness of Beatrice's inquiry, the "medical" hypothesis of a *pseudo-syncope* as a manifestation of conversion syndrome looks likely.

Conversion disorder is a condition where a psychological stress becomes manifest through a physical symptom. According to the classical conception, the term "conversion" is related to the idea that the somatic symptom is the symbolic solution

of an unconscious psychological conflict. The symptom enables the subject to reduce the emotional strain to keep the conflict out of conscience ("primary gain"). It is important to emphasize that the symptom is not produced by design. Moreover, the subject may obtain from symptom manifestations the so-called secondary gain, which means, for example, the avoidance of undesired responsibilities [9].

2.2 A Vasovagal Syncope in the Holy Bible

A very suggestive example of vasovagal syncope is presented by Esther, heroine of the Book of Esther [10]. According to the Bible, she was a Jewish Queen of the Persian King Ahasuerus (better known under the name of Xerxes I): This brave and beautiful young Queen risked her life to serve God by convincing the King to stop the persecution against the Jewish people.

Having this plan in her mind, when for the first time she met as Queen the King Ahasuerus, Esther was deeply moved and scared, also because she had not been bidden to his presence, and therefore she risked death. The clinical picture of vasovagal syncope is perfectly illustrated in Chap. 5, 1–5, of the Book of Esther:

> …she was radiant with perfect beauty and she looked happy as if beloved, but her heart was frozen with fear when she had gone through all the doors, she stood before the King. He was seated on his royal throne clothed in the full array of his majesty, all covered with gold and precious stones. He was most terrifying. Lifting his face, flushed with splendour, he looked at her in fierce anger. The Queen faltered and turned pale and faint, and collapsed on the head of the maid who went in front of her. Then God changed the spirit of the King to gentleness and in alarm he sprang from his throne and took her in his arms until she came to herself. He comforted her with soothing words and said: Speak to me! She started to answer: I saw you, my lord, like an angel of God and heart was shaken with fear at your glory. For you are wonderful my… and while she was speaking she fainted and fell. The King was upset and all the servants tried to comfort her…

As it does occur in many cases of vasovagal syncope, the subject can faint a second time, after a brief recovery, when the determinants of the first collapse are not removed. There are three types of vasovagal syncope: the *vasoinhibitory* where the loss of upright vasoconstrictor tone predominates and produces hypotension, the *cardioinhibitory* when bradycardia or asystole lead and prevail, and the mixed one [5].

Esther possibly suffered from a mixed type of vasovagal syncope based on the fact that her heart was frozen by fear; she showed *presyncope symptoms* and signs such as faltering, pallor, and loss of postural tone. If the subject resumes the upright posture before adequate blood pressure and/or heart rhythm restoration, short-term relapse will occur necessarily. This happened to Esther who was prematurely helped to stand again while being still nervous in trying to speak to the King.

The number of previous syncope episodes is the most powerful predictor of *syncope recurrence* [11]. Considering long-term recurrences, population studies demonstrated that approximately one-third of subjects have syncope relapse in a 3 years follow-up [11]. The highest rate of recurrence characterizes pseudo-syncope in

patients with psychiatric disorders, whereas gender, tilt test response, or the presence of cardiovascular disease have minimal predictive value [5]. It is worth remembering that even a typical vasovagal syncope or its recurrence, both characterized by a short- and long-term optimal prognosis [12], have serious effects on the quality of life. Particularly in old subjects, the physical impairment due to syncope is comparable with chronic illness like chronic arthritis [13]. In addition, a recurrent benign vasovagal event may become fatal in a *work setting intrinsically hazardous*. In this context, a new quantitative model that might guide the physician in stratifying the risk in these patients has been recently proposed [14].

Incidentally, the second faint of Esther was very successful for her, because after that the King asked Esther: "which is your wish, Esther please speak to me! I will give to you half of my kingdom…"

2.3 Conclusive Remarks

In the examined texts, the drama of the loss of consciousness, mimicking death, is used in a figurative sense. It has been utilized to highlight the drama of a situation generating an exceeding fear, such as in the case of the earthquake (Divina Commedia Canto III Inferno) or in the case of the young Esther who feels scared before the King and inadequate to accomplish her brave mission. Recovery from syncope has been metaphorically used to allude to the human resurrection (Divina Commedia Canto XXXI Purgatorio) from the sin. Finally, the typical vasovagal faint can be utilized as a "filmic" artifice to effectively change scene (Divina Commedia Canto III and Canto V Inferno).

Conflicts of Interest None

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Definition and Classification of Transient Loss of Consciousness

3

Ludovico Furlan, Giorgio Costantino, Monica Solbiati, and Paolo Alboni

Key Points

- Syncope is defined as a transient loss of consciousness (T-LOC) due to transient global cerebral hypoperfusion characterized by rapid onset, short duration, and spontaneous complete recovery. Syncope can be classified, according to the underlying mechanism, as neuromediated, orthostatic hypotension and cardiac.
- Neuromediated syncope is the most common form of syncope and occurs due to a vagal overactivity with consequent bradycardia and/or hypotension caused by different types of triggers.

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- Orthostatic hypotension is caused by the inability to maintain adequate blood pressure during the passage from clino- to orthostatism.
- Cardiac syncope is due either to a rhythm or structural heart abnormality. Rhythm disturbances are classified into brady- and tachyarrhythmia.
- T-LOC not definable as syncope may be caused by either traumatic or non-traumatic brain injuries and is usually associated with an alteration involving cerebral hemispheres or brain stem reticular formation.
- Non-traumatic T-LOCs of non-syncopal origin can be classified according to their aetiology into those which provoke a dysfunction of the nervous system (seizures, TIA, carbon monoxide intoxication, hypoxia and hypoglycaemia) and those which do not (pseudosyncope and cataplexy).

Consciousness is defined as the ability to maintain awareness of self and of the environment. Unconsciousness is a condition in which this ability is lost and there is a marked reduced responsiveness to environmental stimuli [1]. *Loss of consciousness (LOC)* can last briefly and resolve with no clinical intervention, be prolonged until a specific cause is treated and then be followed by a complete recovery or neurological symptoms, or sustain indefinitely.

The National Institute for Health and Clinical Excellence defines transient loss of consciousness (T-LOC) as a brief and spontaneous loss of consciousness with complete recovery [2].

The purpose of this chapter is to describe briefly the causes of T-LOC and then more thoroughly the possible aetiologies of syncope.

3.1 T-LOC of Presumptive Syncopal Origin

Syncope is defined as a T-LOC due to transient global cerebral hypoperfusion characterized by rapid onset, short duration and spontaneous complete recovery [3]. Syncope was responsible for 81 % of T-LOCs in the Framingham study [4] and for 85 % of non-traumatic T-LOCs in a more recent prospective study on 1308 patients [5].

Although the definition of syncope is neat, the recognition of its defining characteristics in clinical practice is much more complicated. First, the peculiar pathophysiological mechanism of syncope, global cerebral hypoperfusion, is hard to be demonstrated, particularly in clinical settings such as the Emergency Department (ED). Moreover, LOC in the case of syncope is defined to be of rapid onset. However, a syncopal event might be preceded by typical pre-syncope symptoms such as sweating, nausea, light-headedness and visual alteration or, in other circumstances, it may occur abruptly without a warning period. In a study on 2388 patients referred to the ED for syncope, only 57 % of subjects reported the presence of prodromal symptoms or awareness of being about to faint [6]. Even in the presence of symptoms, time lapse before passing out varies from a subject to another, spanning from

few to many seconds. Also, typical warning symptoms are not necessarily followed by a T-LOC, as occurs in pre-syncope.

Duration of LOC in syncope is short, usually lasting not more than 20 s [7]. However, there is wide variability among subjects: LOC may indeed last up to several minutes or subside after a couple of seconds. In this regard, it has to be underlined that, even in the presence of witnesses, the exact duration of LOC cannot be clearly defined due to the emotional and subjective involvement of bystanders. Finally, recovery from syncope should be spontaneous and complete. However, in some clinical situations, recovery may not be complete and may be characterized by symptoms such as retrograde amnesia or marked fatigue lasting several hours [7].

3.2 T-LOC of Non-syncopal Origin

T-LOC not definable as syncope may be caused by either traumatic or non-traumatic brain injuries and is usually associated with an alteration involving cerebral hemispheres or brain stem reticular formation (Fig. 3.1).

Traumatic T-LOC

Concussion refers to a sudden and transient alteration in consciousness induced by traumatic biomechanical forces transmitted directly or indirectly to the brain [8]. Rotational forces centred on the midbrain and thalamus may be responsible for T-LOC associated with concussion, inducing a diffuse axonal injury of the neuronal cells of the reticular activating system [9].

Trauma is not only a cause but can frequently be a consequence of T-LOC. As described by a prospective Italian study on 1253 patients referred to the ED for non-traumatic T-LOC, trauma following the LOC occurred in 29 % and was considered

T-LOCs of non syncopal origin
Traumatic T-LOCs→*Cerebral concussion*
Non traumatic T-LOCs
Dysfunction of the nervous system
- Neural cell primary dysfunction→*seizures*
- Neural cell primary dysfunction secondary to
  - Altered oxygen supply
    - Altered focal blood supply→*TIA*
    - Altered blood oxygen concentration
      - *Carbon monoxide poisoning*
      - *Hypoxia*
  - Altered glucose supply→*hypoglycaemia*
- *Cataplexy*

Others
- *PseudosyncopeIPsychogenic or psychiatric syncope*

Fig 3.1 Classification of transient loss of consciousness of non-syncopal origin. *TIA* transient ischaemic attack

to be severe in 5 % of total subjects [5]. Not surprisingly, patients with suspected cerebral concussion are thus typically excluded from studies on syncope.

Non-traumatic T-LOC

Consciousness is a complex cerebral activity warranted by both normal, organized neuron discharge and efficient supply of substrate, mainly oxygen and glucose, necessary for normal neuronal activity. In other circumstances, even in the presence of a normal neurological activity, T-LOC can be the consequence of a psychiatric illness.

Thus, according to the mechanism responsible, non-traumatic causes of T-LOC can be classified as in Fig. 3.1.

Seizure is defined as a clinical or subclinical disturbance of cortical function due to a sudden, abnormal, excessive and disorganized discharge of brain cells. Guidelines on epilepsy underline that seizure represents a symptom of an underlying neurological disorder and not a precise clinical entity [10].

Seizure may be either focal or generalized, according to the cerebral extension of epileptic activity. Moreover, focal seizures can be classified as complex or simple, whether consciousness is impaired or not.

Through a retrospective analysis of the Framingham Heart Study and the Framingham Offspring Study, among 7814 patients with T-LOC, seizure was believed to be the primary cause of T-LOC in 7 % of males and 3 % of females [4]. In the study performed by Bartoletti et al., a positive history for seizures or epilepsy was found in 5 % of non-traumatic T-LOCs [5].

There are several medical conditions in which normal neurological activity is altered because of the lack of the nourishment and/or substrates for neuronal cells. The two main substances neurons cannot get along without are glucose and, most importantly, oxygen (Fig. 3.1).

Transient ischaemic attacks (TIAs) are transient episodes of neurological dysfunction caused by focal brain, spinal cord or retinal ischaemia, without acute infarction [11]. In this case, there is a focal blood hypoperfusion with local deprivation of both oxygen and glucose and consequent dysfunction of a group of cells. If the neurons affected are involved in the maintenance of consciousness, T-LOC occurs. This may happen when blood flow obstruction affects the vertebro-basilar circulation. Most of the times there are focal neurological signs other than LOC, thus making distinction with syncope easier.

Cerebrovascular diseases were believed to be responsible for 11 % of total non-traumatic T-LOC in the study by Bartoletti et al. [5] and 4 % of total T-LOC in the Framingham Heart Study [4].

As described above, glucose is the main energetic substrate for neuronal cell metabolism. Thus, *hypoglycaemia*, a condition of abnormally low blood glucose, may cause altered cerebral function. Clinical manifestations are initially consequences of the activation of neurohormonal responses, including the overall enhancement of the sympathetic nervous system activity, aimed at restoring normal glycaemic values. Clinically, in this phase patients experience pallor, hunger and sweating as a

consequence of sympathetic activation. If the rescue system fails to control hypoglycaemia or if hypoglycaemic state is sustained, more severe symptoms directly related to neuronal lack of glucose may occur, including altered mental status and LOC. The prompt correction of blood glycaemia restores normal neurological functions. Although consciousness is usually impaired until normal glycaemic values are restored, spontaneous recovery can sometimes occur as a consequence of the efficacy of physiological rescue mechanism. In a recent retrospective cohort study on 3964 patients with T-LOC, transient hypoglycaemia was found to be responsible for 1 % of cases (0.03 % of all ED access). Patients at increased risk were diabetic, with long-lasting illness and on oral hypoglycaemic medications [12].

It has to be remarked that, even in the presence of normal plasma glucose levels, neuronal cells' functionality may be impaired by oxygen deprivation, a condition in which neurons survive no longer than few minutes. Thus, although rare, *hypoxia* may potentially be a cause of T-LOC.

Carbon monoxide poisoning, by displacing oxygen from blood haemoglobin because of its higher affinity, may reduce the total amount of oxygen transported by a unit of blood. As a consequence, neuronal cells normal activity may be affected, causing LOC. As in the case of hypoglycaemia, LOC in the case of hypoxia and carbon monoxide poisoning usually lasts until the underlying cause is removed and only rarely subsides spontaneously.

Cataplexy is a condition characterized by transient weakness or paralysis of somatic musculature triggered by an emotional stimulus or physical exertion. During a cataplectic attack, there is a marked reduction in muscle tone similar to the normal physiological hypotonia that accompanies rapid eye movement sleep [1].

Finally, T-LOC may be the consequence of a *psychiatric illness.*

Psychiatric diseases may not only be responsible for pseudosyncope, but also are more frequent among patients with syncope. Psychiatric conditions are thought to be responsible for about 1–7 % of total syncopal episodes [13–16]. In 2002, a small prospective controlled study on 80 subjects found that up to 65 % of patients with recurrent unexplained syncope met at least one criterion for the diagnosis of a psychiatric disorder (anxiety, panic and depressive disorders). Moreover, this prevalence was significantly different compared to the prevalence among control patients ($p = 0.01$). Control patients were selected among those with a diagnosis of cardiac arrhythmia and no previous history of psychiatric disease, a group of patients already known to be at increased risk of psychiatric illness [17].

3.3 Classification of Syncope

As described above, syncope is a symptom related to global cerebral hypo perfusion.

The pathophysiological classification of syncope proposed by the European Society of Cardiology (ESC) [3] is shown in Fig. 3.2. It should be remembered that syncopal episodes can sometimes be caused by a combination of the different mechanism described below.

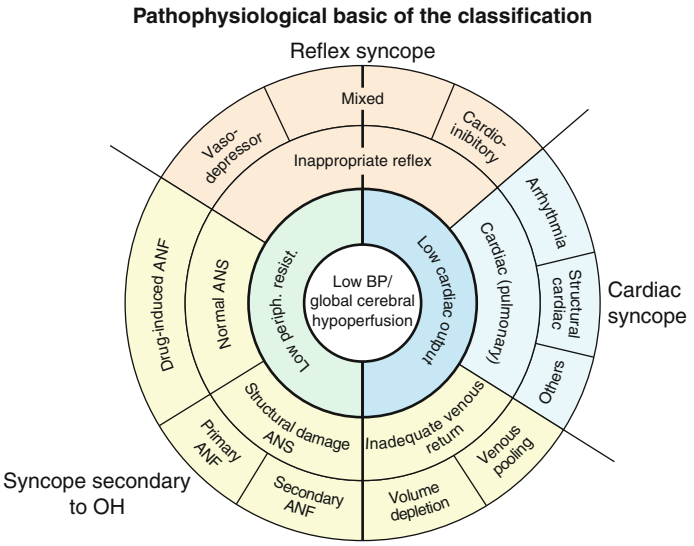

Fig. 3.2 European Society of Cardiology pathophysiological classification of syncope (From Moya et al. [3], with the permission of *Eur Heart J*). *BP* blood pressure, *ANS* autonomic nervous system, *ANF* autonomic nervous failure, *OH* orthostatic hypotension; low periph, *resist* low peripheral resistance

Efficient global cerebral perfusion depends on complex interactions involving heart, vessels and blood volume and the regulatory activity exerted by the autonomic nervous system.

Cerebral perfusion is strictly dependent on cerebral perfusion pressure and local vascular resistances. Brain blood flow undergoes autoregulatory mechanisms by baroreceptor, chemoreceptor and the ischaemic responses. Cerebral perfusion is maintained for arterial pressure values between 50 and 170 mmHg. Below and above these values, an alteration of cerebral blood perfusion occurs.

Any reduction in systemic perfusion pressure overwhelming the local cerebral auto-regulatory mechanisms may cause syncope. Heart rate (HR), stroke volume (SV) and systemic vascular resistances (SVR) are essential to keep a correct systemic perfusion pressure.

HR is maintained through the correct function of heart pacemakers and electric conduction system, while SVR are directly influenced by the calibre of blood vessels, mainly arterioles.

SV is a direct index of heart pump effectiveness and depends on preload and afterload. Preload is defined as ventricular end-diastolic pressure and is affected by venous return and ventricle filling time. Afterload is the ventricle pressure needed to obtain blood ejection. In normal conditions it coincides with the aortic pressure.

Finally, the *autonomic nervous system (ANS)* regulates SV, HR and SVR to adapt systemic perfusion pressure to the organism needs. This regulatory function is warranted by peripheral receptors, afferent and efferent neurons and central integrating

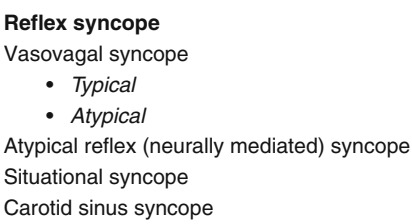

Fig. 3.3 Clinical classification of neuromediated syncope

centres. An alteration in any of these components of the ANS may affect cerebral perfusion, thus leading to syncope.

It has to be remembered that not only is pathophysiological mechanism of syncope elusive but also the identification of the aetiology of a syncopal episode in clinical practice is challenging, especially when patients are evaluated for the first time. Accordingly, 10–50 % of patients with syncope do not have a definite diagnosis after routine evaluation [3]. Moreover, in some circumstances, more causes of syncope can occur simultaneously, making a precise classification impossible.

Neuromediated/Reflex Syncope

An inappropriate reflex increase of the parasympathetic activity may provoke syncope. Fainting ensues through two main mechanisms that can occur alone or simultaneously: bradycardia and hypotension. Such cases are referred to as *neuromediated or reflex syncope (NMS)*, which, according to the prevailing mechanism, is defined as vasodepressive, cardio-inhibitory or mixed. Cardioinhibitory NMS is defined when asystole for more than 3 s or HR <40 bpm/min for more than 10 s occurs. In vasodepressive NMS the prevalent mechanism is hypotension and heart rate does not fall more than 10 %, from its peak, at the time of syncope. Finally, in the mixed form HR falls to an extent not sufficient to define either cardiac or vasodepressive NMS [18].

Prevalence of NMS varies according to the setting where patients are evaluated.

In the Framingham Heart Study the prevalence of NMS was 21 % of all syncopal episodes in the general population [4]. Prevalence among patients with syncope evaluated in the ED varies from 35 % up to 48 % [16–19].

Reflex syncope may be classified according to the trigger responsible for vagal over-activation into the following (Fig. 3.3):

- *Typical vasovagal syncope:* It is a form of syncope triggered by emotion or orthostatic stress, in the presence of autonomic symptoms.
- *Atypical vasovagal syncope:* It can be diagnosed in subjects with T-LOC not preceded by any evident trigger, but with *positive tilt test*, in the absence of any competing diagnosis.
- *Atypical neurally mediated syncope:* In this case trigger is either uncertain or absent and *tilt test negative*. Most of the times a careful exclusion of other causes of syncope, including vasovagal syncope, is essential to confirm the diagnosis.

- *Situational syncope:* It is caused by specific situations like micturition or defecation, in which the peripheral stimulation of specific receptors is the trigger for a reflex vagal overactivity. Post-exercise is also considered a form of situational syncope.
- *Carotid sinus syncope:* This clinical condition is characterized by an increased sensibility of the carotid baroreceptors. Carotid sinus massage is essential to confirm the diagnosis. Rarely, direct mechanical baroreceptor stimulation may happen during neck turning, shaving or because of a tight collar.

In the study by Bartoletti et al., vasovagal, situational and carotid sinus syncope were thought to be responsible, respectively, for 33, 6 and 2 % of total syncopal episodes evaluated in a syncope unit [5].

Orthostatic Syncope/Orthostatic Intolerance

Under the influence of gravity, blood tends to accumulate in the lower parts of the body, especially in veins that through their high compliance can contain up to one-third of total blood volume. Muscles squeezing during march, the presence of valves and direct venous contraction normally warrant efficient venous return. As described above, venous contraction is finely regulated by the autonomic nervous system. This regulation is particularly important during the passage from clino- to orthostatic position when venous return rapidly decreases under the influence of gravity. In this situation the unloading of the baroreceptor activity produces a reflex activation of the *sympathetic nervous system*, with an increase of both HR and veins smooth muscles contraction to maintain an efficient cardiac output and venous return.

There are however different medical conditions in which a malfunction of the ANS or a decline in total blood volume may produce *orthostatic hypotension* (OH) by affecting venous return or SVR. In such cases syncope or pre-syncope symptoms such as light-headedness, asthenia, fatigue or dizziness may occur defining *orthostatic intolerance*.

Orthostatic hypotension (OH) is defined as the presence of a drop in systolic blood pressure of more than 20 mmHg or diastolic blood pressure of more than 10 mmHg when assuming the upright position.

Classical OH develops usually in a period of 1–5 min. There are two variants of the classical form of OH:

- *Initial OH*: It is a condition in which blood pressure decreases more than 40 mmHg after standing, and then returns quickly to normal values [3]. It is usually associated with a brief period of symptoms.
- *Delayed/progressive OH*: It is defined as a delayed drop in blood pressure after assuming the upright position. Unlike vasovagal syncope, usually reflex tachycardia can be demonstrated.

Prevalence of OH, as for NMS, varies according to the setting in which patients with syncope are evaluated. Soteriades et al. reported a total prevalence of 9.5 %

among the general population with syncope. When syncopal episodes are evaluated in a hospital setting, prevalence varies from 4 to 6 % [16, 19, 20].

There are many medical conditions that can cause OH. As for all causes of syncope, more than one mechanism may simultaneously be present.

- *Primary autonomic failure*: This condition is characterized by a primary dysfunction of the ANS, with a consequent inability to properly react to hemodynamic changes secondary to postural changes. Primary autonomic failure has been described in *pure autonomic failure* (PAF)*, multiple system atrophy* (MSA), *Parkinson's disease with autonomic failure* and *Lewy body dementia.*
- *Secondary autonomic failure:* Many illnesses, not initially involving the ANS, may at some point cause an autonomic failure. *Diabetes mellitus, uraemia* and *amyloidosis* are responsible for a direct insult to autonomic peripheral nerves. *Alcohol acute consumption* may, instead, functionally impair vessels reaction to sympathetic stimulation, while *chronic abuse* might cause autonomic polyneuropathy. *Spinal cord injury* may as well affect ANS functionality.
- *Volume depletion: Vomit, diarrhoea, haemorrhage* and *diuretic overdosage* are all conditions in which an absolute or relative hypovolemia occurs. This obviously affects organism ability to maintain an efficient venous return, particularly during postural changes.
- *Drug-induced OH:* Medications should be considered one of the most common causes of OH, acting through different mechanism. OH is indeed a common side effect of potentially all *antihypertensive agents*. Also, other medications like *tricyclic antidepressants* and *phenothiazine* may induce OH as a side effect.

Cardiac Syncope

Potentially any transient alteration of normal heart activity can cause syncope (cardiac syncope).

Causes of cardiogenic syncope can be classified as follows:

- *Rhythm disturbances*;
- Structural abnormalities with *impaired cardiac output*.

Rhythm Disturbances

Altered heart rhythmicity may cause syncope because of a reduction of stroke volume due to either an exceeding decline of HR (bradyarrhythmia) or a decrease of ventricular filling time (tachyarrhythmia). There are no clear cut-offs at which HR surely causes syncope, because each subject has a different tolerance threshold for both lower and higher HRs.

Bradyarrhythmias reduce HR up to a point at which systemic arterial pressure is insufficient to maintain an adequate cerebral perfusion and syncope occurs.

Diseases causing bradyarrhythmia may involve any section of the heart conduction system. When the sinoatrial node is involved because of either altered automaticity or delayed conduction, *sinus bradycardia* or *sinus pause asystole* occurs. Usually, in the presence of symptoms, 40 beats/min or asystole for more than 3 s are the cut-offs at which a therapeutic intervention should be considered. *Sick sinus syndrome* and *tachy-brady syndrome* are the most common disorders affecting the sinoatrial node. Syncope usually ensues because of a long sinusal pause associated with no discharge by any other ectopic focus or as a consequence of a marked bradycardia. In tachy-brady syndrome pauses arise immediately after the end of an atrial tachycardia.

Atrioventricular blocks are the consequence of an alteration, either functional or anatomic of the atrioventricular (AV) node. Mobitz block type I and II or complete AV blocks may cause syncope. AV blocks may be due to an ischaemic damage typically related to the obstruction of the right coronary. Antiarrhythmic medications such as *beta-blockers, calcium-channel inhibitors* and *digoxin* may provoke a functional alteration of the AV node, causing high degree AV blocks.

Recently, a new form of syncope without prodromal symptoms secondary to adenosine-mediated paroxysmal AV block in subjects without heart disease, normal ECG and without progression to complete AV block has been proposed [21]. At present, we classify this type of syncope as cardiac syncope, but its classification is uncertain (see Chap. 7).

In a study by Sarasin et al. on 650 patients, sinus bradycardia and sinus pause were thought to be responsible for 2.3 % of all syncopal episodes. A similar prevalence was found for patients with AV block [22]. In a more recent study bradyarrhythmias were found in around 5 % of patients with unexplained syncope after routine evaluation [23].

Tachyarrhythmias, instead, may cause syncope due to a reduction of ventricular filling time. Indeed, when the ventricular rate is too high, the duration of diastole becomes exceedingly short to allow an efficient ventricular filling. This causes a reduction of SV with possible syncope.

Tachyarrhythmias may be caused by either a primary increased ventricular rate or by an increased ventricular response to a high atrial rate. *Ventricular tachycardia* (VT) and *supraventricular tachyarrhythmias* may thus cause syncopal episodes. There are even 'mixed' forms of syncope in patients with paroxysmal supraventricular tachycardia, where a vasovagal reflex, besides the high heart rate, seems to play a major role in causing severe hypotension, responsible for LOC (see Chap. 13).

According to the pathophysiological mechanism, causes of VT leading to syncope can be classified into the following:

- Structural heart abnormalities
  - Acute cardiac ischaemia
  - Chronic cardiac ischaemia
  - Cardiomyopathies
    - Restrictive cardiomyopathies
    - Hypertrophic cardiomyopathies

    - Dilative cardiomyopathies
    - Right ventricular arrhythmogenic dysplasia
- Channelopathies
  - *Long QT syndrome*
    - Inherited long QT syndrome
    - Acquired long QT syndrome
  - Short QT syndrome
  - Brugada syndrome
  - Catecholaminergic Polymorphic VT
- Others
  - Idiopathic Outflow Tract VT
  - Idiopathic Left Ventricular Septal/Fascicular VT
  - Fascicular tachycardia due to digoxin toxicity.

SVT only rarely cause syncope.

In the study by Sarasin et al. VT and SVT were found in 1.4 and 0.6 % of all syncopal episodes, respectively [22]. The study of Farwell et al. found a similar prevalence among patients with unexplained cause of syncope [23].

When evaluating the possible cardiologic aetiology of a syncopal event, medications and recreational drugs should always be considered. Pacemaker (PM) and intracardiac cardioverter defibrillator (ICD) malfunction might also be a cause of syncope in patients with known underlying cardiac disease.

Globally, cardiac arrhythmia was found to be responsible for 11 % of all syncopal episodes [5].

Structural Abnormalities with Impaired Cardiac Output

Syncope caused by structural heart abnormalities is less common than arrhythmic syncope. Stroke volume may be impaired due to a mechanical obstruction affecting either preload or afterload.

- Increase in afterload: The most common causes of obstruction of ventricle blood ejection are *aortic stenosis* and *hypertrophic cardiomyopathy*. Heart contractility may effectively compensate afterload increase only in standard resting condition. If other factors reducing systemic perfusion pressure coexist, such as hypovolemia or excessive vasodilatation, or if the organism needs increase, such as during exercise, the reflex increase in stroke volume may be insufficient and syncope may occur. In addition, patients with hypertrophic cardiomyopathies are also at increased risk for VT [24].

  Aortic dissection may as well cause syncope by different mechanisms, namely, affecting both preload and afterload. In proximal dissection, aortic wall rupture inside the pericardium may compromise diastole and effective left ventricular filling and preload. Preload may also be impaired by the hypovolemia following aortic rupture. In some circumstances afterload may also remarkably increase because of the effect of a blind-ended false lumen. Finally, cerebral artery may be directly occluded by the dissection.

Pulmonary embolism can cause T-LOC due both to an increase in afterload of the right ventricle and a reduction of preload to the left ventricle. By a similar mechanism, severe pulmonary hypertension can induce syncope, even if rarely.

- Reduction in preload: Sudden syncope may rarely be caused by *atrial mixom*a, causing obstruction of ventricular filling during diastole.

In many structural heart diseases, with increase in afterload or reduction in preload, syncope may also be induced by a vagal reflex activation produced by the stretching of ventricular mechanoreceptors.

Prevalence of heart structural abnormalities was found to be about 1.8 % in a study on 672 patients evaluated in the ED for T-LOC [25], about 4 % in the study by Sarasin et al. [22] and 2.6 % in the study by Bartoletti et al. [5].

Conclusions

T-LOC of syncopal origin may be classified into various ways. In this chapter, we proposed a pathophysiology-based classification in keeping with what stated by the ESC guidelines [3]. In addition, a clinical classification of vasovagal syncope identifying typical and atypical forms has also been proposed.

Conflict of Interest None

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Epidemiology of Vasovagal Syncope

4

Monica Solbiati and Robert S. Sheldon

Key Points

- Vasovagal syncope is a common symptom, but its true incidence is difficult to estimate because only a small percentage of patients with syncope seek medical advice.
- It is likely that up to 40 % of people faint at least once in their life and prevalence is higher in females.
- Syncope incidence shows a bimodal distribution, with two peaks: before 20 and after 65 years old.
- Vasovagal syncope is the most frequent type of syncope in young people; cardiovascular diseases, orthostatic hypotension and multiple causes are more prevalent in the elderly.

4.1 Introduction

Reflex syncope traditionally refers to a heterogeneous group of conditions in which cardiovascular reflexes that are normally useful in controlling the circulation become intermittently inappropriate in response to a trigger, resulting in

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vasodilatation and/or bradycardia and thereby in a fall in arterial blood pressure and global cerebral perfusion. Commonest among the reflex syncopes, vasovagal syncope (VVS) is usually triggered by emotion or orthostatic stress in the presence of symptoms due to autonomic activation [1].

In this chapter we will review published studies examining the epidemiology of vasovagal syncope in the general population and in different health care settings.

4.2 General Population Versus Clinical Settings

Syncope in general, and especially vasovagal syncope, is a common symptom, but its true incidence is difficult to estimate due to variation of definition, differences in population prevalence and under-reporting in the general population. Indeed it is likely that only a small percentage of patients with syncope seek medical advice. Observational studies showed that only half of the subjects with an episode of syncope reported that they seek medical advice [2, 3]. The proportion of patients not seeking medical evaluation in the younger population is much higher because syncopal episodes in young subjects are generally considered to be innocent [4, 5].

Different studies on the Dutch population gave some information about the incidence of syncope in the general population and in different clinical settings. Syncope was responsible for 2–9 per 1,000 general practitioners encounters [6]. The age distribution of these patients visiting a general practitioner shows a peak in females around 15 years of age and a second peak in older patients. A summary of the results of the Dutch studies [5, 2] is shown in Fig. 4.1.

The causes of syncope differ depending on the clinical settings in which the patient is evaluated and the age of the patients. Furthermore, other differences depend on diagnostic definitions, geographical factors, and local care pathways, making a comparison between different studies difficult. Reflex syncope is the most frequent type of syncope in any setting and is more prevalent in young people. Cardiovascular diseases are the second most common cause of syncope. The number of patients with a cardiovascular cause varies widely between studies; higher frequencies are observed in emergency settings mainly in older subjects, and in settings oriented toward cardiology. Orthostatic hypotension is frequent in very old patients. While in the young reflex syncope is by far the most frequent cause of transient loss of consciousness, in the elderly multiple causes are often present and the medical history may be less reliable than in the young [7–10].

The rate of unexplained syncope is about 30 % in people discharged from the ED and has been decreasing in the last few years thanks to dedicated syncope units [11].

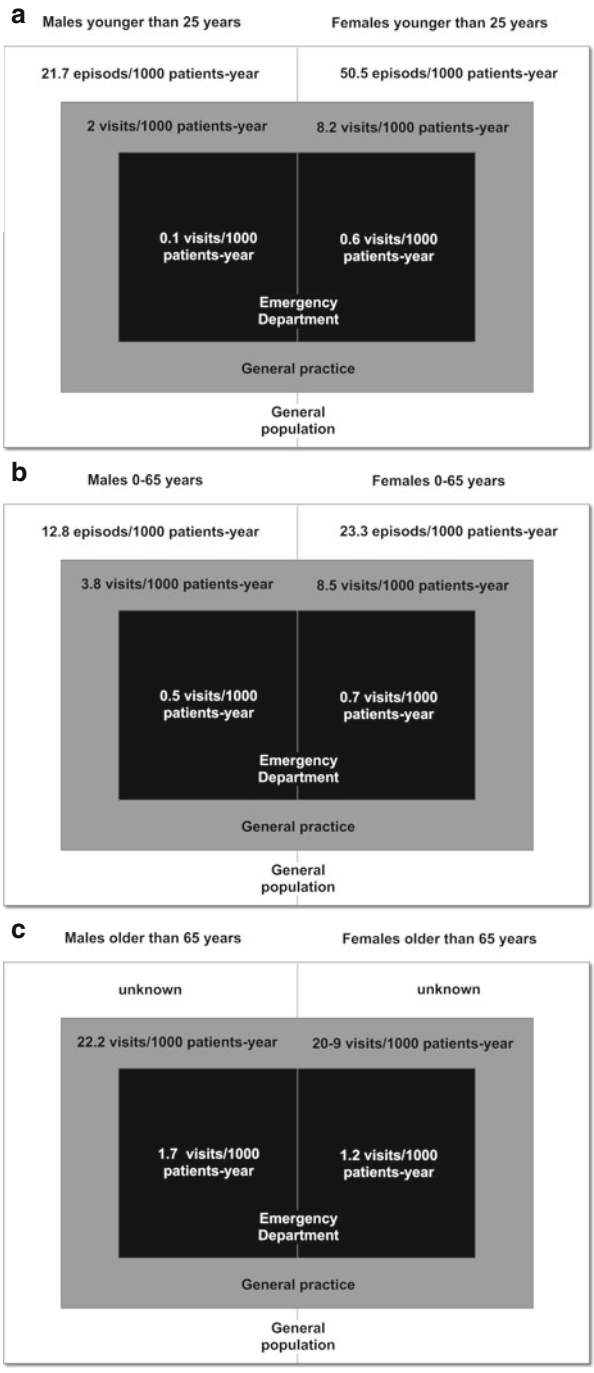

Fig. 4.1 Incidence of syncope in the general population and in different clinical settings in The Netherlands [8]. Panel **a**: in subjects younger than 25 years; panel **b**: in subjects from 0 to 65 years; panel **c**: in subjects of above 65 years

4.3 Syncope in the General Population

The Framingham Study

The first epidemiological study assessing syncope incidence in the general population came from the Framingham Heart Study. The objective of the Framingham Heart Study was to identify the common factors or characteristics that contribute to the development of cardiovascular disease by a prospective analysis of healthy subjects [12]. The first syncope report from the Framingham study showed that, during 26 years of follow-up (from 1952 to 1978), 3 % of the men and 3.5 % of the women (171 subjects overall, aged 30–62 years old) reported at least one episode of syncope [13]. Most of the subjects had isolated syncope (i.e., transient loss of consciousness in the absence of prior or concurrent neurologic, coronary or other cardiovascular disease stigmata, which was likely to have been vasovagal syncope). The mean age of the first episode of isolated syncope was 52 years (range 15–78) for men and 50 years for women (range 13–87). The prevalence of isolated syncope increased with age in both sexes with a prevalence ranging from 7 to 8 per 1,000 person-exams at 35–44 years old to about 28 per 1,000 person-exams at 65–74 years old. After the age of 75 the incidence of isolated syncope was significantly greater in men than in women: 56 per 1,000 person-exams in men versus 36 per 1,000 person-exams in women.

The offspring of the original Framingham subjects and the spouses of the offspring were enrolled in a prospective study in 1971. Subjects who participated in the fifth examination of the offspring cohort, which began in January 1991 and was completed in January 1995, were analysed to assess the prevalence of congestive heart failure, atrial fibrillation, cerebrovascular disease and syncope in subjects with and without mitral prolapse [14]. The cumulative 4-year incidence of syncope was 3 %.

The latest report from the Framingham Heart Study involved 7,814 participants with a mean (±SD) age of 51.1 ± 14.4 years (range, 20–96) [3]. The overall incidence rate of a first report of syncope was 6.2 per 1,000 person-years. The incidence rates of syncope increased with age among both men and women, with a sharp rise at 70 years (from 3 to 4 per 1,000 person-years in people below 70 years old, to 11–20 per 1,000 person-years in subjects above 70 years old). Twenty-one percent of subjects were classified as having vasovagal syncope.

Syncope in Selected Populations

Syncope in the Young (Students, Athletes and Air Force)

The relatively low syncope prevalence observed in the Framingham Study is in sharp contrast to data from cross-sectional surveys in young populations, which show a syncope prevalence of about 30–40 %. The most likely explanation for the much lower prevalence of syncope in the Framingham Study appears to be that this study focused on the incidence of syncope. Only subjects with incident syncope after the beginning of the study were included; those who did not faint after entering the study, but had experienced syncope before the study, were not counted. Moreover, the population analysed consisted of subjects of 35 years. This might

have led to underestimation of the prevalence of syncope in the younger population. Furthermore, there may have been a significant recall bias in the Framingham Study, because a group of subjects with a mean age of 46 years was interviewed about episodes of syncope in their youth.

Studies involving subjects from the United States Air Force personnel revealed that 27 % had experienced a syncopal spell during their lifetime [15].

In a cross-sectional survey among Dutch medical students, Ganzeboom et al. analysed 394 subjects (median age 21 years) [5]. Thirty-nine percent of them reported that they had experienced at least one episode of syncope. Since the majority of students identified as triggers stresses or conditions that affect orthostatic blood pressure regulation, it is likely that most of syncopes were reflex. Female students reported a higher prevalence of syncope than males (47 % vs 24 %; relative risk 1.9, 95 % CI 1.3–2.7). Median age at which students experienced their first syncope was 15 years in women and men.

Similarly, a Canadian study recruiting 62 medical students and their families (above 200 subjects overall) showed a vasovagal syncope prevalence of 32 % and the median age of first faint was 14 years. More females than males fainted (42 vs. 31 %, hazard ratio [HR] 1.34 [95 % CI 1.07–1.68]) [4].

In a Portuguese report, 2,047 young adults were requested to fill in a simple questionnaire regarding their health and cardiac status at the end of classes or during work breaks [16]. Of the 2011 consecutive volunteers (aged 18–40 years) that accepted to participate in the study, about 30 % reported a previous episode of transient loss of consciousness. In this case too, transient loss of consciousness was more frequent in subjects of female gender (OR 2.4, 95 % CI 2.0–2.9). Notably, the study didn't distinguish syncope from other causes of transient loss of consciousness, and this might lead to an overestimation of its prevalence in this population.

An Italian study evaluated the epidemiological features and the prognostic implications of syncope in young competitive athletes at two centres for sports medicine [17]. The overall 5-year prevalence of syncope was 6.2 % (1.2 % per year) in the study sample. Prevalence was found to be higher in female athletes than in male athletes (7.3 % versus 5.7 %, $p=0.01$).

Syncope in the Elderly

Syncope is a major cause of morbidity and mortality in older patients, with enormous personal, social and health-care costs [18]. Beyond the risk of injury, a decrease in quality of life and functioning has been described [19]. Increased susceptibility to syncope with advancing age is accounted for by age-related physiological impairments of heart rate and blood pressure regulation and alterations in cerebral blood flow combined with comorbidities and polypharmacy [9, 18]. On the other hand, the real prevalence of syncope in older individuals may be significantly underestimated because of the overlap with presentations classified as falls [20] or because elderly people might forget having fallen [21]. Moreover, amnesia for loss of consciousness during reflex syncope [22] and a higher incidence of atypical vasovagal syncope [23] have been described in this population. Because of the overlap with falls, the true incidence and therefore true costs of syncope are unknown but likely to be considerably high. Furthermore, cardiac, orthostatic and mixed syncopes are more prevalent in the elderly, thus making it more difficult to estimate the prevalence of vasovagal syncope in this population.

Prospective data of the elderly subjects come from very selected populations, such as among the elderly confined to long-term care institutions. A retrospective analysis of syncope in 711 very old (mean age 87 years) institutionalized patients revealed a 10-year prevalence of 23 % and 1-year incidence of 7 % [24]. A 2-year prospective follow-up of this population revealed a yearly incidence of 6 % and recurrence rate of 30 %. Of 67 patients who developed syncope during follow-up, a cause was established in 46; 14 had cardiac and 32 had non-cardiac aetiologies. Twenty-one cases remained unexplained.

A high incidence of syncope was also found in a study involving older nursing home residents: a total of 72 episodes of syncope were counted over 29 months in 499 persons [25].

The frailer nature of institutionalized populations and the more accurate reporting in institutional settings may explain the considerably higher incidence of syncope among institutionalized elderly populations.

The Irish Longitudinal Study on Ageing (TILDA) is a large-scale, nationally representative, longitudinal study on ageing in Ireland. TILDA collects information on all aspects of health, economic and social circumstances from people aged 50 and above in a series of data collection waves once every 2 years. Syncope-related questions were asked to 8,163 community dwelling adults (mean age 62 years, range 50–105 years) [26]. A percentage of 16.9 acknowledged fainting and 4.4 % had fainted in the past 12 months. Thirty-eight percent of fainters experienced one or more falls in the past year compared with 18.3 % of non-fainters.

Syncope in the Emergency Departments

European observational studies reported that the prevalence of syncope referrals to the emergency department (ED) range from 0.9 to 3.36 % [27–31]. European prevalence seems to be lower than the 3 % reported in an old US study by Day et al. [32]. However, the frequency of 3 % in the study by Day et al. is based on patients visiting an ED because of transient loss of conscience. The causes included syncope but also seizures, head trauma and cerebrovascular accidents. Similar prevalence data were reported by ED studies aimed at developing or validating clinical decision rules in the UK (1.3 %) [33], USA (1.4 %) [34] and Canada (1 %) [35].

Reflex syncope is the most common cause and found in about 30 % of the patients, while about one-third of patients are discharged without a diagnosis [36].

The proportion of patients that are admitted to wards after ED evaluation is highly variable across countries (12–83 %) [37, 38].

4.4 Registry Studies

A recent Danish study from Denmark identified all patients with a registered hospitalization for syncope from the entire population of Denmark [39]. All hospital admissions, ED contacts and non-acute referrals, that is outpatients, were included.

Syncope was classified as a primary discharge diagnosis. During the study period (1997–2009), a total of 127,508 patients were seen in the ED (45.3 %), in outpatient

clinics (11.7 %) or in hospital (43 %). The age distribution of the sample showed three peaks: the first peak was represented primarily by females around 20 years of age, a second and quite smaller peak in older patients around 60 years of age and a third peak around 80 years of age. The overall incidence rate of a first-time episode of syncope was 17.2 per 1,000 person-years, women accounting for 17.8 and men for 16.5. Syncope accounted for 0.9 % of the total admissions in the period and 0.6 % of the total ED visits.

Conclusions

As already mentioned, one of the main limitations in describing vasovagal syncope epidemiology is that most of the subjects escape clinical evaluation, thus probably leading us to underestimate the real prevalence of vasovagal syncope in the general population.

Cross-sectional survey-based studies might overcome this problem, but recall bias, the selection of the study sample and the lack of information on syncope aetiology might be limitations to their quality.

Finally, epidemiological data almost completely refer to Europe and North America. Data suggest that climatic changes and temperature variability influence syncope incidence in the same population [40]. This could mean that other countries might have a different epidemiology just because of a different climate and make it impossible to generalize what we have reported to the global population.

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Part II

Pathophysiology of Vasovagal Syncope

Role of the Autonomic Nervous System in Vasovagal Syncope

5

Rogelio Mosqueda-Garcia

Key Points

- Autonomic nervous system branches that are involved in the initiation and development of vasovagal episodes
- Central and peripheral neural autonomic mechanisms triggering VV syncope
- Role of neurohumoral autonomic mechanisms in the development of VV syncope

5.1 Role of the Autonomic Nervous System in Vasovagal Syncope

Vasovagal syncope (VVS) syndrome is a prime example of dysregulation of the autonomic nervous system. As indicated by the term coined by Lewis [1], vasovagal underlines the abrupt slowing of the heart rate (probably "vagally mediated") with the development of profound hypotension presumably related to withdrawal of vasomotor sympathetic neural traffic or neurohumoral vasodilation.

In this chapter, we will outline the contribution of many parts of the autonomic nervous system that are involved in the initiation and development of vasovagal episodes. Main points of discussion will be the role of central and peripheral autonomic mechanisms that triggers the event, contribution of the main components of the parasympathetic and sympathetic branches, and the potential role of neurohumoral autonomic mechanisms in the development of VV syncope.

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Autonomic Neural Circuitry Involved in the Vasovagal Response

It has been recognized for some time that, in susceptible individuals, different stimuli can result in the development of vasovagal episodes [2]. Depending on the stimulus, either central or peripheral autonomic pathways come first into play with subsequent activation or inhibition of autonomic regulatory centers [3]. While the final clinical picture is loss or near-loss of consciousness, the initial triggering centers and resulting activation of efferent pathways lead to a complex and varied autonomic response that may produce a VV response with somewhat different patterns. Therefore, it is not surprising that the resulting sympathetic withdrawal, parasympathetic activation, and neurohumoral changes involved in VV episodes are expressed in somewhat varied cardiovascular responses (VV syncope characterized by a vasodepressor, bradycardic, or mixed type of response) [2] and with different predominance of preceding or concomitant symptoms (e.g., nausea, sweating, pallor, lightheadedness, abdominal discomfort, etc.).

Afferent Neural Signals and Integrative Centers in Centrally Initiated VV Syncope

Central VV syncope may develop in response to strong emotional stimulation. In susceptible individuals, emotional distress (i.e., severe fear or extreme mental stress), visual clues (i.e., gruesome scenes), or some phobias (e.g., blood phobia) can trigger a VV episode characterized by hypotension, bradycardia, and rapid loss of consciousness [3] (Fig. 5.1). In this respect, it has been postulated that central VV episodes appear to be an evolutionary remnant of the "playing dead" reaction [4]. In some animal species, when the organism is confronted with serious danger, a response develops, which includes loss of muscle tone, apnea, hypotension, and

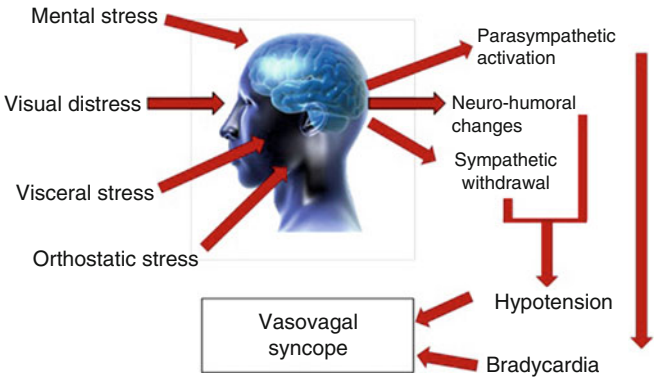

Fig. 5.1 Graphical representation of initiating factors and general autonomic systems involved in the vasovagal response

bradycardia. Interestingly, the "playing dead" reaction appears to be in an opposite spectrum of the "fight-or-flight" response (which may also involve many of the same autonomic centers) and is characterized by increases in blood pressure and heart rate with concomitant anxiety and preparation for muscular activity.

In central VV episodes of the "emotional" type, the afferent signals triggering the event probably originate solely within the cerebral cortex (Fig. 5.2). On the other hand, visual, olfactory, or pain afferents may relay the signals for events associated with unpleasant sights, unpleasant smells, or anticipation to painful stimulation (proprioceptive stimulation). Prominent cortical stimulation can result in intense activation of pathways relaying information from the cortex to hypothalamic centers and then to medullary cardiovascular nuclei, controlling parasympathetic and sympathetic outflow [3] (Fig. 5.2). While in humans, the exact location of sites within the CNS has not been identified, in animals investigators have characterized the "defense reaction area" in the limbic lobe and the limbic sympatho-inhibitory center as likely structures involved in responses resembling VV syncope.

Early studies in monkeys indicated that resection of limbic areas including the hippocampal formation and the cingulated amygdaloid complex affected emotional responses [5, 6]. Some previous observations advocated that some limbic areas were involved in the sense of smell [7]. While more recent assessments have questioned direct involvement of these areas in emotion and olfaction, activation or inhibition of these limbic areas may explain some of the cardiovascular changes preceding VV episodes or the old observation that loss of consciousness in emotional fainting can be reversed by smelling/inhalation of ammonia salts (olfactory input).

Additional studies in animals have confirmed the presence of autonomic sympatho-inhibitory centers in the limbic lobe, the hypothalamic area, and the nucleus of the solitary tract (NTS) [8]. Electrical stimulation of prelimbic and infralimbic areas (such as the "limbic sympatho-inhibitory center") results in hypotensive and bradycardic effects. Similarly, the somatic sensory cortex can process information from sympathetic fibers relaying information from visceral and cardiovascular areas which, under specific circumstances, result in emotional syncope [8]. Stimulation of certain parts of the anterior cingulate gyrus (in cats) causes a general inhibition of vascular sympathetic tone, vagal-mediated bradycardia, loss of muscle tone, and decrease in respiration [9, 10]. On the other hand, stimulation of the "defense reaction area" increases heart rate and blood pressure [11]. In conjunction, it is possible to speculate that either sequential activation of these areas or selective activation followed by inhibition of one of them could form the pathophysiological basis of central VV syncope. Many of these cortical and hypothalamic areas can affect medullary nuclei regulating reflex cardiovascular function (i.e., NTS) and produce parasympathetic stimulation and sympathetic inhibition.

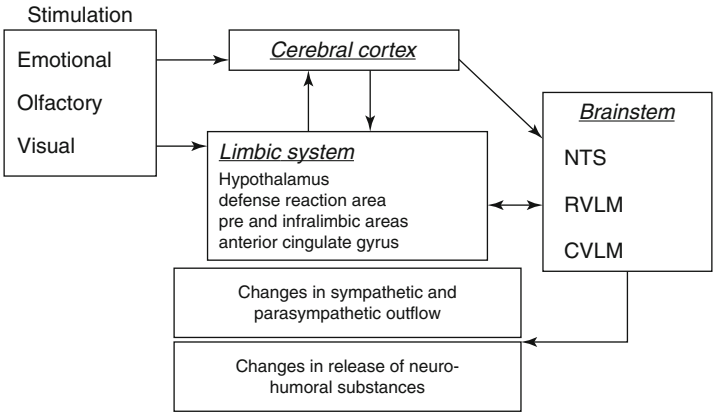

Fig. 5.2 Central nervous system structures involved in "central" vasovagal syncope

Afferent Neural Signals and Integrative Centers in Peripherally Initiated VV Syncope

VV episodes related to orthostatic stress (e.g., prolonged standing, hypovolemia), stimulation or dysfunction of some neuro-vascular regions (e.g., carotid sinus region), or pronounced increases in intra-thoracic or abdominal pressure (e.g., prolonged Valsalva maneuver, paroxysmal cough, defecation syncope) may result from initial activation of neuronal afferents located outside the central nervous system (CNS) [8] (Fig. 5.3). For instance, in VV syncope associated with pain or severe discomfort in a particular anatomical region, peripheral pain receptors in the area are the most likely afferent candidates triggering the syncope episode.

For postural syncopal events (related to relative or absolute loss of circulating blood volume in combination with changes in gravitational forces), arterial baroreceptors, cardiac, pulmonary, or other thoracic receptors have been postulated to be the relevant afferents. For syncopal events related to micturition, defecation, or endoscopic instrumentation, receptors located in the gastrointestinal or genitourinary tracts are thought to be the most relevant afferents.

VV syncope resulting from orthostatic stress is considered to be the result of a disruption of the normal reflex response to gravitational forces. Upon assuming the upright position, the increase in gravitational forces results in the pooling of blood in the lower extremities. After standing, between 500 and 800 mL of blood is trapped in the distensible veins below the level of the heart, plasma moves to the interstitial fluid, and venous return, cardiac output, and blood pressure decrease [12]. These changes are detected by baroreceptors that in the case of arterial baroreceptors (carotid and aortic baroreceptors) relay information via vagal and glossopharyngeal afferents to the brainstem, particularly to the NTS. Afferents from other visceral areas, vascular and nonvascular peripheral sites also seem to converge in the hypothalamus, the NTS, and the area postrema (AP) [8]. In several of these centers, information is integrated, and via different connections to other areas, such

as the vasomotor center in the reticular formation, sympathetic and parasympathetic outflow can be modulated (Fig. 5.3). Likewise, associated symptoms preceding VV episodes such as nausea and vomiting could be related to stimulation of specific areas within the AP (a nausea/vomit brainstem center), while respiratory changes may result from changes in nuclei in brainstem areas such as the NTS.

In the case of postural VV syncope, some authors [13–15] have postulated that in the presence of factors leading to reduced venous return and cardiac filling there are three main conditions or postulates leading to VVS: (1) an enhanced reflex increase in sympathetic tone to the heart (first postulate, resulting in positive chronotropic and inotropic cardiac effects), (2) the development of ventricular hypovolemia in combination with an increased cardiac sympathetic stimulation results in large pressure transients on an "hypovolemic ventricular chamber" (second postulate). The vigorous contraction of the hypovolemic ventricle, in turn, distorts ventricular muscle with stimulation of "ventricular" afferents in the left ventricle (third postulate) that initiate a VV response. These three postulates form the basis of the "ventricular theory" of VV syncope and activation of these ventricular afferents appears to trigger an inhibitory response similar to that of Bezold-Jarisch reflex [13], resulting in hypotension and bradycardia.

The ventricular theory for VV syncope gained wide acceptance because it appeared to explain some clinical observations (e.g., exertional syncope in patients with aortic stenosis) or provide rational basis for the use of beta-adrenergic agonists on the diagnosis (isoproterenol plus tilt table testing) or in the treatment (beta-adrenergic antagonists) of VV syncope. However, a number of observations have challenged the universality of this theory in explaining postural VV syncope.

The first postulate, excessive sympathetic overstimulation, has been challenged by observations that have found normal [16] or even decreased [17–20] plasma norepinephrine levels preceding syncope. Similarly, studies using norepinephrine spillover have recorded decreases in norepinephrine release during syncope [21, 22], or blunted norepinephrine increases in response to orthostatic stress in patients who subsequently developed VV syncope [18] (Fig. 5.4). The most conclusive evidence for the absence of pronounced sympathetic reflex response before VV syncope comes from studies documenting that muscle sympathetic nerve activity (MSNA) does not increase before VV syncope [18, 23] (Fig. 5.5), that decreases in cardiac norepinephrine spillover are observed in subjects experiencing VV syncope [22], and that reduced cardiac sympathetic tone can be documented in VV syncope patients when evaluated with spectral analysis of heart rate variability [24, 25].

Another way to further test the first postulate of the "ventricular theory" is to investigate whether sympathetic stimulation is an essential requirement for the development of VV syncope. If increase in sympathetic stimulation is essential for the development of VV syncope, then an increase in sympathetic tone should worsen VV syncope, whereas a reduction in sympathetic outflow could potentially prevent it. At least one series of studies demonstrated that increases in sympathetic tone evoked by yohimbine (a centrally acting alpha 2-antagonist)

enhanced orthostatic tolerance and prevented syncope in most VV syncope patients in which this agent was tested [23]. On the other hand, a reduction in sympathetic tone produced by clonidine (a centrally acting antihypertensive agent) resulted in a worsening of tilt-induced syncope [23]. Overall, this evidence argues against increases in sympathetic activity as a necessary requirement for the development of VV syncope.

The second postulate, "ventricular hypovolemia", in combination with excessive sympathetic stimulation, resulting in pronounced ventricular wall distension, has been challenged by observations demonstrating no significant changes in cardiac chamber size or volume during tilt, at the time of presyncope, or syncope in well characterized VV syncope patients [26]. Similarly, others were unable to demonstrate significant changes in left ventricular end-diastolic or end-systolic dimensions [27].

Finally, the third postulate, "ventricular heart afferents initiating the VV response", has been challenged by observations documenting that in humans VV syncope can be evoked even in patients where heart ventricles have been denervated (e.g., patients with heart transplants) [28]. Similar observations have been recorded in preclinical models where inhibition of sympathetic nerve activity evoked by hemorrhage remained intact, even with total denervation of the heart [29].

In summary, all the evidence presented above casts serious doubt on the validity of the "Ventricular theory" for the development of VV syncope, and, instead, supports other mechanisms for the development of this syndrome [2]. From the other potential mechanisms, baroreflex dysfunction has been experimentally documented as a likely cause for the development of this syndrome and discussed elsewhere in this book.

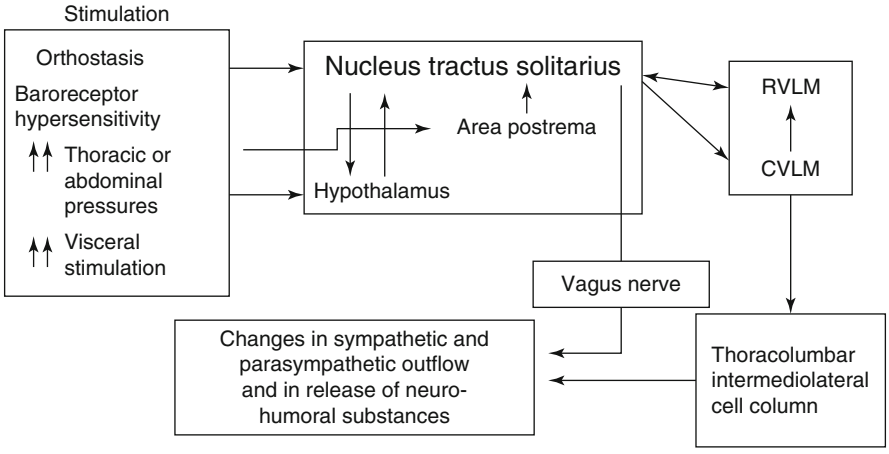

Fig. 5.3 Schematic representation of peripheral and central structures involved in the peripheral vasovagal syncope

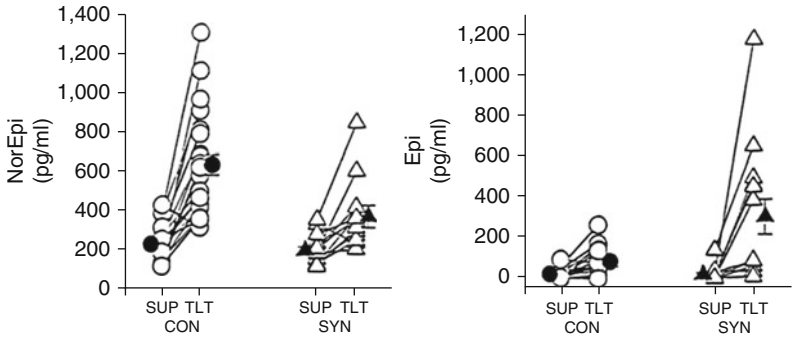

Fig. 5.4 Changes in plasma norepinephrine and epinephrine levels in postural vasovagal syncope. This figure represents mean values (*filled black circles*) and individual (*open circles*) norepinephrine (*NorEpi*) and epinephrine (*Epi*) levels in vasovagal patients (*SYN*) that also experience syncope during upright tilt (*TLT*) or in subjects with no history of syncope and who tolerated an entire 45 min tilt test without developing syncope. Note that SYN subjects had a blunted increase in plasma norepinephrine along with pronounced increases in epinephrine levels. In contrast, CON subjects exhibited a mirror response with healthy increases in norepinephrine levels and minimal increases in plasma epinephrine (From data presented in Mosqueda-Garcia et al. [18])

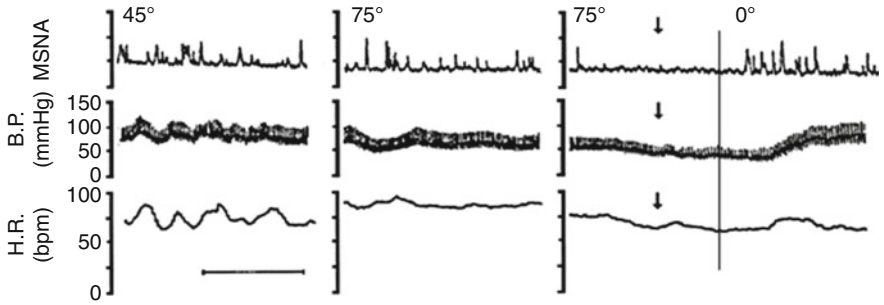

Fig. 5.5 Microneurographic, intra-arterial blood pressure, and heart rate tracings from a vasovagal syncope patient undergoing upright tilt table test. The first panel on the *left*, under the 45° label, presents the recording of sympathetic nerve traffic (*MSNA*) at the *top*, the blood pressure (*BP*) levels in the middle, and the heart rate tracings at the *bottom* (*HR*). The same order is followed in the middle panel but after immediately reaching the 75° tilt angle. Note in this panel that there is minimal to no increase in MSNA, blood pressure is lower and with less oscillatory pattern, and the heart rate has increased slightly compared to the 45° tracings. The panel at the right presents the tracings when the subject developed syncope (*arrows*) during the 75° tilt angle. Note in this panel the disappearance of MSNA and the pronounced hypotension and bradycardia. All these three variables recovered after the subject was returned to the supine position

Efferent Autonomic Signals in VV Syncope

It has been proposed that many of the autonomic integrative and efferent pathways in VV syncope are similar for the central and peripheral types. In the brainstem, two main brain areas regulating efferent autonomic tone (and likely involved in the VV response) include the NTS and the ventrolateral medulla [8] (Figs. 5.2 and 5.3). The

dorsal NTS receives neuronal afferents from higher brain nuclei relevant to central VV syncope (such as the paraventricular and lateral hypothalamic areas) and from peripheral structures (e.g., baroreceptors; relevant for the postural VV syncope) [8]. The NTS, in turn, projects connections carrying baroreceptors information to areas such as the rostral and caudal areas of the ventrolateral medulla (RVLM and CVLM, respectively). After processing of the signals, it appears that some of the same (RVLM) and other brain nuclei (such as the noradrenergic A5 cell group) send, in turn, afferents to the NTS, regulating autonomic function [8]; these reciprocal connections may serve as feedback regulatory mechanisms that result in changes in arterial blood pressure and heart rate during normal homeostasis and VV episodes.

Changes in autonomic tone regulated by the RVLM are produced by efferents that relay information to the thoracolumbar intermediolateral cell column of the spinal cord. It is in this area where preganglionic fibers that modulate sympathetic activity originate. The RVLM, in addition, contains aminergic (particularly, adrenergic neurons in the C1 area) and non-catecholaminergic neurons that participate in vasomotor function [8]. Increase in RVLM neuronal activity results in release of catecholamines and vasopressin and increases in blood pressure and heart rate. Reduction of neuronal activity in the RVLM, on the other hand, results in pronounced hypotension. Similarly, the CVLM contains neurons that reduce blood pressure by decreases in sympathetic tone.

The final efferent response in VV syncope is characterized by an increase in parasympathetic efferent activity to the sinus node, producing bradycardia, or in extreme cases, complete sinus arrest. There is also a decrease in sympathetic activity, which seems to be responsible, at least partially, for the fall in blood pressure. In most of the cases of VV syncope, bradycardia does not appear to be the driving factor for the development of hypotension. Several observations have now established that ventricular pacemakers prevent the bradycardia but do not prevent the hypotension or abort the syncopal event [30, 31].

The decrease in blood pressure has been postulated to be related to either an active or a passive neural effect or, alternatively, related to neuro-humoral mechanisms [2]. For the active neural mechanisms a cholinergic effect has been advocated. A sympathetic cholinergic vasodilator mechanism has been reported in the cutaneous circulation [32, 33]. Furthermore, after cervical sympathectomy, vasodilation seems to be absent during post-hemorrhagic-induced syncope [34], and, during fainting, blood flow in the forearms is higher when intact vasomotor innervation is present than after neural blockade [35]. However, failure to prevent vasodilation by intra-arterial cholinergic blockade has been reported, which may argue against an active neural cholinergic mechanism [36].

Evidence for a passive vasodilation mechanism in VV syncope seems, on the other hand, better supported by experimental evidence. The most compelling observation comes from recordings of human sympathetic nerve traffic in subjects experiencing VV episodes [18, 23, 37–39]. In several of these studies, the reflex increase in muscle sympathetic nerve activity (MSNA) appears to be blunted in susceptible individuals (Fig. 5.5). With prolongation of the precipitating factor (e.g., orthostatic stress), MSNA progressively falls until total disappearance, a few

seconds before syncope [18, 23]. There is also evidence for a decrease in cardiac and renal sympathetic nerve activity during VV episodes [40]. Adding to these observations, some other authors have reported a progressive decrease in subcutaneous blood flow (consistent with progressive sympathetic withdrawal) before the onset of syncope [41], and reduced cardiac sympathetic tone during VV syncope episodes (documented by spectral analysis of heart rate variability) [24, 25, 38, 42]. There are, however, some observations that appear to suggest that sympathetic withdrawal alone may not explain all the instances of VV fainting. For instance, some investigators have documented that the skeletal muscle vasodilation seen during VV syncope seems to be greater than the one observed as a result of just disappearance of sympathetic nerve activity [39, 43]. Others have documented, in selected number of subjects, that MSNA does not disappear during VV syncope [44] and this may suggest that, in some cases, alternative mechanisms are involved in the pathogenesis of this syndrome.

Neurohumoral Mechanisms in VV Syncope

Epinephrine

Some studies have provided evidence for a humoral vasodilating mechanism in the VV response. One consistent observation is the pronounced increase of plasma epinephrine in subjects experiencing VV syncope [16, 18, 19] (Fig. 5.4). Epinephrine is known to produce beta-adrenergic vasodilation in skeletal muscle and splanchnic vascular areas during stress conditions [45], and it has been postulated that during VV episodes, dissociation between the noradrenergic and the adrenomedullary response seems to develop [2]. In these conditions, epinephrine may produce unopposed vasodilation, resulting in severe hypotension [46]. While the epinephrine hypothesis may provide basis for the diagnostic use of isoproterenol in VV syncope, it is important to note that epinephrine infusions in susceptible individuals do not reproduce VV episodes [47].

Vasopressin

The involvement of vasopressin in VV syncope has been advocated by some authors [48]. Pronounced increases in plasma vasopressin levels have been noted in response to severe decreases in blood pressure observed not only during VV syncope but also during hypotensive shock related to hemorrhage [49]. Increases in vasopressin levels in VV syncope appear to be a compensatory mechanism attempting to restore blood pressure levels and to be associated with some of the clinical observations reported before the syncope (e.g., vasopressin release by nausea or vasopressin reduced diuresis in the post-syncope period) [11, 50].

Beta-Endorphin

The endogenous opioid peptide, beta-endorphin, has been implicated in VV syncope. Some experimental evidence first indicated that endogenous opioids appear to contribute to the hypotensive effect observed in response to acute blood loss

[51]. This was supported by the finding that selective opiate antagonists like naloxone partially reverted the fall in blood pressure observed after experimentally induced hypovolemia in an animal model [52]. In addition, beta-endorphin levels have been reported to increase in VV syncope [53], and some authors have speculated that, by acting within the CNS, beta-endorphin could increase efferent parasympathetic activity and diminish efferent sympathetic signaling [54]. However, some other studies in humans have not supported the potential involvement of opioids in VV syncope. For instance, Smith et al. [55] reported that pretreatment with a selective opiate antagonist did not prevent vasovagal syncope during simulated orthostasis.

Serotonin

Serotonin has also been proposed to be involved in VV syncope [56]. Some authors have proposed that serotonin surges may occur in humans before syncope and that serotonin reuptake inhibitors may decrease the sensitivity of the corresponding receptors and therefore be useful for the treatment of this condition [57]. However, most of the studies in humans using serotonin blockers have demonstrated failure of these agents to prevent syncope induced by orthostatic stress (e.g., tilt test). In fact, these studies using different types of serotonin-receptor antagonists documented a decrease tolerance to tilt, an acceleration of the development of hypotension, and a reduction of the sympathetic and adrenomedullary response to hypotension, without prevention of syncope [58].

Renin

Renin is another humoral agent implicated in the pathogenesis of VV syncope [19]. Plasma renin activity appears to fall before VV syncope evoked by upright tilt [59]. However, the decreases observed before syncope may be more likely related to autonomic changes precipitated by the VV response. The release of renin is controlled, at least in part, by efferent adrenergic fibers in the kidney. Upon assumption of the upright posture, renin along with other factors (e.g., plasma catecholamines) increases, and the extent of the increase is dependent on the fluid balance of the subject as well as the magnitude of the orthostatic challenge [12]. Renin in turn favors increases in angiotensin II, a well-known vasoconstrictor agent participating in the vascular regulation of arterial blood pressure. In this respect, the decrease in renin levels may contribute to the hypotensive effect observed during VV episodes but is unlikely to be a main pathophysiological factor involved in the response [2].

Nitric Oxide and Endothelin

Other internal substances such as nitric oxide [17] or endothelin [60] have been advocated to participate in the VV response. Until now, the experimental evidence has been limited and for the most part has not supported a primary role of these substances in the pathogenesis of VV syncope. For instance, pretreatment with nitric oxide synthase inhibitors did not prevent syncope or the vasodilation associated with VV episodes [39]. In the case of endothelin, no studies have been reported assessing the effects of specific antagonists for the prevention or modification of VV syncope.

5.2 Summary

The autonomic response before, during, and after VV episodes is complex and still not well delineated. The relevance of different CNS centers as well as the predominance of efferent pathways appears to be variable and dependent on the initiating stimulus. Irrespective of the precipitating event and of the selected afferent autonomic pathways, it seems that the final response is characterized by augmented parasympathetic activation and reduced sympathetic tone (either by active or by passive mechanisms). Nevertheless, the entire VV response is a dynamic process sometimes with rapid transition from activation to inactivation of some areas and with the possibility of predominance of some mechanisms over others in individual subjects. This could explain the variability of observations reported in the literature and strongly arguing against universal simple autonomic reflex mechanisms responsible for this syndrome.

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Pathophysiology of Vasovagal Syncope: Role of Baroreceptor Mechanisms

6

Rogelio Mosqueda-Garcia

Key Points

- Physiology of baroreceptor function
- Contribution of the baroreflex to the development of VV episodes
- Role of high- and low-pressure baroreceptors in the development of VV episodes
- Baroreflex evaluation in VV syncope patients

In many living organisms, performance of vital and complex mental functions depends on an adequate cerebrovascular perfusion pressure. Cerebral perfusion levels are highly dependent on systemic arterial blood pressure, which in turn is regulated by cardiovascular reflexes such as the baroreceptor reflex. The baroreflex maintains arterial blood pressure within narrow ranges by rapid modulation of autonomic efferent function resulting in changes in heart rate, cardiac output, and total peripheral resistances. These changes are aimed to restore arterial blood pressure to prior homeostatic levels [1].

Disruption of the baroreflex appears to be a hallmark of the vasovagal syncope (VVS) syndrome, as it is evident from the concomitant development of hypotension and bradycardia. In VV syncope, baroreceptor mechanisms appear to be overridden and unable to prevent the extreme low pressure and/or heart rate levels that lead to cerebral hypo-perfusion and ultimately result in syncope. More importantly, dysfunction of baroreflex function also appears to be a primary initiating cause that in many cases results in VV syncope events [2].

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In this chapter, we will outline the role and potential contribution of several baroreceptors to the development of VV episodes. Main points of discussion will be the role of high- and low-pressure baroreceptors and a critical assessment of whether increase or decrease in sensitivity of baroreceptors is responsible for the development of VV syncope.

6.1 Physiology of High- and Low-Pressure Baroreceptors

Baroreceptors, specialized neuronal tissue located in key vascular and cardiac areas, serve as the initial sensing mechanism for changes in blood vessels or cardiac fluid pressure [3]. These structures alter their neural firing in response to stretch caused by pressure changes in the arterial wall and in other hemodynamic regions (i.e., cardiac or pulmonary areas). Changes of baroreceptor activity are relayed to the CNS, where integrative centers process this information and then initiate efferent neural activity that results in cardiovascular adjustments (i.e., changes in heart rate or arterial pressure). This "negative feedback" mechanism maintains arterial pressure and aims to preserve adequate perfusion pressure to different organs including the brain [4].

Baroreceptors have been subdivided as those responding by stretching in response to low pressure and those activated by high-pressure changes (low- and high-pressure baroreflexes) or by their anatomical location (arterial, pulmonary, cardiac, etc.) [5]. Arterial baroreceptors are mainly located in the carotid sinus and in the aortic arch and are thought to contain the primary nerve afferents responding to high-pressure changes. Afferent baroreceptor impulses from these areas travel via myelinated and unmyelinated nerve fibers within the carotid sinus and aortic nerves to the medulla, specifically within the nucleus of the solitary tract (NTS) where the first synapse of the baroreflex is located [6].

Cardiac baroreceptors, located in the walls of the atria and heart ventricles, may respond to both low and high pressures, while pulmonary baroreceptors, located in the walls of intrathoracic vessels (e.g., the superior and inferior vena cavae, pulmonary and artery veins) appear to respond to low-pressure changes [5]. Afferents from cardiopulmonary receptors travel with sympathetic nerves to the spinal cord and with the vagus nerve to the medulla. Along with the arterial baroreceptor afferents, nerve fibers from cardiopulmonary baroreceptors converge in the NTS, which is therefore considered as the major integrative CNS center for processing arterial and cardiopulmonary baroreflex information [6].

From the NTS, efferent projections relay information to other medullary centers such as the ventrolateral medulla or to hypothalamic centers. These areas further integrate baroreflex activity and ultimately orchestrate the final autonomic efferent response that results in adaptive changes in arterial blood pressure and heart rate [6]. The efferent autonomic response to arterial baroreflex activation (stretching due to increase in pressure) is characterized by a reduction in sympathetic activity (aim to reduce vascular resistances), increase in cardiac parasympathetic tone (aim to decrease heart rate), and changes that decrease the release of vasoactive and cardiac acting substances such as epinephrine, renin, and angiotensin (Fig. 6.1). Opposite

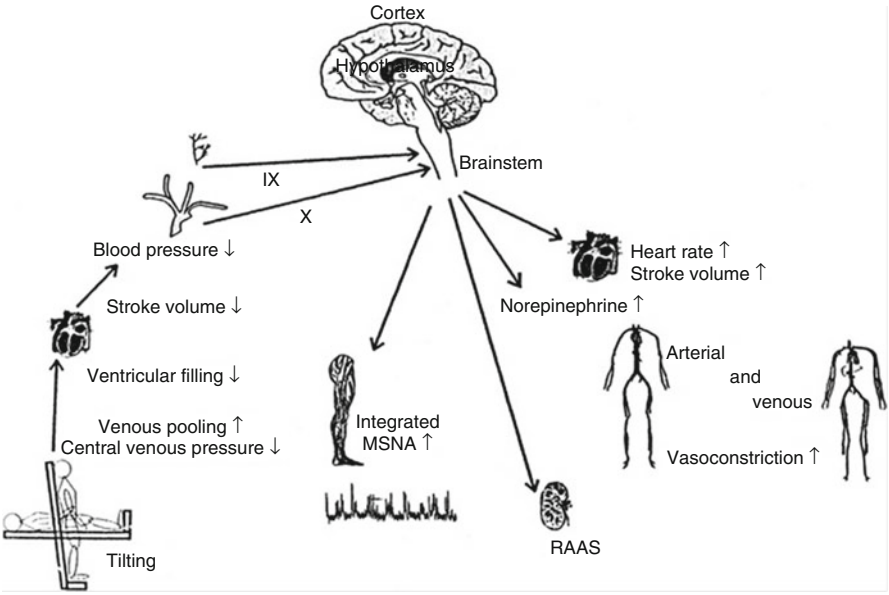

Fig. 6.1 Neurohumoral and baroreflex responses to orthostatic stress. Some of the changes set in motion by passive upright tilt (or standing) are shown. *IX* indicates the glossopharyngeal nerve, *X* the vagal nerve, *RAAS* the renin angiotensin system

effects develop in response to baroreflex deactivation (due to decreases in arterial blood pressure) and are distinguished by increases in sympathetic activity, decreases in parasympathetic outflow, and increases in epinephrine renin, and angiotensin release, among other substances [3].

6.2 Baroreflex Dysfunction in VV Syncope

Several lines of evidence have supported the notion that altered or defective baroreflex function is a primary mechanism accounting for the development of VV syncope [2]. Evidence for increased sensitivity [7–10] or, alternatively, for decreased function [11–16] has been described and theoretical frameworks have therefore been postulated.

The primary importance of baroreceptors in VV syncope first came from preclinical studies. In an animal model [17], the hypotension and sympathetic inhibition evoked by hemorrhage were prevented by deafferentation of carotid baroreceptors. This indicated that the function of carotid baroreceptors was important for the development of sympathetic withdrawal similar to the one observed in VV episodes. In the clinical setting, most of the available literature indicates that some type of baroreflex dysfunction is present and somehow results in the inability to sense or compensate for changes in gravitational forces in subjects with VV syncope [2].

Enhanced Baroreflex Sensitivity as Etiological Factor for VV Syncope

The possibility of augmented baroreflex sensitivity or, alternatively, a paradoxical activation of baroreceptors has been supported by some studies [7–10]. In one clinical study, Sneddon and collaborators [10] studied baroreflex function in patients with recurrent VV syncope and with positive or negative tilt-table test (a clinical study that is often used to reproduce VV episodes). While no differences were seen in arterial high-pressure baroreflexes between tilt-positive and tilt-negative patients, the increase in forearm vascular resistance in response to lower-body negative pressure (LBNP, a test that activates cardiopulmonary receptors) was greater in the tilt-positive patients, suggesting an increased sensitivity in this subgroup of VV syncope patients. Alder and collaborators [8] performed clinical studies in which baroreflex sensitivity was tested under conditions of rest and during stress in subjects with history of VV syncope. They reported that, in comparison to normal controls, VV syncope subjects displayed greater baroreflex sensitivity. In a more recent study, Pitzalis and collaborators [9] reported that some subjects with tilt-positive VV syncope exhibited greater resting baroreflex sensitivity as documented by an enhanced reflex tachycardic response to arterial baroreceptor deactivation. Similarly, another study documented that in VV syncope patients the initial tachycardic response to tilt, as the response of pulse interval to neck suction, was significantly larger in VV syncope patients than in controls [7]. Finally, a study in older subjects with positive tilt-table test exhibited exaggerated arterial baroreflex sensitivity at baseline but a much larger decrease in overall arterial baroreflex sensitivity than the tilt-negative group during the orthostatic test [18].

Resetting of Baroreflex Function as Etiological Factor for VV Syncope

Resetting of baroreceptor function (paradoxical or restarting activity at low-pressure levels) has been implicated in the development of sympatho-inhibition during severe hemorrhage [19], and some authors have postulated it to be also occurring during episodes of VV syncope [20]. Some clinical studies have documented that plasma norepinephrine first increases and then decreases during progressive reductions of arterial blood pressure [4]. In accordance with the concept of resetting baroreceptor activity is the observation that the inhibition of muscle sympathetic nerve activity (MSNA) declines during continuous stimulation of the carotid sinus nerve in humans [21] and the "paradoxical" activation of arterial baroreceptors observed at very low pressures in some animal studies [22]. Additional evidence for abnormal resetting of baroreflex function and/or altered response of low-pressure baroreceptors came from a study by Jacobs and colleagues [23]. They reported that subjects experiencing syncope during −40 mmHg LBNP stimulation exhibited an already abnormal response to non-hypotensive negative pressures. This response was characterized by a failure of forearm norepinephrine spillover to increase.

Decreased Baroreflex Sensitivity as Etiological Factor for VV Syncope

An increasing number of observations and well-designed experimental studies have documented decrease in baroreflex sensitivity or function as a likely etiological factor for VV syncope. One clinical study performed a comprehensive assessment of baroreflex function in controls and in patients with spontaneous VV syncope [11] (confirmed by tilt-table test). In this study, VV syncope patients exhibited a severe impairment of cardiopulmonary sensitivity as demonstrated by the absence of forearm vasoconstriction or, in some patients, by the development of paradoxical forearm vasodilation during non-hypotensive LBNP. In the same study, the authors evaluated arterial baroreflex sensitivity and reported a trend for reduced sensitivity in the VV syncope patients when compared with control subjects [11]. In a different study, other authors reported that although baroreceptor response did not differ significantly at rest, subjects who developed VV syncope at the end of 45 min tilt exhibited a markedly reduced baroreceptor response [13].

Decrease in baroreflex sensitivity was well documented in a study that defined the entire sigmoidal baroreflex curve in VV syncope patients and in healthy control subjects [20]. In this study, baroreflex curves were obtained by determining cardiac vagal, blood pressure, and MSNA responses to both activation and inactivation of baroreceptor activity by stepwise infusion of sodium nitroprusside (threshold and linear parts of the curve) and phenylephrine (linear and saturation parts of the curve). Patients with recurrent VV syncope (confirmed with repeat positive tilt-table tests) exhibited a clear reduction in cardiac (Fig. 6.2) and sympathetic (Fig. 6.3) baroreflex responses when compared to control subjects. The study concluded that at even low levels of stimulation, baroreflex function is impaired in subjects with VV syncope and this impairment is likely to be an etiological factor.

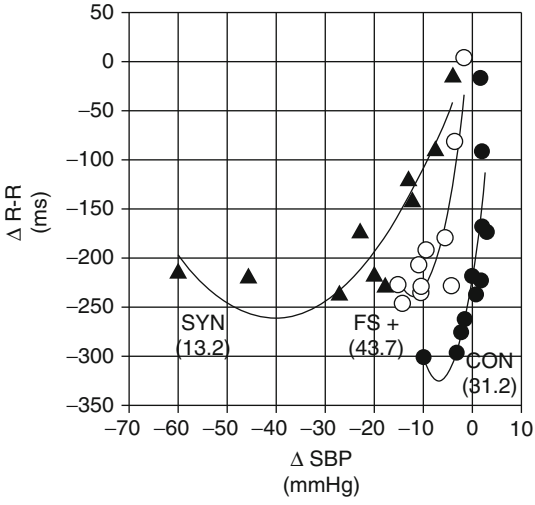

Fig. 6.2 Relationship between changes in R-R interval and systolic BP during tilt. The figure presents the plotted values and regression lines obtained from correlating the changes in R-R interval (ΔRR) with the changes in systolic BP (ΔSBP) in controls (●), false-positive subjects (○), and NMS patients (▲). Values between parentheses indicate the regression slope (Reproduced with permission from Mosqueda-Garcia et al. [20])

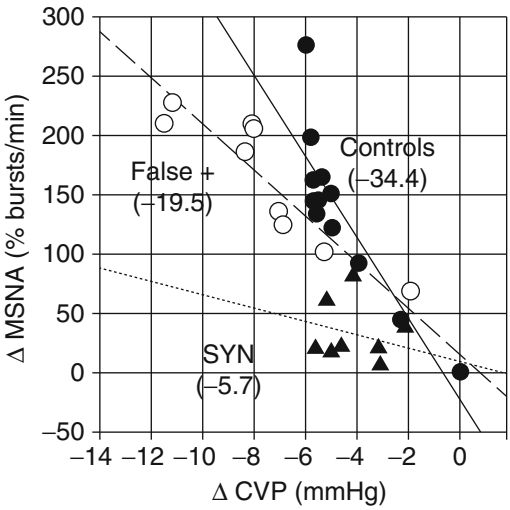

Fig. 6.3 Relationship between changes in MSNA and changes in central venous pressure (*CVP*) during upright tilt. The *symbols* represent the plotted values and the *lines*, regression lines obtained from correlating the changes in R-R interval (Δ*R-R*) with the changes in systolic BP (Δ*SBP*) in controls (●), false-positive subjects (○), and NMS patients (▲). Values between parentheses indicate the regression slope (Reproduced with permission from Mosqueda-Garcia et al. [20])

Other authors also have reported reductions in baroreflex sensitivity in subjects developing VV syncope induced by the combination of nitrate infusion with upright tilt-table test [15]. In this study, patients with VV syncope exhibited significant depression in baroreflex sensitivity and in baroreflex effectiveness index (a measurement that quantifies the number of times the baroreflex is effective in driving the sinus node) [15]. Ellebogen et al. [24] also found evidence of pronounced reductions in baroreflex sensitivity in patients with VV syncope with positive tilt tests when compared with patients with negative tilt tests. In a subsequent report, the same authors, using a neck-chamber technique to affect baroreflex function in the carotid areas, found evidence of reduced vagal baroreflex gain during pressure reduction/elevation sequences but intact function with the pressure elevation/reduction algorithm [25].

Some authors have suggested that baroreflex function is preserved but suddenly suppressed by a potent depressor reflex originating in the heart [26]. Supporting this notion, a study [16] reported that arterial baroreflex function ceases during VV episodes. In contrast, other studies have found reductions in baroreflex function during the early phases of an orthostatic stimulus [20]. This study reported that when compared with controls, patients with VV syncope have important reductions when baroreflex function is estimated by correlation slopes between heart rate and systolic blood pressure, or between MSNA and central venous pressure during upright tilt [20].

Conclusions

Overall, most of the available studies report some type of baroreflex dysfunction that is thought to result in the inability to sense or compensate for changes in gravitational forces in subjects with VV syncope. While the extent and exact type of dysfunction remains to be completely characterized, it is clear that

evaluation of baroreflex function should be implemented in a systematic fashion that will allow the treating physician or investigators to propose or design better therapeutic alternatives for VV syncope patients.

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Role of Adenosine

7

Michele Brignole, Jean-Claude Deharo, and Regis Guieu

Key Points

- Different central or peripheral baroreceptor reflex abnormalities, alterations in neurohumoral mechanisms or both can play a role in causing the different clinical manifestations of neurally mediated syncope.
- The patients with typical vasovagal syncope and those with a positive vasovagal response during tilt-table testing have a typical purinergic profile which is characterized by high adenosine plasmatic values, high expression of A_{2A} R and predominance of CC variant in the single nucleotide c.1364 C > T polymorphism of the A_{2A} R gene. These forms of syncope should be regarded as 'high adenosine syncope'.
- The patients with syncope without prodromes and normal heart and the patients with idiopathic AV block have a purinergic profile which is opposite to that observed in vasovagal syncope patients and is characterized by very low APL values, low expression of A_{2A} R and the predominance of TC variant in single nucleotide c.1364 C > T polymorphism of the A_{2A} R gene. These forms of syncope are 'low adenosine syncope'.

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- In ‘high adenosine syncope’ most A_1 receptors in the AV node are saturated and AV block is unlikely to occur. The final clinical result is dependent on the combination of the direct neural outflow – vagal activation and sympathetic inhibition – and the vasodilatory effect of the A_{2A} R activation.
- In ‘low adenosine syncope’ a transient release of endogenous adenosine is sufficient to block conduction in the AV node when a high number of free high-affinity A_1 receptors in the AV node are available.

7.1 The Wide Clinical Spectrum of Neurally Mediated Syncopes

Typical vasovagal syncope differs from other neurally mediated reflex syncopes not only in terms of its precipitating factors (fear, strong emotion, etc.), which constitute predefined diagnostic criteria, but also in the variety of its clinical features. The presence of a trigger of a recognizable type is important for the diagnosis of reflex syncope (in which case the general term ‘situational syncope’ is often employed) [1]. Most variants are in fact named for their triggers, such as cough syncope, micturition syncope, swallow syncope, etc. Except for the presence of a trigger, autonomic activation is an important clue to diagnose vasovagal syncope in adolescents and most adults, with the exception of the elderly in whom the autonomic activation is less noticeable and therefore causes fewer warning symptoms.

Often, reflex syncope has an ‘atypical’ presentation. The term ‘atypical form’ is used to describe those situations in which reflex syncope occurs with uncertain or even apparently absent triggers. The diagnosis then rests less on history taking alone and more on the exclusion of other causes of syncope (absence of structural heart disease) and on reproducing similar symptoms with carotid sinus massage, tilt-table testing or other tests. On this extreme is a distinct form of syncope characterized by unexplained sudden-onset syncope without prodromes, normal heart and normal electrocardiogram (i.e. absence of structural heart disease) [2]. Since the patients with syncope due to idiopathic AV block [3] have features very similar to these latter patients, an overlap between these two forms is likely to exist. This wide clinical spectrum is even more complicated by the fact that much overlap exists among the clinical forms which can occur frequently in the same patient in different periods of their life.

Despite the final effect being similar in all forms, that is, a combination of various entities of hypotension and bradycardia, different central or peripheral baroreceptor reflex abnormalities, alterations in neurohumoral mechanisms or both can play a role in determining the different relative contribution of hypotension and bradycardia in causing the different clinical manifestations of syncope. Among the several biochemical mediators that have been advocated to play a role

(e.g. epinephrine, serotonin, tyrosine hydroxylase, norepinephrine transporter proteins, etc.), adenosine has recently been investigated in typical vasovagal syncope and in syncope without prodromes and normal heart.

7.2 Vasovagal Syncope (High Adenosine Syncope)

Compared with normal control without syncope, the patients with typical vasovagal syncope and those with a positive vasovagal response during tilt-table testing have a typical purinergic profile which is characterized by high adenosine plasmatic levels (APLs) [2–5], high expression of A_{2A} receptors [5–7] and the predominance of CC variant in the single nucleotide c.1364 C > T polymorphism of the A_{2A} receptor gene [8]. In four studies [2–5], the mean APL found in vasovagal syncope patients ranged between 0.85 and 2 μM/l, compared with a mean value of 0.49 μM/l found in healthy controls (range 0.38–0.68 μM/l) (Fig. 7.1), and was compatible with the activation of low-affinity A_{2A} receptors (Kd 1.8 μM) [9], which are located in the vessels and cause vasodilation [10].

7.3 Syncope Without Prodromes and Normal Heart (Low Adenosine Syncope)

The patients with syncope without prodromes and normal heart have a purinergic profile which is opposite to that observed in vasovagal syncope patients and is characterized by very low APL values [2], low expression of A_{2A} receptors and the predominance of TC variant in single nucleotide c.1364 C > T polymorphism of the A_{2A} receptor gene (personal communication, Guieu 2014). Finally, also the patients with idiopathic AV block had very low APL values, similar to those of the patients with syncope without prodromes (Fig. 7.1). In both groups, the rapid i.v. injection of

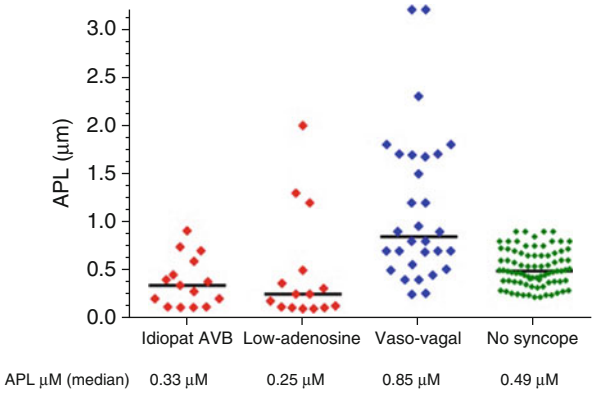

Fig. 7.1 Individual APLs in 18 patients with idiopathic paroxysmal atrioventricular block, in 15 'low adenosine syncope' patients, 30 patients with VVS, and 81 control subjects without syncope (From Ref. [2]). The individual adenosine plasmatic levels (*APLs*) of the four groups of patients are plotted. The median APL of each group is also shown. *AVB* atrioventricular block

18 mg of adenosine or 20 mg of adenosine triphosphate (ATP test) caused a positive response defined as a pause >6 s in 60 and 66 %, respectively, which was higher than the 28 % rate observed in the general population of unexplained syncope.

7.4 Role of Adenosine: A Proposed Explanation

From the above findings, both high and low APLs are associated with different forms of neurally mediated syncope. Intermediate situations are also expected. We suppose that APL may play a causal role in the genesis of such forms (and eventually of other reflex forms) (Fig. 7.2).

The effect of adenosine on different structures and organs involves activation of membrane receptor subtypes, named A_1, A_{2A}, A_{2B} or A_3, depending on their primary sequence and affinity for ligands. The effect of adenosine on the AV node is mainly due to the stimulation of high-affinity A_1 receptors, which are much more numerous in the AV node than in the sino-atrial node [10–12]. Like many other cell surface receptors, a number of cardiac adenosine A_1 receptors undergo upregulation and downregulation when cardiac tissues are chronically exposed to low or elevated concentrations of adenosine receptor agonist (i.e. adenosine). A transient release of endogenous adenosine could be sufficient to block conduction in the AV node when a high number of free high-affinity A_1 receptors (with a constant of dissociation at 0.7 μM) in the AV node are available (‘*low-APL patients*’). Conversely, when APL is high, as in patients with vasovagal syncope or positive tilt testing, most A_1 receptors in the AV node are saturated and AV block is unlikely to occur (Fig. 7.3). In vasovagal syncope, a combination of both neural and purinergic activation is supposed. The high APL value found in such patients is compatible with the activation of low-affinity A_{2A} receptors (with a constant of dissociation at 1.8 μM) [9] which are located in the vessels and cause vasodilation [10]. The final clinical result is dependent on the combination of the direct neural outflow – vagal activation and sympathetic inhibition – and the vasodilatory effect of the activation of the A_{2A} receptors. Despite differences in their receptors, adenosine and the neurotransmitter acetylcholine have remarkably similar effects on cardiac function [13–16].

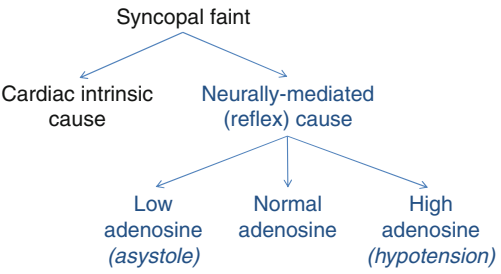

Fig. 7.2 A proposed new classification of syncope based on aetiology and adenosine profile

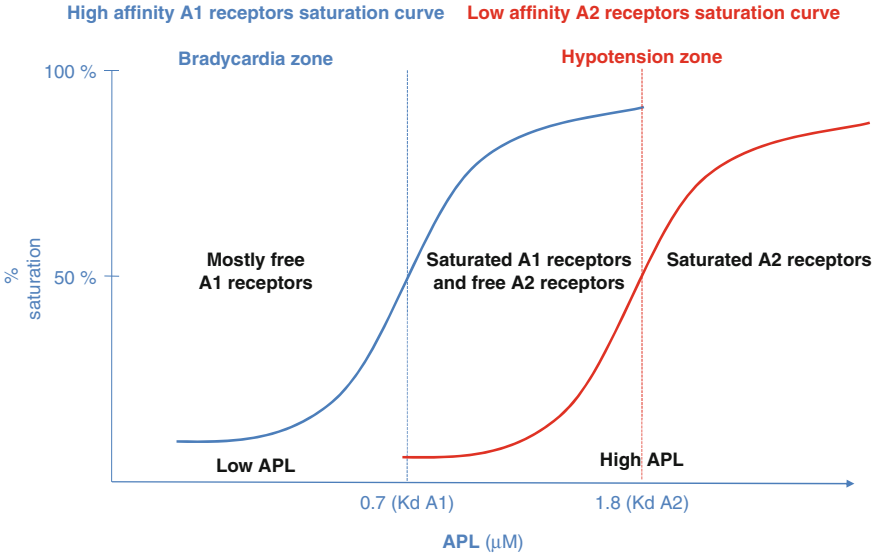

Fig. 7.3 Schematic description of the adenosine receptor-effector coupling system. The effect of adenosine on the AV node is mainly due to the stimulation of high-affinity adenosine A_1 receptors. Like many other cell surface receptors, a number of cardiac adenosine A_1 receptors undergo upregulation and downregulation when cardiac tissues are chronically exposed to elevated concentrations of adenosine receptor agonist (i.e. adenosine). The constant of dissociation (*Kd*) of A_1 adenosine receptors is 0.7 μM. Around the Kd value, a high number of free high-affinity A_1 receptors in the AV node are available for activation. In this range, even a moderate increase in endogenous APL binds a high number of A_1 receptors, leading to AV block. Conversely, at high APL values, most A_1 receptors in the AV node are already saturated and further endogenous adenosine is unlikely to cause AV block. Conversely, high APL values are still compatible with the activation of low-affinity A_{2A} receptors (Kd 1.8 μM) which are located in the vessels and cause vasodilation. The final clinical result is dependent on the combination of the direct neural outflow – vagal activation and sympathetic inhibition – and the vasodilatory effect of the activation of the A_{2A} receptors

A possible explanation is the similarity of their receptor-effector coupling systems. In addition to having direct effects, acetylcholine and adenosine act synergistically against the stimulatory action of the sympathetic neurotransmitters noradrenaline and adrenaline on adenyl cyclase. Thus, excitatory and inhibitory effects of the adrenergic cholinergic and purinergic outflows are integrated at the level of the receptor-effector coupling system, resulting in the final cardiac and vascular effect (Fig. 7.4). The various combinations of excitatory and inhibitory outputs integrated in this model could explain the different clinical forms of neurally mediated syncope observed in the clinical practice.

The cause of the transient release of endogenous adenosine responsible for paroxysmal AV block is unknown. Adenosine is a ubiquitous substance, which is released under several physiological and pathological conditions (e.g. in the case of myocardial hypoxia or during reflex beta-adrenergic stimulation) [13, 14].

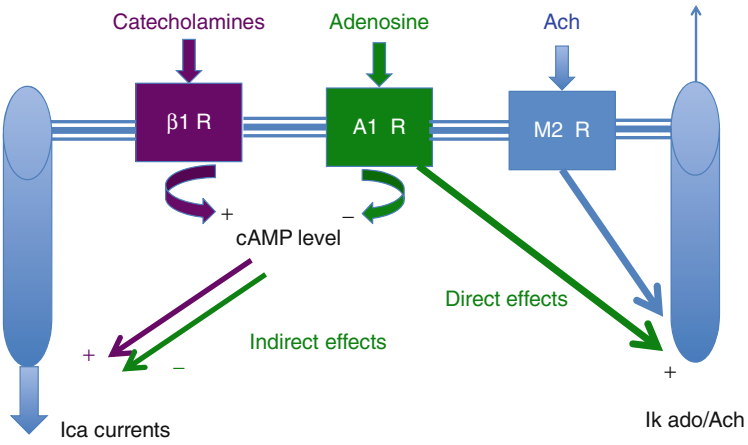

Fig. 7.4 The final effect of adenosine on heart rate is mediated by direct and indirect mechanisms. The indirect mechanism is the anti-adrenergic action of A1 adenosine receptors by opposing the effect of sympathetic nervous activation and ß1 stimulation by lowering intracellular cAMP levels in target cells. The direct mechanism is due to the induction of a potassium current through an inward rectifier potassium channel which leads to hyperpolarization of sinus node and AV node cells (*IK ado*). This latter effect is very similar to that obtained with acetylcholine, Ach, on muscarinic receptors. *Ach* acetylcholine, *A1 R, A1* adenosine receptor, *ß1 R* beta 1 adrenergic receptor, *M2 R, M2* muscarinic receptor, *IK* inwards-going rectification

Conclusion

Specific purinergic profiles characterize different clinical forms of neurally mediated syncope.

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Cardiovascular Rhythms in Vasovagal Syncope

8

Raffaello Furlan, Nicola Montano, and Alberto Porta

Key Points

- Heart rate and blood pressure spontaneous fluctuations may reflect the functional state of the cardiovascular neural control.
- Power-spectrum and cross-spectrum analysis methodologies enable the automatic assessment of both the frequency and the power of the nonrandom fluctuations in the cardiovascular parameters and in the neural sympathetic discharge variability and of their relationships.
- Vasovagal syncope can be considered a *disorder of regulation* in which different *quantities* of neural sympathetic and vagal activities interact, resulting in an unstable autonomic profile before the loss of consciousness.

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- Fluctuations at 0.1 Hz characterize blood pressure and heart rate variability, and the pattern of the discharge activity of the sympathetic vasomotor control. Disruption of these rhythms and of their strict relationships typifies the period just preceding typical orthostatic vasovagal syncope.

8.1 Introduction

In this chapter, we will address the hypothesis that heart rate and blood pressure spontaneous rhythms may reflect the functional state of the cardiovascular neural control [1]. The automatic analysis of these rhythms, by *power-spectrum* algorithms assessing their amplitude and relationships before a loss of consciousness, may furnish a valuable insight into the complex pathophysiological mechanisms underlying *vasovagal syncope*.

It is just a reminder that vasovagal syncope is characterized by a wide range of clinical presentation. The actual loss of consciousness can be abrupt with only few and transient symptoms or, conversely, slower with presyncope signs and symptoms such as dizziness, sweating, and nausea preceding the loss of consciousness by seconds or even minutes. It is plausible that these different clinical presentations might be related to different cardiovascular neural changes preceding the vasovagal event. In keeping with a fairly old definition, originally referred to as arterial hypertension [2], in this chapter vasovagal syncope will be considered as a *disorder of regulation* in which different *quantities* of neural sympathetic and vagal activities interact, resulting in an autonomic profile liable to undergo quick variations over time. These variations are mirrored by concomitant quantitative changes in the amplitude of the spontaneous *fluctuations of heart rate and blood pressure*. The pivotal role of the rhythms characterizing the neural sympathetic discharge activity to the vessels, as they can be measured by microneurography techniques, and their relationship with blood pressure and heart rate variability will also be addressed in the vasovagal syncope context.

8.2 Methodological Aspects

Cardiovascular variables exhibit spontaneous fluctuations around their main values, usually referred to as *spontaneous variability* (Fig. 8.1). Since the time course of cardiovascular variables is not completely predictable [3], cardiovascular variability series cannot be considered a deterministic signal. In addition, since they show periodicities in the low frequency (LF, from 0.04 to 0.14 Hz) and high frequency (HF, from 0.14 to 0.5 Hz) bands [4], cardiovascular variability series cannot even be deemed as fully unpredictable [3]. They should be considered realizations of partially predictable stochastic processes [5]. Accordingly, they were modeled as an autoregressive process, meaning that the current value of the series was described as sum of two components: the first component is fully predictable and computed as a linear combination of p previous samples weighted by constant coefficients, where

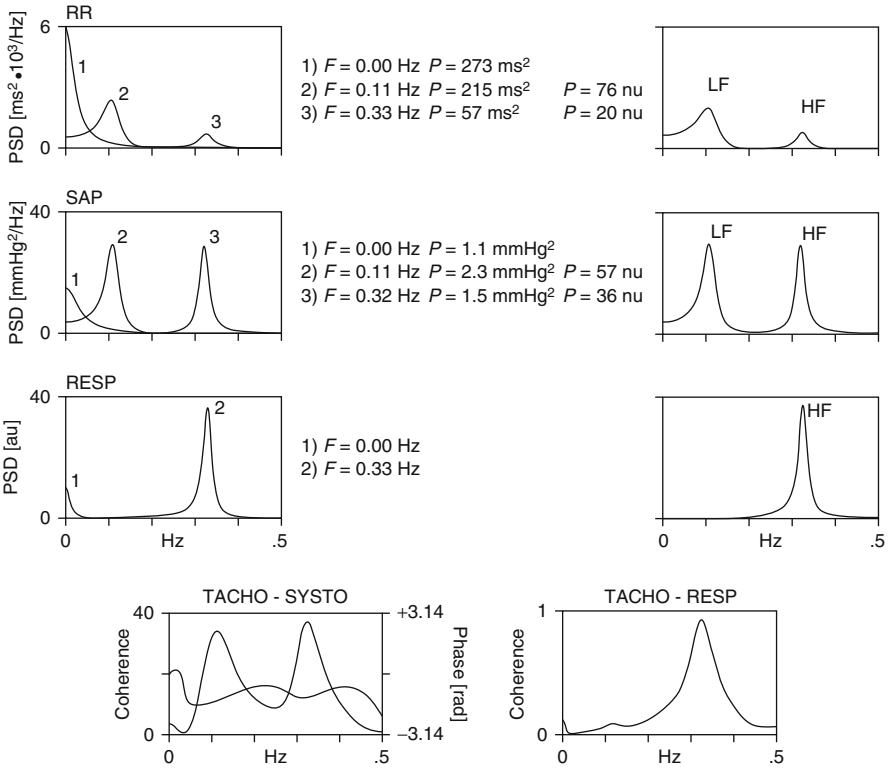

Fig. 8.1 Frequency analysis of RR interval, systolic arterial pressure variability, and of respiration. Notice the spectral decomposition of the variability signals in the nonrandom low frequency (*LF*) and high frequency (*HF*) components. Cross-spectrum and coherence analysis are also shown. *RR* indicates RR interval, *SAP* systolic arterial pressure, *RESP* respiratory activity, *TACHO-SYSTO* and *TACHO-RESP* are the cross-spectra between RR interval and systolic arterial pressure and between RR interval and respiratory variability, respectively

p is the so-called model order, and the second one is fully unpredictable and modeled as a white noise. Given the stochastic nature of cardiovascular variability series, its power spectral density has been estimated directly from the coefficients of the autoregressive process [5] according to a parametric approach. This method was largely exploited as a viable alternative to the classical Fourier method [6] (i.e., the so-called nonparametric technique) that is, conversely, more suitable in the case of fully deterministic signals [7].

Power spectral tools require stationary data within the frame selected for the analysis (i.e., at least the preservation of the mean and variance). Checking this prerequisite is important because the absence of stationary variables significantly bias spectral markers in the LF and HF bands [8]. On the other hand, finding a stationary sequence in cardiovascular parameters may be difficult, particularly when analyzing vasovagal events due to the intrinsic clinical instability of the disorder. To overcome this

limitation, new approaches such as *time-variant spectral methods* [9] have been developed. The estimate of power spectral density under nonstationary conditions requires strategies to reduce progressively the importance of the values present in the frame under analysis with the time distance from the most recent sample. This can be achieved by weighting the data by an exponential function with negative decay. Conversely, nonparametric approaches for the estimate of power spectral density in nonstationary conditions are based on the definition of specific time-frequency distributions devised to locate in time a rhythm with the finest frequency resolution. Results of the analysis are plotted over a time-frequency color-coded plane. Even though both time-variant parametric and nonparametric approaches are extremely powerful, applications to real data provided less impressive results as a consequence of the intrinsic inertia of the algorithm that prevents the possibility to track changes with a swiftness adequate to the physiological modifications under scrutiny.

8.3 The Neural Control of the Cardiovascular System: A Model

Figure 8.2 depicts a schematic representation of the *neural control of the cardiovascular system*. The anatomical pathways (left cartoon) are represented by baroreceptor and vagal afferents and efferent nerves connecting the bulbar structures with the heart. In addition, there are sympathetic afferent and efferent neural fibers projecting to the spinal cord. Bulbar and spinal nuclei are linked to sovraspinal and cortical structures.

From the functional standpoint, this complex neural network can be modeled as operating as a dual feedback system (right flowchart). *Excitatory positive feedback*

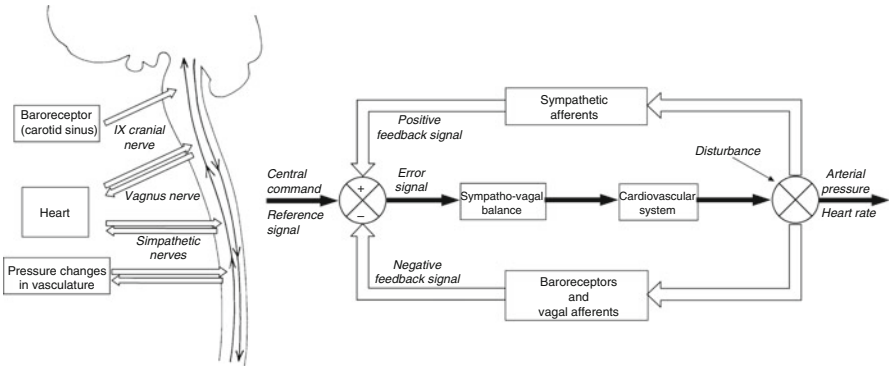

Fig. 8.2 Schematic representation of the neural control of the cardiovascular system. The anatomical pathways are represented in the left cartoon. From the functional standpoint, this complex neural network can be modeled as operating as a dual feedback system (right flowchart). Sympathetic afferents are functionally excitatory (+), whereas vagal and baroreceptive afferents are inhibitory (−). The instantaneous relationship between functionally opposite neural influences (sympathovagal balance) results in RR and blood pressure spontaneous variability

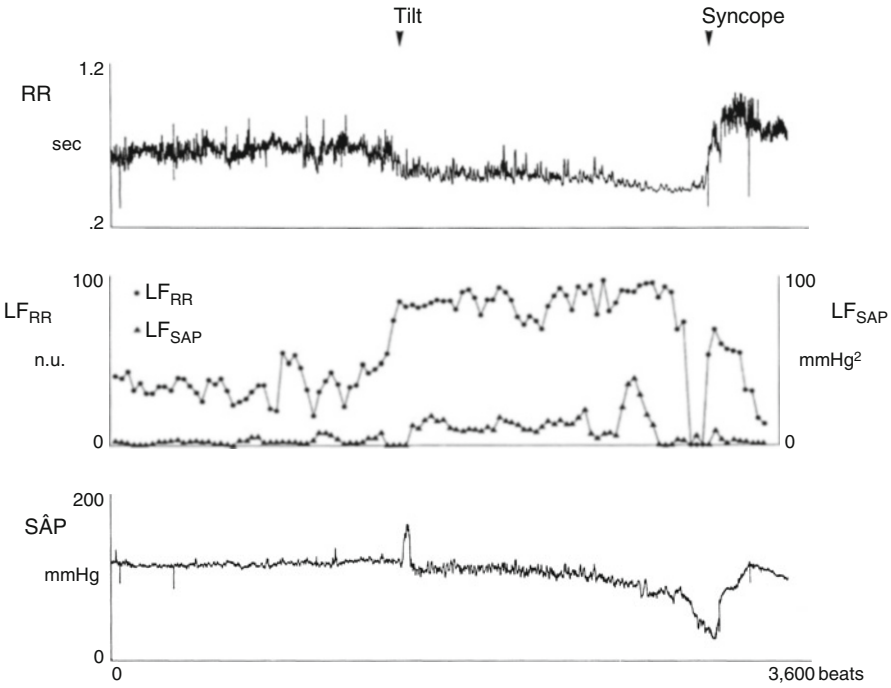

Fig. 8.3 Representative example of typical syncope during a tilt test ending up with a reflex bradycardia. Upper and lower traces are RR interval and systolic arterial pressure (*SAP*) values expressed as a function of beat number, respectively. The central cartoon depicts the low frequency oscillations (~0.1 Hz) extracted from both RR interval (LF_{RR} normalized units, n.u., *filled circles*) and SAP (LF_{SAP}, *filled triangles*) variability. Spectrum analysis was performed by overlapping by 75 % RR and SAP series, each being of 125 beats length

mechanisms depend upon sympathetic afferents, whereas inhibitory negative feedback mechanisms rely on baroreceptors and vagal afferents [10].

Therefore, the immediate cardiovascular neural control can be considered as the result of the instantaneous relationship between excitatory sympathetic stimuli and vagal/baroreceptor inhibitory influences, with a further modulation exerted by the cortical structures, that is, the central command. The prevalence of sympathetic excitatory activity or, conversely, of the vagal inhibitory tone results in beat-by-beat variations in heart period and systolic arterial pressure (Figs. 8.1 and 8.3).

8.4 Functional Meaning of the Cardiovascular Spontaneous Fluctuations

Autonomic profile is traditionally inferred from the analysis of the spontaneous fluctuations of heart period, approximated as the temporal distance between two consecutive QRS complexes from the ECG (RR interval), and arterial pressure values,

usually systolic arterial pressure (SAP). Two major nonrandom oscillatory components can be identified and quantified both in absolute and normalized values in RR interval spontaneous variability by means of autoregressive power-spectrum methodologies [7, 4, 11] (Fig. 8.1): a *high frequency component*, HF_{RR}, synchronous with the respiration (~0.25 Hz), a recognized index of the vagal efferent modulation to the senoatrial node [6, 4], and a *low frequency oscillatory component* (LF_{RR}) at about 0.1 Hz (Fig. 8.1), the functional meaning of which has been largely debated [4, 7, 12]. On the basis of both animal and human studies, there is strong scientific evidence that, when expressed in normalized units (n.u.), LF_{RR} is a convenient index of the cardiac sympathetic modulation and of its changes [7, 13]. Indeed, in *conscious animals*, this component was found to increase during baroreflex unloading obtained by nitroglycerine administration [14] or by brief coronary artery occlusions, which elicits a sympathetic excitatory reflex originating from the heart [14]. Conversely, LF_{RR} n.u. did not increase after nitroglycerine infusion [14] in animals that underwent chronic selective bilateral stellectomy, a procedure which selectively abolishes cardiac sympathetic innervation, after beta-blocker administration [14] or ganglionic blockade [14]. In humans, mental stress increased LF_{RR} n.u. [15] as well as did the sympathetic activation obtained by the tilt maneuver [11, 16] or mild intensity physical exercise [17]. The neural degeneration of the cardiac sympathetic innervation, as observed in patients affected by Pure Autonomic Failure [18], was characterized by the absence of LF_{RR} in heart rate variability. As to systolic arterial pressure variability, there is large agreement that the low frequency component (0.1 Hz, LF_{SAP}) is related to the sympathetic vasomotor control and to its changes [7, 4].

8.5 Heart Rate Rhythms During Vasovagal Syncope

Figure 8.3 represents a typical example of syncope during a tilt test ending up with a reflex bradycardia. The central cartoon depicts the power of the low frequency (LF) oscillations extracted from *RR interval variability* (LF_{RR} normalized units, n.u., filled circles). Notice the expected increase of LF_{RR} in response to the gravitational stimulus (Tilt). Importantly, the progression of tilt was characterized by a gradual enhancement of LF_{RR}, spectral index of the cardiac sympathetic modulation, which in addition showed wide fluctuations suggestive of a marked instability of the cardiac autonomic modulation before syncope. Having reached a maximum, LF_{RR} suddenly dropped to zero concomitantly with the onset of bradycardia. This pattern, characterized by a cardiac sympathetic overactivity preceding vasovagal syncope, is in keeping with previous findings obtained in patients with isoproterenol-independent orthostatic vasovagal syncope [19], in young adults [11], in subjects exposed to heat and orthostatic stress [20], and in children [21] and adolescents with presyncope or vasovagal syncope compared to age-matched healthy controls [22].

However, this pattern appears less consistent when the changes in RR variability are assessed by algorithms more suitable for addressing transients and hemodynamics instabilities [23]. In a study based on a time-variant autoregressive approach, Furlan et al. [24] also observed a second and quite different oscillatory pattern in

RR interval variability preceding the vasovagal syncope. Indeed, in 9 out of 22 subjects, *in the absence of major changes in mean heart rate*, after an initial plateau, LF_{RR} underwent a slow decrease with a final reduction at the time of syncope. The oscillatory component reflecting the cardiac vagal modulation, that is, HF_{RR} showed a marked progressive increase during tilt, up to the onset of bradycardia and syncope. Therefore, in these subjects, syncope was preceded by a progressive sympathetic inhibition and vagal enhancement, which was not paralleled by concomitant changes in mean heart rate. Thus, an alternative pathophysiological mechanism independent of an exaggerated sympathetic activity to the heart seemed to be present before typical vasovagal syncope. Accordingly, Morillo et al. [25] found reduced values of LF_{RR} during the first 5 min of tilt, suggestive of a blunted sympathetic activation in subjects with vasovagal syncope. Another study based on time-frequency mapping of RR variability concluded that subjects prone to neurally mediated syncope were characterized by elevated HF_{RR}, spectral index of the parasympathetic activity to the heart, during orthostatic stress [26]. Similarly, a significant increase of HF_{RR} before tilt-induced syncope was more recently observed in children [27].

In conclusion, different *quantities* of neural sympathetic and vagal modulatory activity to the heart are likely to interact in the period preceding vasovagal reactions in humans, resulting in an unstable cardiac autonomic profile. This complexity can be profitably tracked by analyzing the changes in the spontaneous fluctuations of heart beat in the LF_{RR} and HF_{RR} bands. In addition, such a *frequency domain approach* may disclose subtle changes in the *cardiac autonomic profile* that would remain hidden if more traditional analyses of heart rate were performed. Finally, in patients with typical syncope, the recognition of different cardiac *pathophysiological mechanisms underlying the loss of consciousness* might also help to select different drugs such as β-adrenergic receptor blockers or α-adrenergic receptor agonists.

8.6 *Blood Pressure Rhythms* and Vasovagal Syncope

The filled triangles in the central cartoon of Fig. 8.3 depict the time course of the low frequency oscillations of systolic arterial pressure variability (LF_{SAP}) in a subject with a typical orthostatic syncope. Notice the increase of LF_{SAP} during early tilt, its wide fluctuations when approaching the onset of syncope, and its remarkable late increase when hypotension was already detectable. The final LF_{SAP} decline to near zero was followed by a rapid hypotension, a pattern consistently described by other authors [28, 29].

Notably, the drop of LF_{SAP} and hypotension occurred when still heart rate and LF_{RR} were at their maximum. Therefore, the concomitant assessment of the changes in both RR and systolic blood pressure spontaneous fluctuations before typical syncope unveiled a temporal mismatch between cardiac and vascular autonomic control, characterized by a *vascular sympathetic inhibition* which preceded by seconds the cardiac sympathetic withdrawal. This observation is in keeping with the findings of Moak et al. [28], suggesting that the decrease of LF_{SAP} exceeded and occurred before the decrease in LF_{RR}.

8.7 Relationships Among Neural Sympathetic Discharge Activity to the Vessels, Blood Pressure, and RR Variability During Orthostatic Vasovagal Syncope

Figure 8.4 shows fluctuations at 0.1 Hz, characterizing blood pressure recording (upper trace) in an asymptomatic subject during the up-right posture. In keeping with a previous study [11], spontaneous oscillations with a period of about 10 s (LF_{SAP}) are present in the arterial pressure recording and are mirrored by analogous oscillations (LF_{RR}) in the heart rate trace (Fig. 8.4). Fluctuations with a similar period (0.1 Hz) characterize the pattern of the discharge activity of the sympathetic vasomotor control (*muscle sympathetic nerve activity, MSNA*). It is just a reminder

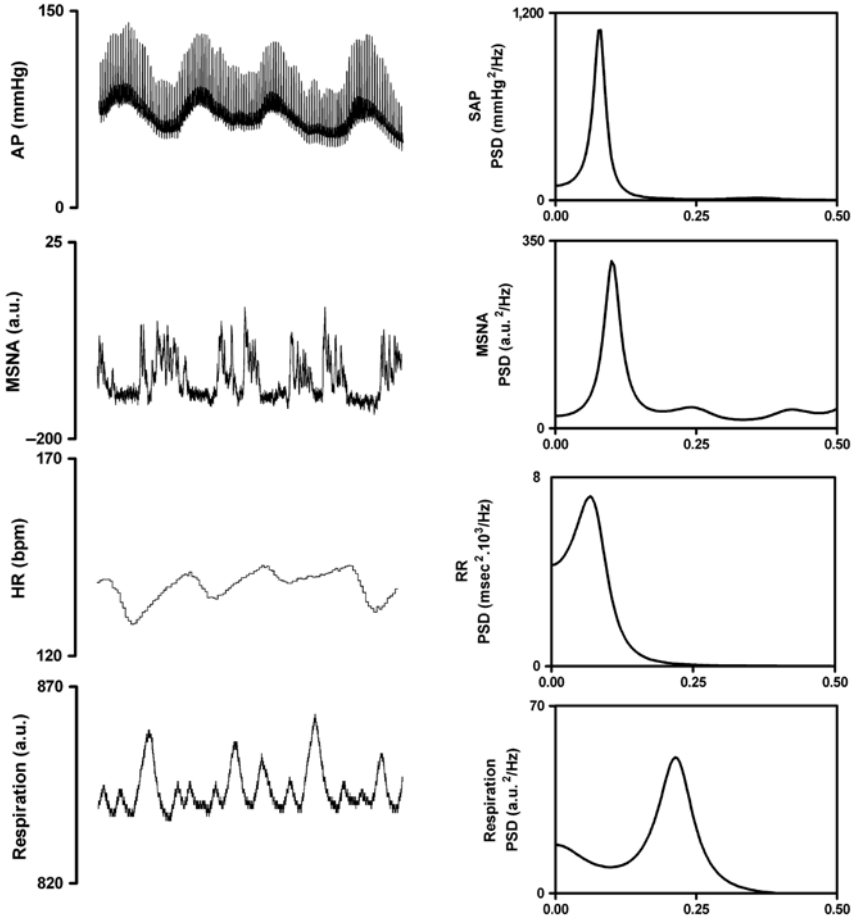

Fig. 8.4 Rhythmic fluctuations with a period of about 10 s (0.1 Hz) in arterial pressure (*AP*), muscle sympathetic nerve activity (*MSNA*), heart rate (*HR*), and respiration (*left traces*), and corresponding power spectra (*right panels*) in an healthy subject during tilt. Notice that in the up-right position AP, MSNA, and HR share a frequency code based on 0.1 Hz oscillations

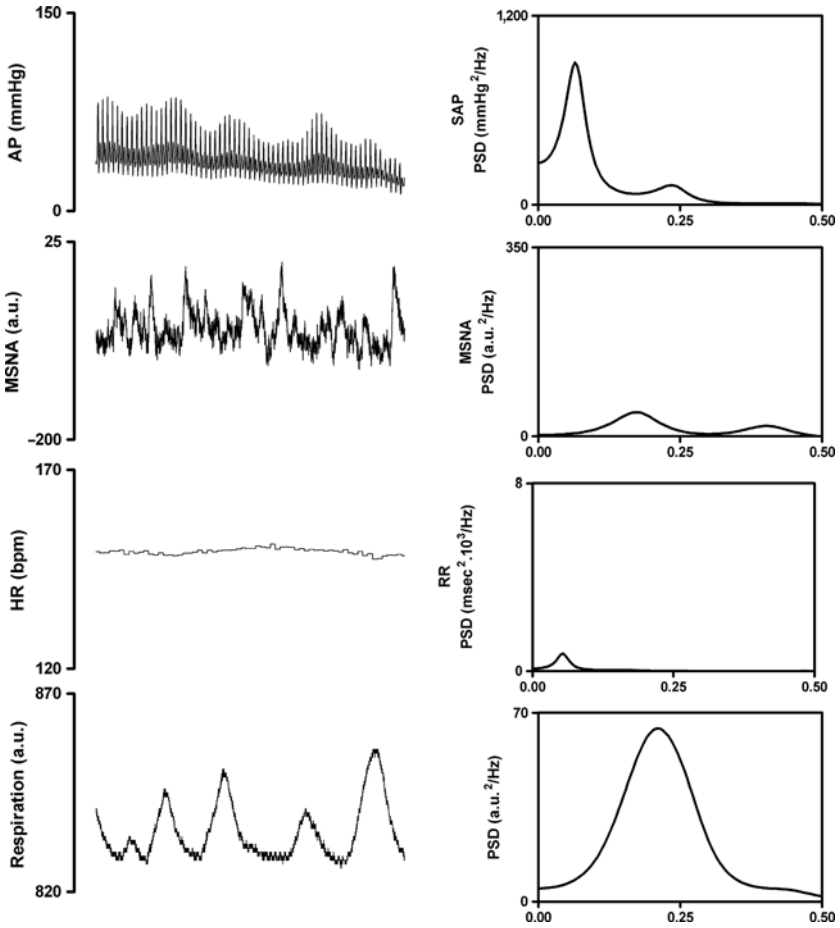

Fig. 8.5 The same variables as in Fig. 8.4 recorded ~1 min before a typical orthostatic syncope. Compared to Fig. 8.4 recordings, there was the loss of rhythmic 0.1 Hz fluctuations in AP, HR, and in the neural pattern of sympathetic discharge activity to the vessels (MSNA). In spite of a persistent sympathetic discharge, a progressive decline of AP was evident, suggesting an ineffective sympathetic vasoconstrictor activity. The power spectra indicate the shift of the frequency content of single parameter variability towards a high frequency, respiratory-related, pattern (~0.21 Hz)

that in physiological conditions baroreceptor mechanisms controlling the reflex response of heart rate and modulating MSNA are responsible for such a strict coupling among variables based on a 0.1 Hz rhythm [11]. Power-spectrum analysis of RR interval, SAP, and MSNA variability showed a prevailing LF component in all the spectra (Fig. 8.4, right graphs).

In the period immediately preceding (~1 min) syncope (Fig. 8.5), in spite of the fact that the sympathetic discharge activity to the vessels (MSNA) was still detectable, the 0.1 Hz discharge rhythm was lost and the neural efferent activity to the vessels appeared disorganized. A similar decrease of the LF_{MSNA} before syncope

was previously described by Kamiya et al. [30]. In the example of Fig. 8.5, the MSNA variability underwent a rapid shift from prevailing 0.1 Hz fluctuations (LF) toward a respiratory rhythm, ~0.2 Hz, as indicated by the power spectrum. In this context, a progressive decrease of blood pressure was also present, suggesting the likely incapability of the vasculature smooth muscles to adequately respond to sympathetic vasoconstrictor stimuli. Notably, such a pattern of neural discharge activity showing significant respiratory linked frequencies does not correspond to the optimal frequency characteristics of sympathetic neural transmission to the vasculature. Indeed, it has been reported in humans that the gain of the transfer function between sympathetic activity and skin arterial blood vessels reaches its maximum around 0.1 Hz, that is, in the LF range, decaying progressively [31].

Conclusions

Vasovagal syncope is a *disorder of regulation* where different *quantities* of neural sympathetic and vagal activities interact, resulting in an unstable autonomic profile before the loss of consciousness. In the period preceding the loss of consciousness, the computerized analysis of the spontaneous fluctuations characterizing *blood pressure and heart rate variability*, the pattern of the discharge activity of the sympathetic vasomotor control, and the assessment of their relationship may furnish valuable insight into the complex autonomic changes leading to *syncope*.

Conflict of Interest None

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Pathophysiology of Vasovagal Syncope: Conclusive Remarks

9

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9.1 Introduction

In the year 2000, a comprehensive review addressing the pathophysiology leading to vasovagal or neurally mediated syncope [1] concluded that the exact mechanisms responsible for the development of this type of syncope remained unresolved. Fourteen years later, part of this book explores the question whether or not the pathophysiology of VVS has been now clarified. Several specific issues have been addressed in detail in this book, and this chapter will highlight and summarize them.

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9.2 The Vasovagal Reflex

The VVS reflex involves activation or deactivation of complex anatomical and functional pathways that under pronounced conditions results in the development of vasovagal syncope. In Chaps. 5 and 6 of this book, the VVS reflex has been dissected into its primary components, focusing on the neural, cardiac, vascular, visceral and baroreceptor afferents that relay information to medullary cardiac and vascular regulatory nuclei. These chapters also present a framework by which supra-bulbar and cortical centres relay information to brain centres that modulate sympathetic and parasympathetic activity and, in consequence, multiple peripheral organ responses. Transient but pronounced disruptions in the function of some or many of these regulatory centres may therefore lead to the development of VVS subtypes.

In the other chapters of this book, the VVS reflex has been framed within an evolutionary context, pointing out similarities and differences between humans and other species. Evidence has been presented, suggesting similar pathophysiological mechanisms for the development of orthostatic or emotional VVS in humans and other vertebrates undergoing haemorrhagic shock [2] or alarm/fear bradycardia [3] (see Chap. 1).

In some cases of VVS, the reflex may be biphasic in nature [2]. Indeed, in both animals and humans the final sympathetic cardiovascular withdrawal and the increase in cardiac vagal tone may be preceded by a pronounced increase in sympathetic activity. In humans this is observed during typical emotional or sometimes in orthostatic VVS. Interestingly enough, in this context, presyncope symptoms and signs may mirror the autonomic changes. Tachycardia, palpitations and sweating, pointing to a noradrenergic and cholinergic sympathetic over-activity, may be followed and overwhelmed by nausea, pallor, fatigue and bradycardia, suggestive of a vagal enhancement.

Does the VVS reflex have any teleological functional meaning? The question has been addressed by evolutionists who hypothesized two theories (see Chap. 1). Briefly, the *Conflict* theory assumes that VVS is triggered by fear circuitry, developed in the paleolithic era in humans [4]; VVS provided a survival advantage mostly to children and women whenever threats were unavoidable. The second theory, that is the *Clotting* theory, hypothesizes that VVS leading to a concomitant reflex hypotension might act as a defence mechanism in the presence of haemorrhage, by giving 'clotting' mechanisms higher possibility to make an effective clot in a context of reduced arterial pressure [5, 6]. In animals, tonic immobility (or playing dead) is comparable to human VVS. Notably, tonic immobility was identified by Charles Darwin [7] as an anti-predator conduct, alternative to the 'flight-or-fight' response. Subsequent studies suggested that survival rate is indeed increased by this behaviour [8, 9]. In keeping with the above concepts, it can be additionally argued that given the potential harmful effects of exceedingly high plasma values of norepinephrine on both arrhythmias (e.g. the catecholaminergic polymorphic ventricular tachycardia) and cardiac metabolism (e.g. the Tako Tsubo syndrome), the possibility of promptly reducing sympathetic over-activity by the VVS reflex appears highly suggestive for an effective defence mechanism [10].

9.3 Role of the Autonomic Nervous System

Since the original definition by Lewis [11], it has been quite clear that the term *vaso* not only was simply heading the word *vasovagal*, but it reflected the major contribution of vascular tone-inhibitory mechanisms in producing the loss of consciousness during VVS. Indeed, Lewis himself showed that the administration of a vagolytic agent such as atropine, which abolished the vagal component of the reflex, could not avoid the onset of syncope in a setting of profound vascular tone-inhibition. This concept has to be carefully considered when dealing with patients characterized by recurrent syncope in whom cardio-inhibition has been previously documented and a pacemaker *(PM)* implant seems the best therapy of choice. For example, in a recent study, in spite of previous asystole with syncope or a non-syncopal >6 s asystole observed by internal loop recordings, 25 % of patients with *PM on* were found to suffer from syncope recurrence [12]. This suggests that mechanisms different from simple cardio-inhibition may play a role in VVS.

It has been assumed that hypotension attending VVS was due to arterial vasodilation. A study showed that VVS was associated to reduced stroke volume and cardiac output, whereas total peripheral resistance increased [13, 14]. This means that sympathetic inhibition mostly results in a veno-dilation.

As suggested by direct post-ganglionic sympathetic efferent discharge activity recordings (muscle sympathetic nerve activity, MSNA), most of the times VVS is preceded and attended by a withdrawal of the sympathetic vasomotor control [1, 15, 16]. As a general rule, preceding VVS, MSNA burst activity progressively decreases along with hypotension. Before syncope, an MSNA neural silence follows, resulting in a final extreme decrease in blood pressure [15, 16]. However, in selected number of cases, MSNA does not disappear during VVS [17]. In these cases a clear change in the sympathetic discharge pattern, which shifts from a 0.1 Hz prevailing rhythmicity towards respiratory (≈0.25 Hz) linked fluctuations, is observed together with progressive hypotension (see Chap. 8). This suggests that an effective efferent sympathetic control of the vessels not only is based on changes in the neural bursts activity, but is also obtained by a specific frequency code at 0.1 Hz. This burst discharge frequency characterizes the sympathetic activity to the vessels upon standing in healthy subjects [18].

9.4 Role of Neuro-humoral Factors and Adenosine

In VVS, there is evidence of potential neuro-humoral vasodilating mechanisms that may involve substances such as epinephrine, beta-endorphin and adenosine.

Plasma epinephrine levels were found to be exceedingly high in subjects experiencing VVS. Since epinephrine produces β-adrenergic vasodilation in skeletal muscle and splanchnic vessels during stress conditions [19], the existence of a mismatch between noradrenergic and adreno-medullary responses during VVS has been hypothesized, the latter being prevalent compared to the former [1]. It must be

pointed out, however, that epinephrine infusion did not reproduce VVS in susceptible individuals [20]; therefore its role in VVS is far to be established.

Beta-endorphin plasma levels were found to be increased during VVS [21]. It has been hypothesized that this endogenous opioid peptide may play a role in VVS either by a direct vasodilating property and by increasing efferent parasympathetic activity and reducing efferent sympathetic tone [22]. However, beta-endorphin role in VVS is still debated because pretreatment with selective opioid antagonist did not avoid VVS during simulated orthostatism [22].

Adenosine (ADO) is a naturally occurring purine nucleoside that forms from the breakdown of adenosine triphosphate (ATP) in humans. Recently, ADO gained scientific interest as an agent potentially involved in VVS because of its important effects on both cardiac and vascular function [23]. Release of endogenous ADO results in remarkable reduction of AV node conduction by the activation of A_1 purinergic receptors and in direct vasodilation by the activation of peripheral A_{2A} receptors [24]. ADO is part of a complex neuro-humoral network, and its role in VVS has been hypothesized as the result of a combination of neural and purinergic activation (see Chap. 7). ADO has cardiac effects similar to those of acetylcholine [25, 26], and both elements act synergistically against the excitatory effects produced by the sympathetic neurotransmitters noradrenaline and adrenaline. Excitatory or inhibitory effects of the adrenergic, cholinergic and purinergic outputs on the target organs, that is the heart and vessels, are the result of a further integration at the level of the receptor-effector coupling system. This may account for typical VVS and positive tilt-test syncope which tend to be characterized by high ADO plasma values, whereas the clinical form of syncope without prodromes and healthy heart is likely to show low ADO plasma values [27]. Based on these findings, such a different purinergic profile has been proposed to characterize clinical forms of neurally mediated syncope (see Chap. 7).

9.5 Role of Biomarkers

B-type natriuretic peptides (BNP and NT-proBNP, BNPs) are released after cardiac muscle stretch and are currently used to differentiate between cardiac and pulmonary causes of acute dyspnoea [28]. Since their plasma levels increase during enhancements of ventricular filling pressure, BNPs have been proposed as prognostic markers of other cardiovascular disorders including pulmonary embolism [29], atrial fibrillation [30], ventricular tachyarrhythmias [31] and syncope [32]. In addition, BNPs have been included in a risk scale aimed at identifying high-risk patients presenting to the emergency department after syncope [33]. BNPs levels were found to be remarkably increasing by 6 h after a controlled episode of ventricular tachycardia or ventricular fibrillation [34], conditions that are likely to result in a syncope during daily life. Based on these findings, in a recent study, plasma concentrations of BNPs were compared in a group of patients with arrhythmic syncope and vasovagal syncope [35]. Authors observed a greater increase of 6-h BNPs plasma levels

in patients with syncope produced by ventricular tachycardia or fibrillation than in individuals suffering from a typical orthostatic vasovagal syncope. In addition, the area under the curve of the changes in BNPs discriminating arrhythmic from vasovagal syncope suggested that BNPs plasma levels could be used to separate the two conditions [35]. The BNPs (NT-proBNP) high specificity 6-h increase makes the changes in this biomarker a potential confirmatory index of syncope induced by ventricular arrhythmias.

9.6 Effects of Combined Vasovagal and Diving Reflexes

There is evidence derived from animal studies that the simultaneous occurrence of *emotional* vasovagal reflex and a *diving* reflex may result in sudden death. Diving bradycardia is a characteristic of all air-breathing vertebrates and is triggered by breath-hold and face and body exposure to cold water. While the afferent pathway of the diving reflex is far to be fully elucidated, the efferent part of the reflex is mediated by vagal neural efferents, since reflex bradycardia is abolished by atropine pretreatment (see Chaps. 5 and 6). During diving, heart rate decreases and vasoconstriction of selective vascular beds takes place. From the evolutionary standpoint, the overall haemodynamic changes have been interpreted in a context of a global O_2-saving effect. In animals, the concomitant occurrence of a diving reflex and alarm bradycardia during tonic immobility (see Chap. 1) might eventually lead to a further unopposed remarkable enhancement in the vagal activity to the heart, which in turn might result in fatal bradyarrhythmia and sudden death.

Although caution should be exercised in transferring animal observations to humans, the combination of emotional (fear) and diving reflexes might play a role in promoting the loss of consciousness in humans about to drown.

9.7 Effects of Exceedingly Prolonged Orthostatic Stress

Chapter 27 briefly mentions the anecdotic case of a woman with normal heart, suffering from frequent syncope relapses, who died after being kept in the up-right position by her husband after a likely VVS. This finding is in sharp contrast with the prognosis of VVS being benign [36]. The proposed underlying pathophysiological mechanism for such adverse outcome is the presence of an unopposed vagal overactivity, sustaining a long-lasting sinus arrest and pronounced hypotension that triggers malignant arrhythmias and heart and brain ischaemia. Authors pointed out that such an event appears exceptional. Indeed, it should be confined to extraordinary situations where the fainter, after the loss of postural tone, cannot reach the lying-down position. This unusual situation may happen in subjects working with body harness systems.

In the past, dying because of an exceedingly lasting confinement in an up-right position was not exceptional if we consider the crucifixion. Our ancestors quickly

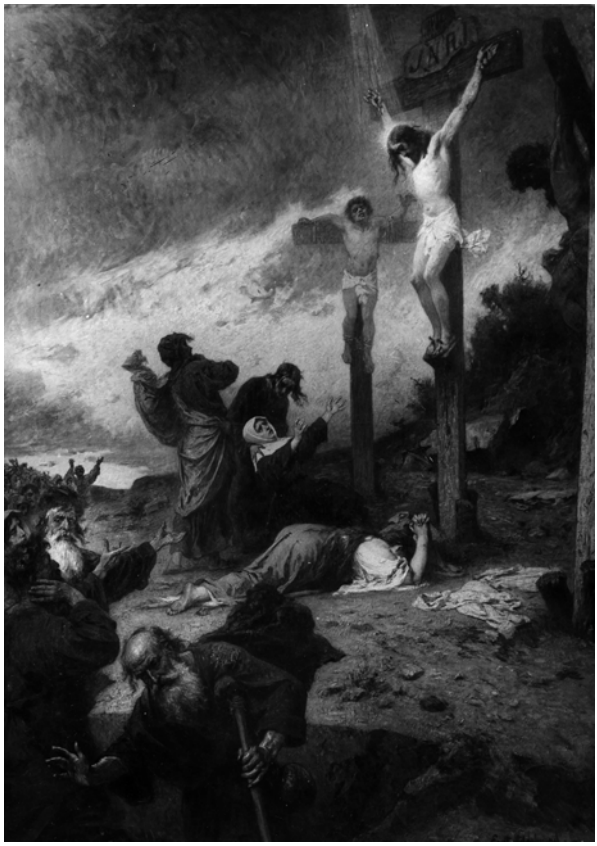

Fig. 9.1 Reproduction of a painting (1913) by E. W. Hildebrand, showing Christ and thieves crucifixion. During crucifixion the prolonged head-up position is likely to result in a orthostatic vasovagal syncope characterized by long-lasting vagal overactivity and reduced venous return to the heart. These in turn may induce profound hypotension and possibly asystolia, eventually leading to death

realized that keeping a human in a forced up-right position without the capability to move limbs would end up in certain death. Figure 9.1 reproduces the E.W. Hildebrand painting (1913) showing Christ and the good and bad thieves' crucifixions. From the physiological standpoint, notice that the thieves were unable to lean the feet on a foot-rest. This appears to be an orthostatic stress sensitization attempt because the absence of any foot-rest is likely to make the lower limb venous return more difficult. The image is even more clear in the Antonello da Messina 1457 oil painting (http://it.wikipedia.org/wiki/Crocifissione_(Antonello_da_Messina_Anversa)#mediaviewer/File:Antonello_da_Messina_027.jpg).

In conclusion, the loss of consciousness resulting from VV reflexes most likely represents a 'defence mechanism' aiming to protect vital organs from severe/extreme ischaemia and permanent damage. In the absence of major trauma, the loss of consciousness and decrease in muscle tone force an organism to assume a lying-down position that counteracts the consequences of gravity on the circulatory system and minimizes the effects of ischaemia on vital organs such as the brain and the heart.

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Part III

Diagnostic and Clinical Aspects

Initial Evaluation of the Patient with Transient Loss of Consciousness

10

Paolo Alboni, Franca Dipaola, Nicola Stucci, and Raffaello Furlan

Key Points

- The initial evaluation of patients with transient loss of consciousness (LOC) comprises a detailed medical history, physical examination, and 12-lead electrocardiogram and is the cornerstone to identify the cause of LOC.
- Since there are many causes of syncopal and nonsyncopal LOC, an adequate history taking is pivotal.
- The first question to answer is whether the patient suffered from a real LOC; events with similar features, such as falls, should therefore be excluded.

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- Once a transient LOC has been diagnosed, a nonsyncopal LOC should be ruled out. Once syncope has been diagnosed, the underlying cause should be identified.
- There is a consensus that some crucial clinical findings obtained from the initial evaluation are sufficient for identifying syncope etiology without further examinations, whereas other findings may only suggest a cause of syncope, thus requiring further tests.
- In general, the absence of heart disease rules out a cardiac cause of syncope. Conversely, the presence of heart disease is a predictor of cardiac cause of syncope, although characterized by a low specificity.

The most challenging problem concerning an appropriate diagnosis of syncope is that at the time of medical assessment most of the patients are completely free of symptoms or worrisome clinical findings. A proper diagnosis is based therefore on a through recording of the events preceding and following the transient loss of consciousness (LOC). Syncope is a LOC due to transient global cerebral hypoperfusion. Unfortunately, there are no signs/symptoms specific of such hypoperfusion, and there are other conditions that resemble syncope (i.e., that may produce or appear to produce transient LOC) but are not due to a generalized reduction in cerebral blood flow (see Chap. 3).

The initial diagnostic approach to patients with transient LOC comprises a detailed medical history (possibly completed by witness accounts), a through physical examination (including supine and standing blood pressure measurements), and 12-lead electrocardiogram (ECG) recording [1]. Other tests, including basic laboratory tests, are not mandatory for a proper initial evaluation of the large majority of patients with syncope. The history and physical examination form the core for an appropriate work-up in patients with transient LOC. Such an approach may define the cause of transient LOC in about 25 % of patients, obviating the need for further evaluation and enabling treatment to be instituted. In 40 % of patients, such methodology does not enable a definitive diagnosis, but strongly suggests causes and, therefore, specific additional tests [2]. A structured history taking should be utilized (Fig. 10.1), because several disorders may lead to transient LOC. Table 10.1 summarizes the most important questions that must be addressed when the patient's history is taken.

10.1 Did Loss of Consciousness Really Occur?

The first question is whether the patient suffered from a true LOC, which is characterized by loss of postural control and unresponsiveness to external stimuli, particularly acoustic. If there are witnesses, the question can generally be answered. A state of altered consciousness and, above all, a fall, must be considered in the

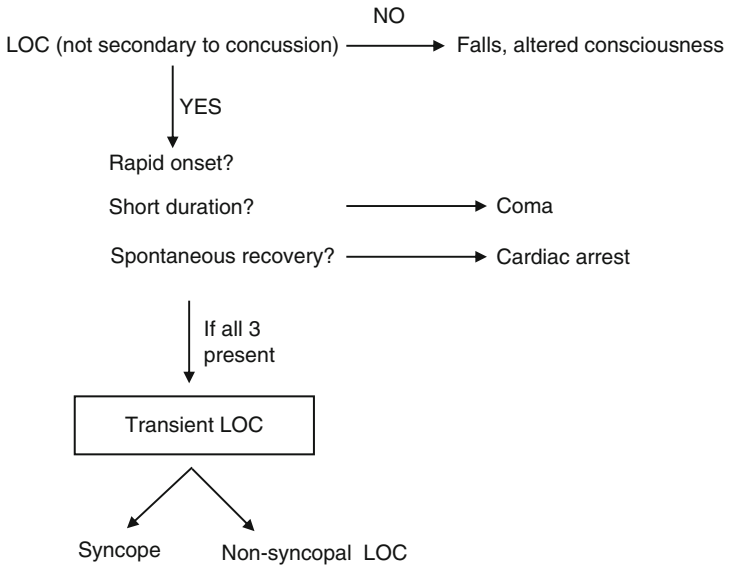

Fig. 10.1 Method to be utilized in clinical history taking. The first question to address is whether the patient has had a real LOC; therefore, events with similar clinical features, such as falls, should be ruled out. Once a LOC has been diagnosed, the presence of the three features defining the presentation of transient LOC (rapid onset, short duration, spontaneous recovery) should be investigated. If a LOC is present, a differential diagnosis between syncope and nonsyncopal LOC should be made. Once syncope has been diagnosed, the cause should be defined. *Abbreviation*: *LOC* loss of consciousness (Modified with permission from Moya et al. [1])

differential diagnosis. Falls may be accidental or "unexplained." An accidental fall is defined as a simple slip, trip, accidental collision, or environmental hazard resulting in fall, whereas an "unexplained" fall is defined as a fall with no apparent cause. Accidental falls are generally easy to be diagnosed, whereas the differential diagnosis between syncopal fall and "unexplained" fall can be difficult because of the marked variability in the clinical presentation of syncope. In this regard, it has been suggested that about 25 % of patients suffer from retrograde amnesia after tilt-induced or carotid sinus massage-induced syncope [3, 4]. Indeed, they do not remember the prodromal symptoms. This makes the final diagnosis more difficult, if not impossible. A crucial question is whether the patient had prodromal symptoms. These symptoms can be due to cerebral hypoperfusion (dizziness, blurred vision, awareness of fainting) or due to the activation of the autonomic system, either sympathetic (pallor, sweating, palpitation) or vagal (nausea, vomiting, abdominal discomfort, urinary incontinence). In the presence of these symptoms, we are dealing with a syncope. If the patient does not remember the prodromes, he/she should be asked to describe every single step of the entire episode. If the patient can clearly describe the entire episode, a fall has presumably occurred. Often, the description of the event is incomplete or confused. In this case, a syncopal fall

Table 10.1 Features that should be investigated during clinical history

Questions about circumstances just prior to the attack	Position (supine, sitting, or standing)
	Activity (rest, change in posture, during or after exercise, during or immediately after urination, defecation, coughing, or swallowing)
	Predisposing factors (e.g., crowded or hot places, prolonged standing, postprandial period)
	Precipitating events (e.g., emotion, fear, disgust, intense pain, neck movements, flashing lights)
Symptoms preceding loss of consciousness	Dizziness, blurred vision, nausea, vomiting, abdominal discomfort, sweating, aura, palpitations, precordial pain, pain in neck or shoulders
Symptoms during loss of consciousness (eyewitness)	Way of falling (slumping or kneeling over, rigidity or flaccidity), skin color (pallor, cyanosis), movements (tonic, clonic, tonic-clonic, myoclonus, or automatisms), duration of movements, onset of movements in relation to fall, duration of loss of consciousness, tongue biting, open or closed eyes
Symptoms during recovery	Nausea, vomiting, sweating, confusion, skin color, palpitations, injury, precordial pain, muscle aches, urinary or fecal incontinence
Questions regarding background	Family history of sudden death, congenital arrhythmogenic heart disease
	Previous major cardiac disease
	Neurological history
	Metabolic disorders (diabetes, etc.)
	Medication (antihypertensives, antianginals, antidepressants, antipsychotics, diuretics, antiarrhythmics, QT-prolonging agents) or other drugs, including alcohol
	In the case of recurrent syncope, information on recurrences, such as the time since the first syncopal episode, and on the number of spells

should be suspected. Witnesses could be very useful for the differential diagnosis, and should be asked whether the patient was unresponsive during the spell and how it took place.

10.2 Was LOC Characterized by Rapid Onset, Short Duration, and Spontaneous Recovery?

Once LOC has been diagnosed, the following questions are crucial: "Did LOC have a rapid onset?" "Was LOC of short duration?" "Was recovery spontaneous?" It must be remembered that the beginning of syncope is rapid, but not necessarily sudden, since prodromal symptoms lasting up to 20–60 s may occur. LOC itself may last 10–30 s, but rarely can it go on for minutes. Notably, if LOC is prolonged, we are dealing with a coma. If recovery is not spontaneous, but requires cardiac massage or other resuscitation maneuvers, we are dealing with cardiac arrest. If the answer to the abovementioned three questions is "yes," we are dealing with a "transient LOC." Now, we should try to identify the cause of the LOC (Fig. 10.1).

10.3 Diagnosis of the Cause of Transient LOC

A transient LOC may result from syncopal or nonsyncopal LOC. From a methodological standpoint, it is advisable, at least for doctors with limited experience of syncope, to exclude a nonsyncopal LOC. This means that the diagnosis of syncope is based on exclusion [1].

10.4 Clinical Findings of Nonsyncopal LOC

The disorders and clinical findings characterizing nonsyncopal LOC are reported in the following sections.

Epilepsy

Like syncope, epilepsy is clinically characterized by transient and (usually) short-lived attacks of a self-limited nature. It is caused by an abnormal excessive or synchronous neuronal activity in the brain. Flashing lights or unpleasant acoustic stimuli may rarely play a trigger role in epilepsy. Typical epileptic auras, such as a rising epigastric sensation, unpleasant smell or taste, or déjà vu, may precede transient LOC and provide important diagnostic clues. ***During generalized epileptic attacks, there are tonic-clonic movements, usually rhythmic, synchronous, and violent, which can affect the whole body. Muscle contractions may last about one or few minutes. Movements may also be present in syncope and are defined as myoclonus; they are asynchronous, small, and nonrhythmic, and their duration is much shorter than in typical seizures (a few seconds). During an epileptic attack, movements often coincide with the beginning of LOC, whereas in syncope, they appear later, after the fall, and are considered to be an expression of severe brain hypoxia. Timing of the muscle contractions is very important in the differential diagnosis and may be ascertained from reliable witnesses. As a rule, during an epileptic attack, the fall to the ground is tonic, whereas in syncope, it is generally flaccid. Thus, flaccidity during unconsciousness argues against epilepsy. Complex movements or automatisms (lip smacking, chewing, fumbling, head raising, etc.) may be observed during an epileptic attack, whereas they are extremely rare in syncope [5]. Eye movements can take place in both epilepsy and syncope; in epilepsy, eye deviation is lateral, while in syncope it is generally upward [5]. Tongue biting, which is common in epilepsy, is very rare in syncope; this occurs at the side of the tongue in seizures and at the tongue tip in syncope [5]. During seizures, most of the time, face is cyanotic, whereas during syncope, it is pale; however, facial cyanosis can be observed in some patients with cardiac syncope. After seizures, confusion is prolonged and is often accompanied by aching muscle and headache. By contrast, after syncope, confusion is of short duration (up to few minutes), though in some patients it may be prolonged. As injuries and urinary incontinence appear to be common in both epilepsy and syncope, they are not useful to differentiate the two disorders.

Obviously, most of these findings can be collected in the presence of reliable witnesses; in their absence, further diagnostic investigation is needed.

Transient Ischemic Attack

A transient ischemic attack (TIA) is caused by temporary regional cerebral hypoperfusion and should not be confused with syncope. LOC during TIA appears to be extremely rare and has been observed only during TIAs involving the posterior (vertebrobasilar) vascular system. To date, no cases of LOC have been described during TIA, secondary to the involvement of the carotid circulation. The differential diagnosis between TIA and syncope is easy, because the former is associated with the following neurological symptoms: limb ataxia, oculomotor palsies, loss of balance, difficulty in sitting without support, veering to one side, frank vertigo, unilateral hearing loss, dysphagia, laryngeal paralysis, pharyngeal paralysis, hoarseness, and facial pain. Patients with TIA of the posterior cerebral vascular system do not have hemiparesis or hemisensory loss. At present, there are no reliable descriptions of a TIA manifesting itself as an isolated LOC [6]. For practical purposes, the following rule can be applied: a TIA concerns a focal neurological deficit, most of the time without LOC, while syncope represents a LOC without a focal neurological deficit [7]. Even steal syndromes, such as the subclavian steal syndrome, can show up as transient LOC associated to focal neurological symptoms. During history taking, patients should always be asked whether they suffered from focal neurological symptoms, in order to exclude a TIA or a steal syndrome.

Hypoglycemia

Hypoglycemia can induce LOC. Usually, it is a long-lasting condition which may resemble coma. Sometimes, however, the LOC is of short duration, and in this case, a differential diagnosis must be made with syncope. In diabetic patients treated with insulin or oral antidiabetic drugs, hypoglycemia should be suspected as a cause of transient LOC after occasional lack of food intake and when the LOC is preceded by symptoms due to sympathetic activation, particularly tremors and intense sweating. During recovery, prolonged confusion may be present.

Psychogenic Pseudosyncope

Psychogenic pseudosyncope is a conversion disorder, that is, the conversion of a psychogenic conflict into a presentation of physical illness, in this case, neurologic symptoms which mimic a LOC. Psychogenic pseudosyncope is not feigned or deliberately produced, but completely involuntary. It mainly affects women. The patient does not lose consciousness, but because postural tone and responsiveness to external stimuli are lost, a differential diagnosis must be made with syncope. There

are some features that help in differentiating this condition from true LOC. In pseudosyncope, there are no triggers, and the attack always occurs in the presence of other people. The attacks are frequent, sometimes several in a day, and are often long-lasting, spanning from few minutes up to 20 min. If the patient can be examined, there are no gross abnormalities except for a lack of responsiveness. The eyes are generally closed, whereas during both syncope and seizures they are commonly open [7, 8]. The patient may tend to close eyes actively or to avert the gaze away from the examiner. Lifted limbs if suddenly released may hesitate in mid-air before falling. Sometimes, there are asynchronous convulsion-like movements, which simulate an epileptic attack [7]. During the attack, blood pressure and heart rate are normal. Contrary to what has been reported in the past, minor traumas can occur. There is no postictal confusion, but patients often become emotional and cry at the end of the attack. Since witnesses are always present, differential diagnosis between psychogenic pseudosyncope and syncope is possible in most cases.

Cataplexy

During cataplexy, there is no LOC, but patients lose postural control and are unresponsive to external stimuli. Cataplexy occurs only in the context of the disease narcolepsy. The loss of muscle tone is due to emotions, particularly mirth associated with laughing out loud. In complete attacks, patients slump flaccidly to the ground. Partial attacks are more common and are restricted to dropping of the jaw and sagging or nodding of the head. Attacks may develop slowly enough to allow the patient to stagger and break the fall before hitting the floor; such attacks therefore look rather unreal and psychogenic.

If signs/symptoms suggestive of nonsyncopal LOC emerge when the patient's history is taken, evaluation by a neurologist or psychiatrist is indicated.

If a nonsyncopal cause can reasonably be excluded, the next step is to investigate the cause of syncope.

10.5 Causes of Syncope

Syncope can be reflex or cardiovascular, or could be due to orthostatic hypotension. There is a consensus that some types of syncope can be diagnosed after the initial evaluation, without further examinations [1]. The diagnostic criteria of these types of syncope are summarized in Table 10.2.

Typical Vasovagal Syncope

Typical vasovagal syncope (VVS) can be diagnosed when transient LOC is precipitated by triggers such as emotional distress (emotion, fear, severe pain, blood phobia, disgust, medical setting) or orthostatic stress (prolonged standing, particularly in hot environments), and is associated to symptoms due to activation of the

Table 10.2 Types of syncope that can be diagnosed on initial evaluation

Typical vasovagal syncope is diagnosed if transient LOC is precipitated by emotional distress or orthostatic stress and is associated with autonomic prodromes
Situational syncope is diagnosed when LOC occurs during or immediately after urination, defecation, coughing, or swallowing
Orthostatic syncope is diagnosed when presyncope/syncope occurs during orthostatic testing and is associated to hypotension
Arrhythmia-related syncope is diagnosed by electrocardiography when there is:
Persistent sinus bradycardia <40 beats/min while awake or repetitive sinoatrial block or sinus pauses ≥3 s
Mobitz II second or third degree atrioventricular block
Alternating left and right bundle branch block
Ventricular tachycardia or rapid paroxysmal supraventricular tachycardia
Nonsustained episodes of polymorphic ventricular tachycardia and long or short QT interval
Pacemaker malfunction with cardiac pauses
Cardiac ischemia-related syncope is diagnosed when transient LOC presents with electrocardiographic evidence of acute ischemia, with or without myocardial infarction
Cardiovascular syncope is diagnosed when transient LOC presents in patients with severe aortic stenosis, pulmonary embolus, severe pulmonary hypertension, or acute aortic dissection

Abbreviation: *LOC* loss of consciousness

autonomic system, either vagal, such as nausea, vomiting, abdominal discomfort, and yawning, or sympathetic, such as pallor, sweating, palpitations, and pupillary dilatation. Besides autonomic symptoms, prodromal symptoms due to cerebral hypoperfusion, such as dizziness, lightheadedness, and blurred vision, are commonly reported by the patient. Unfortunately, none of these symptoms is specific to VVS. However, there is a consensus that when an emotional or orthostatic trigger is associated to autonomic symptoms, the diagnosis of typical VVS can be made [1]. Typical VVS is mainly observed in young subjects and rarely in the elderly.

Situational Syncope

Situational syncope is diagnosed when syncope occurs during or immediately after specific triggers, such as micturition, defecation, swallowing, coughing, and, more rarely, after sneezing, laughing, or brass instrument playing. Autonomic symptoms are present in about 50 % of patients [9]. There is a consensus that when a transient LOC occurs during these circumstances, situational syncope can be diagnosed after the initial evaluation, without further investigations [1].

Syncope Due to Orthostatic Hypotension

Orthostatic hypotension is defined as a decrease in systolic blood pressure of at least 20 mmHg and/or diastolic blood pressure of 10 mmHg, within 3 min of standing. Since asymptomatic orthostatic hypotension is frequent not only in the elderly but

also in adolescents [10], orthostatic syncope can be diagnosed only when the decrease in blood pressure during the orthostatic test is associated to syncope or presyncope. There is a consensus that, in this case, orthostatic syncope can be diagnosed without further examinations [1].

Orthostatic hypotension is due to hypovolemia or inadequate sympathetic vasoconstriction during the upright position and may lead to syncope or presyncope. Autonomic failure can be primary, secondary, or medication-induced. Examples of primary autonomic failure include pure autonomic failure and multiple system atrophy. Secondary autonomic failure refers to the autonomic dysfunction due to diseases such as diabetic or amyloid neuropathy that primarily affect organs other than the autonomic nervous system. In terms of the number of affected patients, drugs are probably the principal cause of orthostatic hypotension. Common culprits include antihypertensive drugs, diuretics, and antidepressants. In autonomic failure, not only active standing in the upright position, but the sudden cessation of exercise may also precipitate hypotension.

10.6 Clinical Findings That Are Only Suggestive of a Cause of Syncope

The findings obtained during the initial evaluation do not often enable a definitive diagnosis, but simply suggest a potential cause of syncope, thus pointing to additional specific examinations (Table 10.3). *Atypical VVS/reflex syncope* should be suspected when there are no triggers, but the autonomic symptoms, particularly nausea, vomiting, and abdominal discomfort, are present before and/or after LOC. Prodromal symptoms due to cerebral hypoperfusion show a similar prevalence in patients with atypical VVS/reflex syncope and cardiac syncope and are not useful for the differential diagnosis, whereas symptoms due to autonomic activation are more frequent and more pronounced in atypical VVS/reflex syncope. These symptoms are not present in orthostatic syncope due to autonomic failure, where no or insufficient activation of the autonomic system is present. The absence of signs/symptoms of heart disease during the initial evaluation strongly suggests a reflex syncope. In this regard, in an Italian multicenter study, the absence of heart disease allowed us to exclude a cardiac cause of syncope in 97 % of patients [11]. A long-lasting history of syncope (>4 years) suggests a reflex syncope. Indeed, the time between the first and the last syncopal episode is generally short in cardiac and orthostatic syncope [11]. Other findings suggestive of reflex syncope are LOC in patients with migraine, after prolonged standing and sitting, after exposure to medical situations, during head rotation or pressure on the carotid sinus (as caused by tumors, shaving, or tight collars); in the latter case, carotid sinus syncope should be suspected. Finally, a LOC appearing just after exercise suggests both reflex and orthostatic syncope; in young subjects, an atypical VVS/ reflex syncope is more likely, whereas in the elderly an orthostatic syncope is more likely [7]. In all the abovementioned situations, autonomic tests should be performed.

Orthostatic syncope should be suspected when LOC occurs after standing up or, as previously mentioned, after cessation of exercise, if the patient remains upright.

Table 10.3 Clinical features that are only suggestive of a diagnosis on initial evaluation

Atypical VVS/reflex syncope	Absence of heart disease
	First episode at young age (<35 years)
	Long history of recurrent syncope (>4 years)
	Nausea, vomiting associated to syncope
	Prolonged standing or prolonged sitting
	After exertion
	Crowded, hot places
	Exposure to medical situations
	Migraine
	With head rotation or pressure on carotid sinus (tumors, shaving, tight collars)
Syncope due to orthostatic hypotension	After standing up
	Prolonged standing
	Pain in the shoulders or neck
	Standing after exertion
	Temporal relationship with start or changes in dosage of vasodepressive drugs
	Presence of autonomic neuropathy or Parkinsonism
	After volume depletion
	Prolonged recumbency and deconditioning
Cardiovascular syncope	Presence of severe heart disease
	During exertion
	During supine position
	Chest pain before syncope
	Abnormal electrocardiogram
	Family history of unexplained sudden death or channelopathy
Electrocardiographic findings suggesting arrhythmic syncope	Left bundle branch block or bifascicular block
	Mobitz I second degree atrioventricular block
	Asymptomatic inappropriate sinus bradycardia (<50 beats/min)
	Nonsustained ventricular tachycardia
	Preexcited QRS complexes
	Long or short QT intervals
	Early repolarization
	Right bundle branch block pattern with ST elevation in leads V1–V3 (Brugada syndrome)
	Negative T waves and epsilon waves, suggestive of arrhythmogenic right ventricular cardiomyopathy
	Q waves, suggesting myocardial infarction

Postexercise hypotension results from the drop in blood pressure that normally occurs after exercise because of the remaining vasodilation. Patients with autonomic failure have difficulty in increasing their blood pressure during exercise. Postexercise hypotension may lead to falls, for example, when patients take rest

after having reached the top of a staircase [7]. Prodromal symptoms due to cerebral hypoperfusion (dizziness, lightheadedness, blurred vision) are commonly present, whereas the autonomic prodromes seen in reflex syncope are distinctly absent in orthostatic syncope; this feature could be important in the differential diagnosis. Moreover, patients may report pain in the neck or shoulders while exercising ("coat-hanger pain"); this is thought to be caused by ischemia of the muscles in the upper part of the body. By contrast, "coat-hanger pain" is very rarely reported in reflex syncope [12]. Finally, orthostatic syncope should be suspected in subjects who are dehydrated as a result of hot environments, diuretics, or inadequate fluid intake; in patients taking drugs such as antihypertensives, antidepressants, and antipsychotics; and in patients affected by an autonomic neuropathy. When an orthostatic syncope is suspected, autonomic tests, including tilt testing, should be performed to investigate the possibility of delayed orthostatic hypotension.

Cardiac syncope should be suspected in the presence of structural heart disease, a history of bradyarrhythmias or tachyarrhythmias, and a family history of unexplained sudden death or channelopathy. Presence of heart disease is generally accepted as the best predictor of cardiac syncope. Nevertheless, in a study by Alboni et al. [11], 46 % of patients with syncope and mild heart disease (mainly hypertensive heart disease) had atypical VVS/reflex syncope, and this limits the utility of this clinical measure in the differential diagnosis. The presence of severe heart disease (dilated cardiomyopathy and previous myocardial infarction) appears to be a better predictor of cardiac syncope [13].

Palpitation preceding LOC is usually considered a typical feature of arrhythmic syncope. However, palpitation could also accompany atypical VVS/reflex syncope, and in few studies, palpitation was reported to be more frequent in reflex syncope than in cardiac syncope [14–16]. Therefore, this symptom appears useless in the differential diagnosis. Likely, sudden-onset palpitation suggests an arrhythmic syncope, though this aspect is difficult to be clarified during history taking.

The appearance of LOC in the supine position suggests a cardiac syncope or an epileptic attack, since reflex syncope is rare in this position, with the exception of VVS during instrumentation. Syncope occurring during exercise also suggests a cardiac cause, whereas postexercise syncope, as previously mentioned, suggests a reflex or an orthostatic cause. Finally, some ECG abnormalities suggest an arrhythmic cause of syncope, as reported in Table 10.3. In these situations, cardiologic tests should be performed first.

Berecki-Gisolf et al. [17] examined seven studies [11, 14, 18–22], where symptoms of cardiac and reflex syncope had been addressed. A model of conditional probabilities and a priori probabilities of cardiac syncope was constructed. Results are summarized in Table 10.4. Ten variables were significantly associated with cardiac syncope: age ≥60 years, male sex, structural heart disease, low number of spells (≤2), brief or absent prodromes, supine syncope, effort syncope, and absence of nausea, diaphoresis, and blurred vision. Model sensitivity was 73–92 % and specificity 52–68 %. These data show that the ten variables identify patients with cardiac syncope with moderate accuracy. Table 10.4 shows that the best predictors of cardiac syncope are LOC during supine position and during physical effort, but,

Table 10.4 Data obtained from seven studies, in which symptoms of cardiac and noncardiac syncope were investigated [17]; prevalence of selected symptoms in relation to final diagnosis

	Cardiac syncope (%)	Noncardiac syncope (%)	*P*	Likelihood ratio
Age <40 years	1	29	<0.0001	
Age 40–60 years	22	38		
Age >60 years	77	33		
Male gender	64	49	<0.0001	1.30
Structural heart disease	87	26	<0.0001	3
Number of spells (≤2)	70	38	<0.0001	1.84
Nausea	8	20	<0.0001	1.15
Diaphoresis	18	43	<0.0001	1.42
(Long) prodrome	39	63	<0.0001	1.66
Blurred vision	21	29	0.0002	1.12
Palpitations	8	11	0.06	1.03
Supine syncope	10	2	<0.0001	4.23
Syncope during effort	13	2	<0.0001	6.92

unfortunately, syncope occurs during these situations only in a small percentage of patients

VVS/reflex syncope appears to be very rare in the supine position. Recently, a new form of VVS that occurs in this position during the sleeping hours has been described and defined as "sleep syncope" [23, 24]. Most of these patients are middle-aged women; they report a history of waking from sleep with abdominal discomfort, an urge to defecate, and nausea, followed by LOC. These symptoms always begin in the supine position, but LOC occurs in this position only in a third of patients. In the remaining two thirds, syncope occurs after standing up while going to the bathroom (see Chap. 13). "Sleep syncope" must be investigated during clinical history, only when the prodromal symptoms begin in the supine position.

10.7 Clinical Scores to Diagnose the Type of Syncope During the Initial Evaluation

Some authors tried to develop evidence-based criteria in order to distinguish the various types of syncope during the initial evaluation [13, 16, 19, 25] (Tables 10.5, 10.6, 10.7, and 10.8). A multivariate regression analysis was performed to identify those variables acting as significant predictors. A score was then developed by assigning points to each of the risk factors, based on the relative magnitude of the regressive coefficient. The points were summed to reach a final score, and a diagnostic threshold was determined by a receiving operating characteristic (ROC) analysis.

The first diagnostic clinical score, the Calgary Symptom Score, was built up by Sheldon et al. [25] in 323 patients without heart disease (mean age 42 years), recruited

Table 10.5 Diagnosing questions to determine whether syncope is due to vasovagal syncope, as determined by Sheldon et al. [25] (Calgary score)

Question	Score
Is there a history of at least one of bifascicular block, asystole, supraventricular tachycardia, diabetes?	−5
At times, have bystanders noted you to be blue during your faint?	−4
Did your syncope start when you were 35 years of age or older?	−3
Do you remember anything about being unconscious?	−2
Do you have lightheaded spells or faint with prolonged sitting or standing?	1
Do you sweat or feel warm before a faint?	2
Do you have lightheaded spells or faint with pain or in medical setting?	3

The patient has vasovagal syncope if the score is ≥−2

Table 10.6 Predictors of cardiac cause of syncope and point scores for the diagnosis of cardiac syncope, as determined by Del Rosso et al. [19] (EGSYS score)

Variable	Score
Palpitations preceding syncope	4
Heart disease or abnormal electrocardiogram, or both	3
Syncope during effort	3
Syncope while supine	2
Precipitating or predisposing factors, or both	−1
Autonomic prodromes	−1

The patient has cardiac syncope if the score is ≥3

Table 10.7 Diagnostic questions to determine whether syncope is due to ventricular tachycardia or vasovagal syncope, as determined by Sheldon et al. [13]

Question	Score
Was your age at first faint older than 34 years?	3
Are you a male?	1
Have you become lightheaded or fainted with prolonged sitting or standing?	−1
Have you become lightheaded with stress?	−2
At times are you tired for more than 1 min after fainting?	−2
Do you have recurrent headaches?	−2

The patient has ventricular tachycardia if the score is ≥1, and vasovagal syncope if the score is <1

from tertiary care clinics, in order to distinguish VVS from other types of syncope. The score consists of seven diagnostic questions about the medical history, triggers, circumstances, and signs and symptoms (Table 10.5). If the total score is −2 or more positive, a diagnosis of VVS is made. The point score correctly classified 90 % of patients, diagnosing VVS with 89 % sensitivity and 91 % specificity. These data suggest that a simple score of historical features distinguishes VVS from syncope induced by other causes with excellent sensibility and specificity. However, the authors concluded that these findings need to be tested in a broad-based population.

Two subsequent studies investigated the performance of the Calgary Score in a series of patients presenting with transient LOC [26, 27]. Romme et al. [26]

Table 10.8 Predictors of cardiac cause of syncope and point scores for the diagnosis of cardiac syncope, as determined by Mitro et al. [16]

Variable	Score
Age ≥55 years	3
Chest pain before syncope	3
Present structural heart disease	2
Absent prodromal symptoms	2
Syncope in supine position	2
Syncope after standing up	−3
Prolonged recovery	−3

The patient has cardiac syncope if the score is ≥2

calculated the Calgary Score in 380 patients (mean age 53 years) presenting with transient LOC to several different departments. Diagnoses of VVS, based on the Calgary Score, were compared with the final diagnosis, obtained after additional tests and 2 years of follow-up. The sensitivity of the Calgary Score was 87 %, similar to that reported by Sheldon et al. [25], whereas the specificity was much lower, 32 %, which means that a large number of patients would receive an incorrect diagnosis of VVS, based on the Calgary Score. Romme et al. [26] pointed out some limitations of the Calgary Score:

1. Only patients without heart disease were included.
2. The study deals with selected patients recruited from tertiary cardiological clinics and not from different departments.
3. Patients were excluded if a diagnosis was not well-established and/or they had more than one plausible cause of syncopal spell.

Therefore, the Calgary study should have been carried out in highly selected patients, who are not representative of the total population of patients with transient LOC. Later, Exposito et al. [27] calculated the Calgary Score in 180 elderly patients (mean age 73 years) with suspected VVS. The sensitivity of the Calgary Score was only 51 %, and the specificity 73 %. One hundred patients (55 %) had mild heart disease, and in this population, sensitivity was even much lower – 13 %. The authors concluded that the Calgary Score is not useful for diagnosing VVS in an elderly population presenting with syncope. Determining the cause of syncope in elderly patients is challenging, as this population is characterized by atypical presentation of syncope, which occasionally is consistent with falls with total amnesia of the episode. Age-associated factors, combined with higher rates of cardiovascular disease and other comorbidities, impair the adaptive physiological responses to common physiologic stressors, including gravity force, leading to a multicausal nature of syncope [27, 28]. Typical manifestations of VVS in elderly patients may be absent, since prodromes are usually short-lasting or absent, and, frequently, not recalled by elderly patients [29, 30]. Similarly, typical precipitating factors are frequently not reported. Taken together, these aspects potentially limit the applicability of the Calgary Score for identifying VVS as the cause of transient LOC in the elderly.

In other three studies, clinical scores were built up in order to distinguish cardiac syncope from the other causes of syncope [13, 16, 19]. Del Rosso et al. [19] developed a diagnostic score to identify cardiac syncope in 516 patients (mean age 63 years) referred for syncope to the emergency department of 14 general hospitals. About half of the patients had structural heart disease and/or abnormal ECG. Subjects underwent diagnostic evaluation, strictly adhering to the guidelines of the European Society of Cardiology [31]. Six independent predictors of cardiac syncope were identified (Table 10.6), and a score ≥3 identified cardiac syncope with high sensitivity (95 %), but with a limited specificity, 61 %. Sheldon et al. [13] tried to define the historical criteria that could distinguish between ventricular tachycardia and VVS as a cause of transient LOC in patients with structural heart disease. They enrolled 134 patients (mean age 69 years) with severe heart disease, defined as either a dilated nonischemic cardiomyopathy or previous myocardial infarction. The score consists of six diagnostic questions (Table 10.7). The patient had ventricular tachycardia if the score was ≥1 and VVS if the score was <1. The score correctly classified 92 % of patients, diagnosing ventricular tachycardia with 99 % sensitivity and 68 % specificity. Mitro et al. [16] developed a diagnostic score based on clinical history to distinguish between cardiac and noncardiac syncope. Clinical history was obtained in 248 patients (mean age 55 years) presenting with syncope. Twenty-eight percent of the patients had structural heart disease. Seven independent predictors of cardiac syncope were identified (Table 10.8). A point score ≥2 identified patients with cardiac syncope with a sensitivity of 81 % and a specificity of 84 %.

In these three studies [13, 16, 19], where a clinical score was determined in order to diagnose a cardiac syncope during the initial evaluation, most of the limitations previously reported for the Calgary study [25] were present. In particular, patients were excluded if the diagnosis was not well-established or more than one plausible cause of syncope was present. There is both theoretical and empirical evidence that such an approach can lead to overoptimistic estimates of diagnostic accuracy [27, 32]. Moreover, it should be stressed that there is no gold standard test to diagnose patients presenting with transient LOC. This implies that the final classification in any diagnostic study dealing with transient LOC is challenging and the problem of misclassification always exists. We believe that the diagnostic clinical scores could be useful to proper selection of diagnostic tests, thereby avoiding unnecessary examinations. However, the scores should not be used in the clinical practice as a sole measure to diagnose individual patients presenting with transient LOC, but should be combined with clinical judgment to optimize the patient's risk stratification [33].

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Clinical Presentation and Diagnosis of Vasovagal Syncope

11

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Key Points

- Typical vasovagal syncope (VVS) can be diagnosed after the initial evaluation, without further investigation, when transient loss of consciousness (LOC) is triggered by emotional or orthostatic stress and autonomic prodromes are present.

Vasovagal syncope (VVS) is the most common cause of transient loss of consciousness (LOC). Sir Thomas Lewis' classic description of VVS following venesection in 1932 details dizziness, pallor, nausea, retching, weak slow pulse, and confusion followed by unconsciousness and profound hypotension [1]. Since then, our knowledge on VVS has been markedly improved, above all after the advent of the tilt table

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- Atypical VVS can be diagnosed in subjects with transient LOC not preceded by any evident trigger, but with positive tilt testing, in the absence of any competing diagnosis.
- Clinical presentation of VVS is influenced by age. Older subjects have shorter duration of prodromes and lower frequency of prodromal and recovery symptoms.
- Sleep syncope is a rare form of VVS which occurs in the supine position during the sleeping hours. It is not preceded by any evident trigger and is associated to autonomic prodromal and recovery symptoms.
- The clinical presentation of VVS can be the same as unexplained fall in subjects with retrograde amnesia.

test in the clinical setting, and we have learned that VVS can have different clinical presentations, as reported in Table 11.1 [2].

11.1 Typical Vasovagal Syncope

Typical VVS is a transient LOC characterized by (1) precipitating triggers such as emotional distress (extreme emotions, fear, severe pain, disgust because of unpleasant sights, blood phobia, medical setting) or orthostatic stress (prolonged standing, particularly in hot and/or crowded places) and by (2) symptoms due to activation of the autonomic system, such as nausea, vomiting, abdominal discomfort, pallor, and sweating. Other autonomic symptoms such as feeling cold or feeling warm, palpitations, yawning, sighing, salivation, pupillary dilatation, and urinary incontinence may be present. Besides autonomic symptoms, prodromal symptoms due to cerebral hypoperfusion, such as dizziness, lightheadedness, awareness of fainting, and blurred vision, are commonly reported. From the phylogenetic point of view, a vasovagal reflex triggered by emotional distress or orthostatic stress (thoracic hypovolemia) is present in the mammals and the other vertebrates (see Chap. 1).

There is a consensus that when a transient LOC is precipitated by an emotional or orthostatic trigger and is associated to autonomic symptoms (before and/or after LOC), the diagnosis of VVS can be made after the initial evaluation, without further investigation [3]. In some subjects, syncope cluster is observed, and the syncopal

Table 11.1 Possible clinical presentations of vasovagal syncope

Typical vasovagal syncope
Atypical vasovagal syncope
Sleep syncope
Unexplained fall
Sudden death when the vasovagal reflex occurs simultaneously with the diving reflex

episodes are concentrated in some days, weeks, or months, with very long asymptomatic periods (sometimes years). The mechanism of syncope cluster has not been elucidated yet. Typical VVS is mainly observed in young subjects and rarely in the elderly. It is more frequent in women than in men, particularly when the attack is triggered by emotional distress [4]. The most common age at which VVS first presents is 13–15 years and is rarely reported before the age of 10 years [4, 5].

Typical Vasovagal Attack

Since the classical Lewis' report [1], the typical vasovagal attack has been described several times in the literature. Recently, it has been reviewed by Wieling et al. [6] on the light of new knowledge. On average, prodromal symptoms start 30–90 s before losing consciousness, but this duration is markedly variable. Subjects first begin to feel uncomfortable in an ill-defined way, or experience a feeling of cold or warmth, epigastric discomfort and nausea, abdominal cramps, and a desire to sit down or leave the room. Some subjects report a strong urge to defecate. If subjects act on these warming signs by lying down, LOC may be prevented. However, if these warnings are ignored, lightheadedness, dizziness, cold sweat, fatigue, blurred vision, palpitations, and buzzing in the ears may occur. Hyperventilation is frequently observed, though there is an agreement that if present alone it is an insufficient physiological stressor to induce syncope [7]. Facial pallor is often the first sign of an impending VVS. It may be followed by yawning, sighing, sweating, restlessness, salivation, pupillary dilatation, and accentuated peristaltic sounds. The ghostly white pallor results from reduced skin blood flow due to sympathetically and vasopressin-induced vasoconstriction combined to low blood pressure [8]. The pale color is that of subcutaneous connective tissue, composed principally of collagen fibers of a whitish hue. Deoxygenated hemoglobin is responsible for the additional greenish hue observed in some subjects [9]. Pupillary dilatation occurs just before losing consciousness, probably due to a combination of central inhibition of vagal outflow, peripheral sympathetic overactivity, and high level of circulating adrenaline. As blood pressure continues to fall, symptoms and signs of cerebral and retinal dysfunction come to the fore: subjects have difficulty concentrating, become unaware of their surroundings, and fall down as they lose consciousness (provided they were standing). The prodromal phase is often associated with sinus tachycardia. Younger subjects often complain of palpitations in this phase. The subsequent heart rate decrease is variable and usually occurs after the onset of hypotension.

During LOC, eyes are open in >90 % of cases and directed upward in 60 % [10]. Events such as myoclonic jerks, more often involving the shoulders and arms, sounds made by the subject, complex movements as lip-licking and rubbing the head, roving eye movements, stertorous breathing, jaw dropping, and snoring can occur. Recently, van Dijk et al. [10] investigated the correlation between these events and the electroencephalographic (EEG) changes during LOC. Eyes opening occurred at the beginning of the slow phase of EEG activity and myoclonic jerks during the slow phase. Other signs such as sounds, complex movements, roving eye

movements, and stertorous breathing were mainly observed during the flat phase of the EEG, which denotes more severe hypoperfusion. Jaw dropping and snoring may occur either during slow or flat phases.

Just after the recovery of consciousness, all the signs and symptoms reported during the prodromal phase can be present. Vomiting can be present before and after LOC, and sometimes only during the recovery phase [11, 12].

The typical vasovagal attack has been frequently described in the literature, but, surprisingly, there are scanty data about the prevalence of the various symptoms. Alboni et al. [12] investigated the symptoms before and after the syncopal episode in 39 subjects (age 35 ± 18 years) with typical VVS by utilizing a questionnaire. The most frequent prodromal symptom was pallor (87 %) (evaluated only in the presence of witnesses), followed by awareness of fainting (69 %), sweating (43 %), palpitations (33 %), blurred vision (31 %), weakness (31 %), nausea (26 %), feeling cold (18 %), feeling warm (15 %), abdominal discomfort (13 %), vomiting (10 %), tremors (8 %), and yawning (3 %). During LOC, abnormal movements (evaluated only in the presence of witnesses) were observed in 13 % of subjects, and incontinence of urine was reported by 3 %. During the recovery phase, symptoms were present in 95 % of subjects (pallor, 61 %; sweating, 59 %; weakness, 46 %; feeling cold, 36 %; confusion, 33 %; nausea, 26 %; abdominal discomfort, 10 %; vomiting, 5 %; and feeling warm, 3 %). About 40 % of these subjects mentioned circumstances, which, in their opinions, were important in triggering the syncopal attack, such as warm environment, crowded place, overtiredness, and postprandial period. The same circumstances, besides insufficient food intake and menstruation, were reported by Ganzeboom et al. [4] who investigated young subjects with neurally mediated syncope. Typical VVS occurred during the standing or sitting positions, and only in 5 % of subjects during supine position, always triggered by emotional distress [12]. Khadilkar et al. [13] investigated the prodromal symptoms in young subjects with VVS and reported that prodromal symptoms were similar when the syncopal episode occurred during standing, sitting, or supine positions, whereas emotional trigger was more frequent in subjects with syncope occurring in supine or sitting positions.

The two triggers that characterize typical VVS are emotional distress and orthostatic stress. Sometimes, the presence of these triggers is uncertain, and we are in a gray zone (see discussion in Chap. 13).

VVS has no prognostic implications, but, when recurrent, it can be associated with psychological distress and reduced quality of life. In the elderly, recurrent syncope may result in significant loss of confidence, fear of falling, loss of independence, and increased likelihood of subsequent institutionalization.

Migraine and Vasovagal Syncope

Typical VVS is observed in patients with migraine. Migraine is a severe headache associated with neurologic and autonomic symptoms. Symptoms such as feeling cold, increased urination, anorexia, diarrhea, and fluid retention can occur during the premonitory phase, and nausea, vomiting, diarrhea, pallor, flushing, piloerection,

and diaphoresis can occur during the pain phase [14, 15]. Studies of autonomic nervous system dysfunction in migraine have been performed [14]. Cardiovascular tests, vasomotor reactions to temperature changes, and responses to pharmacological tests suggest abnormalities (hypo- or hyperfunctioning) of both the sympathetic and parasympathetic nervous systems [14]. These different findings may be explained by different types of autonomic dysregulation. VVS and migraine are both highly prevalent in the general population, but both disorders occur more frequently than chance would predict [15, 16]. Studies using the orthostatic test suggest that migraine patients have vagal hyperactivity and alpha-adrenergic sympathetic hypoactivity [14]. Recently, Valleio et al. [17] showed that VVS is more frequent in patients with migraine than in those with headache. Syncope and migraine attacks do not usually occur together. Individuals affected by migraine may have a genetic predisposition leading to autonomic nervous system dysfunction [15]. The higher incidence of syncopal spells in these patients could be due to a high susceptibility to the vasovagal reflex on genetic basis, but that has not been clearly demonstrated.

Blood-Injection Injury Phobia

Typical VVS is observed in subjects with blood-injection injury phobia. Fear of injections is a common concern among individuals in health-care setting. Approximately 10 % of individuals in medical settings report an excessive fear of needles that causes significant avoidance, distress, and/or impairment [18]. For some individuals, this fear may be severe enough to warrant a diagnosis of a specific phobia, blood-injection injury type, also defined as needle phobia. Needle phobia, characterized by an intense and persistent fear of injections, affects approximately 3 % of individuals in the general population [19]. Ost [20] reported that about 50 % of needle-phobics had fainted upon exposure to needles, whereas VVS appears to be extremely rare in subjects with other types of phobia (spider phobia, claustrophobia, agoraphobia, etc.). The reason for the different prevalence of fainting in the various types of phobia is unknown.

Vasovagal reactions in the presence of blood-injection injury stimuli are not limited to individuals with needle phobia. These reactions were observed in 8.2 % of high school Caucasian students and 2.6 % of adults who donate blood, and about 10 % of these reactions evolve to typical VVS, sometimes with prolonged asystolic pause [21, 22]. Vasovagal reactions and VVS during blood donation appear to be extremely infrequent in African-American subjects [21]. Demographic and psychological characteristics associated with needle fear and vasovagal reactions have been identified. Studies conducted with voluntary blood donors indicate that a younger age, a lower body weight, and a first-time donor status are significant predictors of vasovagal reactions [21, 23]. Psychological factors such as blood and injury fear and pain sensitivity appear to predict vasovagal reactions more strongly than do demographic characteristics [24]. Accurso et al. [25] reported that in 80 % of subjects with blood/injury phobia and VVS as part of the phobic response, syncope was reproduced during tilt testing, which further demonstrates that multiple triggers can evoke typical VVS.

11.2 Atypical Vasovagal Syncope

An atypical VVS can be diagnosed in subjects with transient LOC not preceded by any evident trigger, but with positive response to tilt test and in the absence of any competing diagnosis. We can define this form of syncope as vasovagal, because it is triggered by an orthostatic stress, even if not spontaneous (tilt testing). Before the introduction of the head-up tilt test in clinical practice, we were unable to make a diagnosis in these subjects. However, since tilt test, like other tests utilized in the diagnosis of syncope, is not a gold standard and its positivity rate is only about 50 %, there is continuum between atypical VVS and reflex (neurally mediated) syncope.

While typical VVS is mainly observed in young subjects, atypical VVS is observed in middle-aged and older subjects and only rarely in the young. The absence of an evident trigger does not exclude the role of a trigger. It is reasonable to assume that the sudden drop in blood pressure, often associated to slowing of heart rate or asystole, may be due to an unknown stimulus.

The clinical features of atypical VVS (tilt-induced syncope) were specifically investigated in a UK study [26] and in an Italian study [12]. The most common predisposing factors were warm and crowded places, lack of food, head movements, postprandial period, and overtiredness. Prodromal symptoms were absent in 39–24 % of subjects. When prodromes were present, the most common were blurred vision, 68–27 %; fatigue, 68–23 %; pallor, 48–82 %; sweating, 66–32 %; nausea, 60–13 %; palpitations, 37–10 %; feeling cold, 29–12 %; and feeling warm, 18–6 %. Dizziness, vomiting, abdominal discomfort, yawning, and tingling were observed more rarely. Headache was reported as a prodromal symptom only in the UK study (29 %). During the syncopal phase, myoclonic jerks, investigated in the Italian study in the presence of witnesses, were observed in 13 % of subjects, incontinence in 3–12 %, minor trauma in 40–35 %, and fractures in 13–3 %. During the recovery phase, symptoms were present in 76–74 % of subjects. The most common were fatigue, sweating, pallor, and confusion. In the Italian study, vomiting was more frequent during the recovery phase than during the prodromal phase (15 % vs. 4 %). Many subjects had frequent episodes of presyncope. It is well known that VVS is frequent at the restaurant, even if this predisposing factor has never been specifically investigated in studies dealing with syncope. Sutton [27] tried to explain the role of the restaurant as a predisposing factor and claimed that the cephalic phase of digestion, with vagal activation, is prolonged during the decision making of what to eat and the waiting for the food to arrive and that there is often enhancement by a sufficient quantity of alcohol to cause peripheral vasodilation. Furthermore, the thorax is always vertical at this time, and the environment may be overheated. After an heavy meal, even the shift of blood to the splanchnic bed may play a relevant role. Another frequently reported predisposing factor is volume depletion, which can be caused by inadequate introduction of fluids, especially in the elderly, hemorrhage, vomiting, and diarrhea. It may be exacerbated by drugs or heat, which causes additional volume depletion and vasodilation. If sufficiently severe, hypovolemia alone could lead to syncope. Even systemic illnesses and medications are considered important predisposing factors.

On the basis of the results of recent studies dealing with implantable loop recorder (ILR) [28], it has been suggested that tilt testing is useful to investigate a hypotensive reflex rather than to diagnose a VVS [29]. Ungar et al. [28] analyzed both the electrocardiographic recordings and the tilt test results of 187 patients with presumed neurally mediated syncope during syncopal recurrence, after implantation of a loop recorder. In 25 patients (13 %), the ILR revealed another cause of syncope, mainly an arrhythmic syncope. The authors concluded that tilt testing was unable to discriminate between presumed neurally mediated syncope and nonneurally mediated syncope. However, these conclusions deserve some comments as follows:

- ILR confirmed the clinical diagnosis of presumed neurally mediated syncope in a high percentage of patients (87 %).
- About 40 % of these 25 patients had nonsyncopal atrial tachyarrhythmias on clinical history, and a diagnosis of atypical VVS can be made only when tilt testing is positive and other potential causes of syncope are excluded.
- ILR is a gold standard for a single syncopal episode, but not for all the syncopal spells occurring in an individual over time. In this regard, it is well known that older patients can have different potential causes of syncope. In other words, one individual can suffer from both cardiac syncope and neurally mediated syncope, which is frequent in the general population.

However, the data of these studies suggest that an accurate history taking should be made in every patient and the results of tilt testing carefully evaluated in the clinical context.

Exertion-Related Vasovagal Syncope

An exertion-related syncope suggests a cardiac origin, and cardiological examinations should be performed first. However, young and middle-aged subjects, particularly recreational or competitive athletes, can experience VVS after an exertion and very rarely during exertion [30–33]. The mechanism of exertion-related VVS is not entirely clear. Postexertion syncope could be triggered by reduced venous return, particularly when the exertion is abruptly interrupted, with consequent thoracic hypovolemia occurring when vigorous ventricular contractions are still present. Postexercise syncope is usually associated with bradycardia or asystole, besides arterial hypotension [32]. VVS occurring during exertion appears to be due to exaggerated vasodilation triggered by inappropriate baroreceptor response and is characterized by severe hypotension without relevant cardioinhibitory response [31]. Prodromal symptoms due to both cerebral hypoperfusion and autonomic activation are often present and are similar to those of nonexercise-related VVS [30]. The diagnosis of exercise-related VVS can be made only when structural heart disease, coronary heart disease, and primary electrical disease are excluded and tilt testing is positive, though the specificity of this test in trained subjects is rather low. Exertion-related syncope is discussed in Chap. 24.

Influence of Gender on the Clinical Presentation

Romme et al. [34] investigated the influence of gender on the clinical presentation of syncope. They enrolled 503 subjects with reflex syncope, mainly VVS, and found that prodromal signs and symptoms were about 50 % more common in women than in men. Palpitations, abdominal discomfort, and paresthesias were significantly more prevalent in women. Moreover, women had more syncopal episodes during venipuncture and after meal. There is not a clear explanation for these gender differences. Studies on pain perception have reported that women consider pain as more unpleasant than men, because of different sociocultural, psychological, and biological factors [35]. Women appear to have a greater tendency to report pain to healthcare providers than men and are more open to discuss physical phenomena [36]. It seems therefore reasonable to assume that this tendency may also lend women to report more prodromal symptoms associated with their syncope than men.

Influence of Age on the Clinical Presentation

The influence of age on the clinical presentation of VVS has been widely investigated [34, 37–39]. Older subjects had a short duration of prodromal symptoms. The frequency of the prodromes due to global cerebral hypoperfusion or to autonomic activation was lower in subjects >60–65 years [10, 38]. Only pallor showed a similar prevalence in the young and the elderly [34]. During the syncopal phase, myoclonic movements were rarely observed in older subjects; none >74 years experienced myoclonic movements [38], and that could be explained by the less frequent occurrence of asystolic VVS in the elderly. Even during the recovery phase, the frequency of autonomic symptoms was lower in older subjects [38]. Thus, in the elderly, the clinical features of VVS are very similar to those of cardiac syncope. The different clinical patterns of VVS observed in older subjects could be the result of several mechanisms, including an age-related decrease in parasympathetic activity [40], a diminished beta-adrenergic response [41], and a smaller increase in circulating adrenaline when upright [41].

Family History in Vasovagal Syncope

Some studies have suggested that fainting offspring are more likely to have a positive family history for VVS. Mathias et al. [42] studied 119 syncope subjects of various ages. A positive family history of VVS was present for 51 % of 47 confirmed vasovagal subjects and in 28 % of probable vasovagal subjects. Cramfield et al. [43] reported that 90 % of 30 children with VVS had at least one affected first-degree relative, compared with only 33 % of 24 controls. Newton et al. [44] reported an extended family in which syncope occurred in three successive generations of males, all of whom had positive tilt test. Mathias et al. [45] reported a similar multigenerational family with VVS in all three generations. Marquez et al. [46]

reported two sets of monozygotic twins who all fainted. Serletis et al. [47] studied 62 medical students and 228 first-degree relatives. The prevalence of VVS was 32 %. An individual with two fainting parents was more likely to faint than the one with no fainting parents (odd ratio 3.4, confidence index 1.7–7.0). In the proportional hazards model, offspring of either sex whose mother faints are more likely to faint than those whose mother does not faint. Having a father who faints significantly increases the risk of VVS in sons, but not in daughters. Therefore, a family history in VVS subjects appears to be clearly demonstrated, but at present, we do not know whether susceptibility to VVS has a genetic basis or is an expression of cultural, social, and environmental effects.

11.3 Sleep Syncope

Recently, a new form of VVS, which occurs in the supine position during the sleeping hours in the absence of any trigger, has been described and defined as sleep syncope [48–50]. Most of these subjects were middle-aged women; they reported a history of waking up from sleep with abdominal discomfort and an urge to defecate, followed by LOC. Autonomic prodromes, mainly sweating, nausea, palpitations, and feeling warm were present in almost all patients. These symptoms always began in the supine position, but LOC occurred in this position only in a third of subjects; in two thirds, it occurred after standing up to go to the bathroom. During LOC, some subjects had myoclonic movements. After regaining consciousness, most subjects felt intense weakness and could not keep the upright position, but were oriented. The frequency of attacks varied from once a week to one episode a year, and there was no relation to menstruation or alcohol. Some subjects had learned to partially abort the episodes by remaining supine in bed. Fifty-five percent of these subjects also reported episodes of typical VVS during the day, and 74 % reported a history of specific phobia(s), mainly blood-injection injury phobia. It is not clear whether the abdominal symptoms could be the trigger or part of the vagal response to the syncopal attack; the second hypothesis appears to be much more likely [48, 49]. Bradycardia was fortuitously documented in some subjects during the spontaneous syncopal episode. Basal tilt testing was positive in 64 % of subjects with sleep syncope – which appears to be a very high percentage, considering the absence of pharmacological provocation – and in about half of these, an asystolic pause was recorded.

The mechanism of sleep syncope has not been elucidated. Hu et al. [51] preformed tilt testing during both diurnal and nocturnal hours to subjects without the history of syncope and observed that the highest risk of presyncope occurred at about 4:30 am. This suggests that the endogenous circadian system may be mechanistically involved in the pathophysiology of sleep syncope. The possible underlying mechanisms include the circadian-modulated increase in parasympathetic nervous activity, decreased sympathetic nervous system activity, decreased systolic blood pressure, and decreased cardiac output during the night. Some subjects reported nightmares immediately before the attack [48], and, therefore, some

episodes could be, actually, emotional VVS. Sleep syncope can be diagnosed in the presence of typical autonomic prodromes and in the absence of structural heart disease or primary electrical disease. A history of daytime typical VVS and a positive response to tilt testing can support the diagnosis. Some findings suggest that sleep syncope is a form of VVS with a different clinical presentation: high prevalence of autonomic prodromes, of diurnal episodes of typical VVS and specific phobias, and of positive tilt testings with severe cardioinhibition.

11.4 Presentation of Vasovagal Syncope as a Fall

Sometimes, the clinical presentation of VVS is the same as a fall. A fall is defined as an event in which the subject unintentionally comes to rest on the ground or at a lower level. Falls may be accidental or unexplained. An accidental fall is defined as a simple slip, trip, accidental collision, or environmental hazard resulting in fall, whereas an unexplained fall is a fall with no evident explanation for the event. Among patients presenting to the emergency room after falls, the cause of falling is reported to be accidental in 41 %, medical conditions (stroke, alcohol intoxication, epilepsy, etc.) in 22 %, cognitive impairment in 19 %, and unexplained in 15 % [52]. Kenny et al. [53] reported a similar prevalence of unexplained falls (about 20 %) among patients seeking assistance at the emergency department after falling.

If syncope occurs in the upright position, LOC may lead to a fall. Because of the marked variability in the clinical presentation of syncope, the clinical findings of syncope and falls could be very similar [54, 55]. In this regard, retrograde amnesia has been demonstrated in patients with syncope induced in the laboratory; about 25 % of patients have been found not to remember their prodromal symptoms and LOC during tilt-induced or carotid sinus massage-induced syncope [56, 57]. Thus, because of retrograde amnesia, unexplained falls and syncope may be indistinguishable. The clinical presentation of VVS as unexplained fall is discussed in Chap. 13. The investigations to be performed in patients with unexplained falls are reported in Table 11.2.

Another possible clinical presentation of VVS is sudden death, when the vasovagal reflex occurs simultaneously with the diving reflex. This issue is discussed in Chap. 27.

Table 11.2 Cardiovascular management of patients with "unexplained" falls

Investigations
Supine and standing blood pressure measurement
Any other cardiological investigation, as appropriate, in the presence of relevant heart disease and/or arrhythmias or conduction disturbances
Carotid sinus massage with the "method of symptoms"
Tilt testing
Implantable loop recorder?

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Examinations in Suspected Vasovagal Syncope

12

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Key Points

- Dealing with a patient with suspected vasovagal syncope, a pragmatic approach, based on the pretest probability inferred from the initial examination, would assure the use of appropriate tests and avoidance of those inappropriate with a consequential improvement of sensitivity and specificity, diagnostic accuracy, and cost savings.
- Clinicians must acknowledge what information each test can or cannot provide.
- Tilt test is a common, noninvasive test modality with great value when undertaken in the correct clinical context.
- A positive response to tilt test in patients with severe heart disease should be considered with caution because of a potential competing diagnosis with prognostic implications such as ventricular tachyarrhythmia.

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- Tilt testing is useful to identify delayed orthostatic hypotension and psychogenic pseudosyncope; in some cases, it can help patients to better recognize their own symptoms and evaluate the usefulness of therapeutic measurements.
- The laboratory diagnosis of *Carotid sinus syndrome* requires reproduction of spontaneous symptoms and exclusion of competing mechanisms.

12.1 Introduction

The purpose of this chapter is to provide a comprehensive and accurate guide to the clinician to choose the best test or test battery for a patient with a suspected vasovagal syncope (VVS), either typical or nontypical.

Dealing with a patient with a suspected VVS can be extremely frustrating, as on one hand this condition can be considered benign [1], and on the other hand the complexity of the underlying neurocardiovascular mechanisms is such that a precise pathophysiologic diagnosis can be difficult and time-consuming in many cases [2–4].

Autonomic regulation involves reflex arcs which include sensors, afferent and efferent branches, central integration, and neuroeffector junctions [5]. Indeed, approaching the neural net that regulates the cardiovascular system, we may wonder if such an effort is worth. Nevertheless, the interference with normal life for patients with VVS can be relevant [4], and therefore diagnosis and therapy are due. No doubt, the complexity of the autonomic nervous system (ANS) evaluation deserves a systematic approach to avoid fictitious and misleading information. In addition, the variability of clinical presentations and of the underlying mechanisms in VVS is such (see Chap. 13) that to follow fixed and defined test algorithms may be confounding. We think that it is crucial to acquaint each available test in the details. As for these, we suggest to hold an Ariadne's ball of thread, that is, an in-progress etiopathogenetic hypothesis, to find the way in the maze. In other words, we recommend a tailored algorithm for each patient. To do so, we underline the concept that the detailed autonomic clinical history and the physical examination are the essentials to a sound etiopathogenetic hypothesis and to the individualized selection of appropriate autonomic tests. Together with the precise acknowledgment of what information a test can or cannot provide, a pragmatic approach, based on the pretest probability inferred from the initial examination, would assure the use of appropriate tests and avoidance of those inappropriate, with a consequential improvement of sensitivity and specificity, diagnostic accuracy, and cost savings. On the whole, the employed tests would suggest a more precise diagnosis, together with the underlying mechanisms. In addition, in some cases, tests can help patients to better recognize their own symptoms (for example prodromes) and can be useful to evaluate the adequacy and impact of therapeutic measurements. Given these premises, it is clear that very few patients will require the performance of all the tests we describe, while for some patients even a single test will be sufficient.

In VVS, three responses are generally seen, that is, cardioinhibitory, vasodepressor, and mixed response with features of both [6]. Here, we classify the tests of autonomic function, according to the final organ response to be evaluated: (1) tests that integrate the evaluation of blood pressure and heart rate; (2) tests that predominantly evaluate heart rate; and (3) tests that predominantly evaluate blood pressure. For each test, we discuss the theoretical aspects, how the test is administered, interpretation of the results, potential disadvantages, and pitfalls, as well as sensitivity and specificity. In this way, the clinician should be able to utilize the results of the tests to confirm the presence of VVS and the specific mechanism involved in its occurrence.

12.2 Integrated Evaluation of Blood Pressure and Heart Rate

The Orthostasis Test

The orthostasis test (OT), that is, active standing, is a useful and inexpensive test that can be considered an extension of the physical examination [3]. The test corresponds to real-life situations; it is simple to perform; minimal patient cooperation is needed; and the equipment is easily available.

Upon assuming the orthostatic position, regional hemodynamic changes occur because of the gravitational pooling of blood in the lower limbs [7] (see also Chaps. 5 and 6). These modifications are sensed by baroreceptors connected to the central nervous system, which in turn determine decreased parasympathetic tone and increased sympathetic outflow [8].

Evaluation of OT includes blood pressure (BP) measurements by a standard sphygmomanometer with the cuffed arm supported at the heart level and heart rate (HR) recordings by a single lead electrocardiogram (ECG). It is important that the arm is extended horizontally when the subject is standing to avoid the influence of the hydrostatic effect of the column in the arm. BP and HR are measured twice with the patient in the supine state, twice 1 min after active standing, and twice 5 min after standing.

In a normal subject, upon standing [9], a transient increase of about 20–30 beats per minute (bpm) is recorded. This is followed by a slow decline, and at the fifth minute, the HR is about 12 beats over the basal level. In young subjects, HR can rise as much as 25 bpm, while in older subjects the increment can be as small as 8 bpm. The ratio of the shortest and the longest R–R interval after standing is considered normal when ≥ 1 (in young subjects ≥ 1.04). Upon standing, the systolic BP usually declines about 5–10 mmHg or remains unchanged [10]. One to two minutes after standing, circulatory adjustments occur and systolic BP returns to basal values in normal subjects. Diastolic BP upon standing rises 5–10 mmHg, and within 2 min falls back (Table 12.1). Orthostatic syncope is diagnosed when there is documentation of orthostatic-triggered hypotension associated with syncope or near syncope. An asymptomatic abnormal fall in systolic blood pressure is less specific, and competing diagnoses should be evaluated before the diagnosis of orthostatic syncope is

Table 12.1 Normal response to the orthostatic test

	Systolic BP	Diastolic BP	HR
Upon standing	Fall of 5–10 mmHg	Rise of 5–10 mmHg	Rise of 20–30 beats; shortest RR/longest RR >1
After 2–5 min	Back to basal values	Back to basal values	About 12 beats > basal values

made [4]. *Initial orthostatic hypotension* is characterized by a blood pressure decrease >40 mmHg immediately on standing, followed by spontaneous and rapid return to normal (the period of hypotension and symptoms is <30 s) (Fig. 7.3). *Classical orthostatic hypotension* is defined as a decrease in systolic BP >20 mmHg (>30 mmHg in hypertensive patients) or a BP <90 mmHg within 3 min of standing [11]. To evaluate the autonomic pathophysiologic mechanisms, the key point to consider is that the increase in HR is dependent on the BP level. A greater than 15 mmHg BP fall, associated with a greater than 25 bpm HR increase, suggests *inadequate effective volume* [10]. A >15 mmHg fall coupled with <10 bpm increase is suggestive of a *baroreceptor or sympathetic nervous system defect* [10]. A >15 mmHg drop in association with any fall in HR implies a parasympathetic involvement such as that seen in *VVS* [12]. In severe cases of *pure autonomic failure*, there may be no increase in HR, despite a conspicuous drop of BP >50 mmHg [13]. These findings suggest a complete loss of efferent sympathetic and parasympathetic control of the heart and vasculature. In patients with *postural orthostatic tachycardia syndrome*, a very large increase of HR, 50 bpm or more, is often recorded, even if the BP drop is small or minimal [14].

It is clear that a simple and easy-to-perform test can be diagnostic or provide a lot of information on the cardiovascular neural regulation of the specific patient. We must keep in mind that due to the marked day-to-day variability of postural response, active standing test may need to be repeated on different days when abnormality is suspected [4].

Carotid Sinus Massage

Carotid sinus massage (CSM) is a test used to elicit the *carotid sinus syndrome* (CSS) in patients with syncope. Due to the possibility that a "positive" CSM can be observed in the absence of real CSS (see below), the test result must be carefully considered in the setting of both the patient's medical history and possible competitive syncope etiologies.

The carotid sinus reflex arc is composed of an afferent limb arising from the mechanoreceptors of the carotid artery and terminating in the midbrain nucleus tractus solitarius, which is connected to the vagus motor nucleus and vasomotor centers. The parasympathetic efferent limb is directed to the sinus node (mainly via the right vagus nerve) and to the atrioventricular node (mainly via the left one), and the sympathetic efferent limb is directed to the heart and the blood vessels [5, 8]. As

for all the reflex arcs, the site of dysfunction resulting in a hypersensitive response to the massage could be at any level, that is, central at the level of brainstem nuclei, or peripheral at the level of carotid baroreceptors, the latter representing the large majority of the cases.

The test is performed applying a gentle but firm pressure using the second, third, and fourth fingers of the preferred hand over the carotid bifurcation at the site of maximum pulsatility at the anterior margin of the sternocleidomastoid muscle at the level of the cricoid cartilage. The pressure is applied for 10 s (or less in case of induction of syncope) usually over the right side first followed, after recovery of baseline conditions, by the left side. The maneuver is repeated with the patient in an upright posture (usually on a tilt table). When asystole is evoked, the contribution of the vasodepressor component can be hidden. In these cases, CSM could be repeated after intravenous administration of atropine (1 mg or 0.02 mg/kg body weight) (see also section "The atropine test"). Indeed, atropine may unveil the presence of a concomitant vasodepressive component, leading to hypotension by abolishing the concomitant vagal-mediated cardioinhibitory component of the reflex.

The test is positive for CSS if syncope is reproduced together with the demonstration of asystole or hypotension. The response to CSM is generally classified as cardioinhibitory (i.e., marked bradycardia and/or asystole ≥3 s), vasodepressive (fall in systolic blood pressure ≥50 mmHg), or mixed. The mixed response is diagnosed by the association of an asystole of ≥3 s and a decline in systolic blood pressure of >50 mmHg from the baseline value on rhythm resumption. CSS is a frequent cause of syncope, especially in elderly men; the prevalence of CSS as a cause of syncope ranges from 4 % in patients <40 years of age to 41 % in patients >80 years old [15]. Conversely, abnormal responses are frequently observed in up to 40 % patients without syncope, especially if they are older and affected by cardiovascular diseases [16]. For this reason, the laboratory diagnosis of CSS requires reproduction of spontaneous symptoms and exclusion of competing mechanisms [4]. If the history is not suggestive of carotid sinus hypersensitivity despite a positive carotid sinus massage, another diagnosis should be considered. Viceversa, if the history is highly suggestive of CSS, this level of evidence may not be essential in everyday clinical practice. In addition, CSS may be misdiagnosed in half of the cases if the massage is not performed in the upright position [15].

An appropriate methodological approach for a precise classification of CSM responses is relevant in terms of appropriate treatment. Quite obviously, cardiac pacing is more likely to be effective for pure cardioinhibitory forms and ineffective for vasodepressor or mixed forms [17].

The main potential complication of CSM is transient ischemic attack (TIA) or stroke; the incidence of such complications is low, ranging between 0.17 and 0.45 % [15]. The risk is increased in the setting of carotid artery disease; therefore, in the presence of a bruit or previous history of cerebrovascular accident or transient ischemic attack within the previous 3 months, CSM is contraindicated. CSM may elicit self-limited atrial fibrillation of little clinical significance. When atropine is used, side effects such as dry eyes, dry mouth, constipation, and possible urinary retention can occur.

Head-Up Tilt Table Test

The head-up tilt table test (TTT) was first described as a diagnostic test for VVS in 1986 [18] and is now used widespread as a research and diagnostic tool. It is indicated soon after the initial evaluation in patients with syncope of uncertain cause leading to major trauma, when either a neurally mediated vasovagal origin or an orthostatic hypotension is suspected [4].

Passive orthostasis from the supine to the vertical position determines a large gravitational shift of blood and an increase of venous pressure in the feet. It is estimated that about 1/2–1 L of thoracic blood moves to the lower limbs in the first 10 s of upright posture, and that venous pressure increases from 5 to 10 mmHg to about 90 mmHg. With a prolonged passive standing position, the high hydrostatic pressure causes a progressive loss of blood volume through transudation of blood from capillaries into the interstitial spaces. It is estimated that this results in about a 15–20 % (700 mL) decrease in plasma volume in 10–30 min in normal subjects [19]. As a consequence, the return of venous blood to the heart is reduced, cardiac filling pressure rapidly diminishes, and ultimately stroke volume falls. In healthy humans, activation of baroreceptor mechanisms reflexly increases HR and peripheral vascular resistances to prevent hypotension within 30 s of upright positioning. The main sensory receptors involved in the necessary orthostatic neural reflex adjustments are the arterial mechanoreceptors (baroreceptors) located in the aortic arch and carotid sinuses. An additional contribution is furnished by the receptors placed in the cardiopulmonary district. Failure of these compensatory adjustments, either due to disease or as a result of inappropriate neural reflexes, is thought to play a crucial role in patients in whom syncope is triggered by upright posture. Identifying this susceptibility to systemic hypotension with upright posture forms the basis for the use of TTT in the evaluation of patients with syncope [15].

A positive tilt test response is observed in >50 % of the patients with suspected VVS. Different protocols can be employed. Usually, protocols include a rest period in supine position (5–20 min) and a passive head-up tilt phase at 60–70° (up to 30–60 min). This drug-free protocol [18], the Westminster protocol, is physiological, has a low false-positive rate (<5 %), and virtually no complications. However, it is time-consuming and has a low positive rate (25 %). A drug challenge with isoproterenol or nitroglycerin can follow [20–22]. The isoproterenol provocation TTT consists in isoproterenol infusion in progressive doses from 1 to 5 μg/min. The drug is administered with the patient in the supine position. When the HR stabilizes, the patient is then tilted at 70° for 10 min. Increasing doses up to 5 μg/min is repeated with 5-min intervals between each step. Owing to the high rate of false-positive responses in subjects without syncope, a low-dose isoproterenol TTT has been proposed [20]: after 15–20 min of baseline tilt at 60–70°, incremental doses of isoproterenol designed to increase average HR by about 20–25 % over baseline (usually ≤3 μg/min) are administered with or without returning the patient to the supine position. This protocol is short and marked by a high positivity rate (60 %), but it is nonphysiologic; false positivity rate is between 10 and 25 % depending on the infused doses; a venous line is needed; and there are drug-related adverse effects,

such as tachyarrhythmias and hypertension. In addition, it is relatively contraindicated in patients with structural heart disease due to the risk of arrhythmias and myocardial ischemia. The Nitroglycerin challenge (the Italian Protocol) [4, 22] consists of a supine rest phase of at least 5 min, followed by a passive 15–20 min tilt, with the angle at 60–70°; if the test is negative, the patient receives a fixed dose of 400 μg nitroglycerin spray sublingually administered in the upright position; then, the tilt is continued for 15 min. Compared to the isoproterenol TTT, this protocol shows similar diagnostic accuracy without adverse effects. However, the false-positivity rate is about 10 % and may induce exaggerated delayed orthostatic hypotension, especially in the older subjects. Finally, the clomipramine test [23] consists in the intravenous infusion of clomipramine, a central serotoninergic agent, given during the first 5 min of tilting at a dose of 5 mg (1 mg/min), after a 20-min rest phase. There is no passive phase. Following the infusion phase, the patient remains in the upright position for the remaining 15 min. There is only limited experience with this approach. However, it seems that clomipramine test could be complementary to nitroglycerin. While nitroglycerin acts mainly through peripheral vasodilatation, clomipramine seems to act through a central serotoninergic mechanism. Therefore, they could be able to differentiate two clinical forms of vasovagal syncope. Those triggered by central mechanism (fear, pain, emotional distress, instrumentation, etc.) should be more sensitive to clomipramine, while those triggered by peripheral mechanisms (e.g., prolong standing or situational events) should be more sensitive to nitroglycerin. While the main advantage is represented by a high positivity rate (70 %), especially for those forms with central triggers, the protocol has to be confirmed by other studies as it is limited to a single center experience. False-positivity rate is similar to that of the Italian protocol (10 %). A venous cannulation is needed, and only mild adverse gastrointestinal effects have been reported for clomipramine. An alternate method is to tilt the subject at 15° intervals. First, the tilt is stopped at 15° for 3 min, then the tilt is increased to 30°, 45°, 60°, and finally to 75°, with intervals of 3 min between each step. Then, the subject will be maintained at 75° until 30 min of tilt are completed [24]. This protocol is used when microneurography is recorded (see Chap. 9). Briefly, the recording of sympathetic nerve activity, through an electrode placed in a peripheral nerve, usually the peroneal nerve, allows to evaluate the skin and muscle sympathetic nerve activity (MSNA). While the continuous recording of BP, HR, and MSNA is extensively used for research purposes and has contributed to clarify the sequence of events in response to the orthostatic challenge [25], its use in routine clinical evaluation should be limited to selected cases, such as patients with postural tachycardia syndrome, pure autonomic failure, or multiple system atrophy [11, 13].

The room where the test is performed should be quiet and dimly lit. The patients should avoid food, in particular caffeine, for at least 2 h before the test. When venous cannulation is used (for drug injection), the patients should be in a supine position 20 min before tilting to decrease the likelihood of a vasovagal reaction in response to venous puncture. A tilt table with footboard support is appropriate. The tilt table should be electrically driven to achieve the upright position smoothly and rapidly or through graded steps and should reset to the supine position quickly

(<10 s) in case of syncope. An experienced nurse or medical technician should be in attendance during the entire procedure, while the need for a physician to be present throughout the tilt test procedure is less well-established, because the risk to patients of such testing is very low. However, not only a physician should be immediately available in case of problems, but his/her role includes observation of the patient throughout the test, evaluation of possible subtle prodromes, and decision of applying further provocative tests. Monitoring should include continuous surface ECG and continuous beat-to-beat noninvasive arterial blood pressure. Additional useful features are the continuous display of calculated hemodynamic parameters (cardiac output, stroke volume, peripheral resistances, and related parameters). Though not necessary for the diagnosis of syncope, hemodynamic measurements can help in the understanding of the underlying pathophysiological mechanism. Likewise, the use of spectral analysis of HR and BP variability can allow the recognition of different pathophysiological mechanisms in fainters that may have important therapeutic implications. Two different patterns have been recognized in the cardiac autonomic changes preceding an occasional vasovagal event, namely, one characterized by a progressive increase of the marker of cardiac sympathetic modulation up to the onset of syncope, and the other by a sympathetic inhibition with an impending vagal predominance [26].

In healthy subjects, overall mean arterial pressure on tilting is maintained, though the systolic pressure frequently increases at first, then decreases to control levels or slightly below, while diastolic pressure persistently rises, determining a pulse pressure narrowing. HR increases from the beginning of the tilt, without the diphasic response observed with standing.

TTT is considered positive when syncope (or presyncope) occurs either due to a reflex hypotension/bradycardia or delayed orthostatic hypotension. However, how and why BP should suddenly or gradually decrease in response to prolonged standing, rather than the sight of blood, remains largely unexplained [6, 8, 24, 27]. For diagnostic purposes, two different abnormal responses can be recorded during the orthostatic challenge. The first is a vasovagal reaction mediated by a reflex susceptibility leading to hypotension. The second is progressive hypotension due to failure of the compensatory autonomic reflexes to provide appropriate vasoconstriction with standing, that is, orthostatic hypotension. These two different pathophysiological mechanisms can lead to indistinguishable clinical manifestations. Both presentations have a common trigger, namely, blood pooling in the lower extremities and splanchnic bed, and decrease in venous return due to orthostatic stress and immobilization. They also have a common final effect, that is, hypotension, related to impaired vasoconstrictor capability. The absence of a reflex bradycardia (vagal overactivity) differentiates delayed orthostatic hypotension from reflex syncope, but even this difference may be subtle and not so evident.

A positive TTT can be classified into three main patterns according to the various BP and HR changes: the vasovagal, the delayed (progressive) orthostatic hypotension, and the combined delayed orthostatic hypotension and vasovagal patterns. The *vasovagal pattern* is characterized by an initial phase of compensatory reflex adaptation to tilt characterized by a stable BP with increased HR. This phase can last

several minutes. It suggests normal baroreflex function, and it is usually asymptomatic or only symptomatic for palpitation due to the increased HR. An abrupt fall in arterial pressure, sometimes accompanied by a fall of HR, indicates the onset of the syncopal vasovagal reaction. It is thought that a progressive increase in cholinergic mechanisms can contribute to some of the symptoms (sweating, salivation, nausea) that the patient experience for less than 3 min (on average, 1 min), before the sudden appearance of bradycardia and hypotension [28]. A decrease in systolic BP to <90 mmHg is associated with symptoms of impending syncope, and that to <60 mmHg is associated with syncope. Prodromal symptoms are present in virtually all cases of tilt-induced vasovagal syncope, but they may be subtle in the elderly, or there might be a retrograde amnesia. In this latter case, TTT can be used to train the patient to recognize prodromal symptoms and to counteract and avoid the syncope. BP fall frequently precedes the decrease in HR, which can be absent at least at the beginning of this phase. According to the predominance of vasodepressor or cardioinhibitory components, the responses are classified as cardioinhibitory or mixed. The patients with these patterns are largely young and healthy with a history of recurrent episodes since the teenage years (see Chap. 11). Conversely, when a patient shows inability to obtain a steady-state adaptation to the upright position, leading to an early slow progressive decrease of BP until symptoms occur, the pattern of *delayed (progressive) orthostatic hypotension* is found. The absence of bradycardia differentiates this form from the classical vasovagal response. These patients are usually asymptomatic for several minutes after standing, and later on, they develop hypotensive symptoms, such as dizziness, weakness, lightheadedness, fatigue, and palpitations. Less frequently, patients describe visual or hearing disturbances, chest discomfort, and pain in the neck ("coat-hanger distribution"). The typical vasovagal reaction is rare. These patients are predominantly in older age groups, and many have associated diseases, suggesting the presence of some underlying autonomic dysfunctions (see Chap. 1). The pattern of *combined delayed orthostatic hypotension and vasovagal reaction* is initially characterized by impaired adjustment to tilt, leading to progressive hypotension without bradycardia. Later, a clear vasovagal reaction develops with the typical fall in HR of variable magnitude, indicating a cardioinhibitory or a mixed response. Syncope generally occurs at the time of maximum bradycardia. The patients affected are predominantly older, and many have associated diseases. A history of typical vasovagal or situational syncope and associated carotid sinus hypersensitivity are not infrequent.

It should be emphasized that in patients without structural heart disease, the TTT can be considered diagnostic, and no further tests are needed when syncope is reproduced. In patients with structural heart disease, a positive TTT cannot be conclusive, and it is recommended to rule out arrhythmias or other cardiac causes of syncope [29]. On the other hand, a negative TTT does not exclude the diagnosis of VVS [2, 21, 30], while induction of syncope in the absence of hypotension and/or bradycardia should be considered diagnostic of psychogenic pseudosyncope [31].

As the VVS is variable in its occurrence, that is, patients with history of recurrent VVS have also syncope-free period, it is not surprising that the reproducibility of TTT is variable. The overall reproducibility of an initial negative response

(85–94 %) is higher than the reproducibility of an initial positive response (31–92 %). In addition, data from controlled trials showed that approximately 50 % of patients with a baseline positive tilt test became negative when the test was repeated with treatment or with placebo [21]. Despite its apparent limitations, TTT remains the diagnostic tool to differentiate reflex syncope from orthostatic hypotension, which is essential for specific therapy. TTT is also widely accepted as a useful tool to allow the patient the recognition of onset of an episode. This is particularly important to manage self-treatment, for example, physical counterpressure maneuvers [32]. Recently, the use of tilting training has been proposed as a feasible treatment in patients with recurrent VVS triggered by orthostatic stress. The prescription of progressively prolonged periods of enforced upright posture might reduce syncope recurrence over the long term. Unfortunately, the compliance and motivation of the patient are determinant, and some trials failed to confirm short-term effectiveness of tilt training [33]. For this reason, tilt training is ranked class IIB indication for therapy of reflex syncope. However, in selected, highly motivated patients, this should be considered a therapeutic option.

Drug-free TTT is safe; no deaths have ever been reported. Some very prolonged asystoles have been recorded up to 20–30 s, but normal rhythm resumed promptly with the supine position. Some life-threatening ventricular arrhythmias have been described with isoproterenol protocols and in the presence of ischemic heart disease or sick sinus syndrome. Therefore, administration of isoproterenol is avoided in patients with ischemic heart disease, uncontrolled hypertension, left ventricular outflow tract obstruction, significant aortic stenosis, and known complex ventricular arrhythmias. No complications have been published with the use of nitroglycerin, but minor effects such as headache. Atrial fibrillation can be induced during or after a positive tilt test, but it is usually self-limited [34].

Valsalva Maneuver

The Valsalva Maneuver (VM) tests several of the components of the baroreflex arc and is useful to evaluate reflex mechanisms involved in circulatory control [8]. The sudden increase in systemic blood pressure activates the baroreceptors in the aortic arc and carotid sinus, which in turn relay information through the IX and X cranial nerves to the nucleus of the solitary tract where the first synapse of the baroreflex is located. Information from this nucleus to other brainstem and higher centers modulate sympathetic and parasympathetic activity to blood vessels, heart, and adrenal medulla [35].

This maneuver is performed during continuous monitoring of ECG and arterial BP, using a noninvasive BP device, and measuring the pressure by which the subject exhales. A mercury manometer adapted with a suitable mouthpiece can be used to achieve this measurement. After basal BP and HR determinations, the subject is instructed to exhale forcibly into the manometer to create a pressure of 40 mmHg for 20 s. BP and HR are further recorded for additional 1–2 min after the release of the exhalation. In Fig. 12.1, the four phases that describe and relate the mechanical

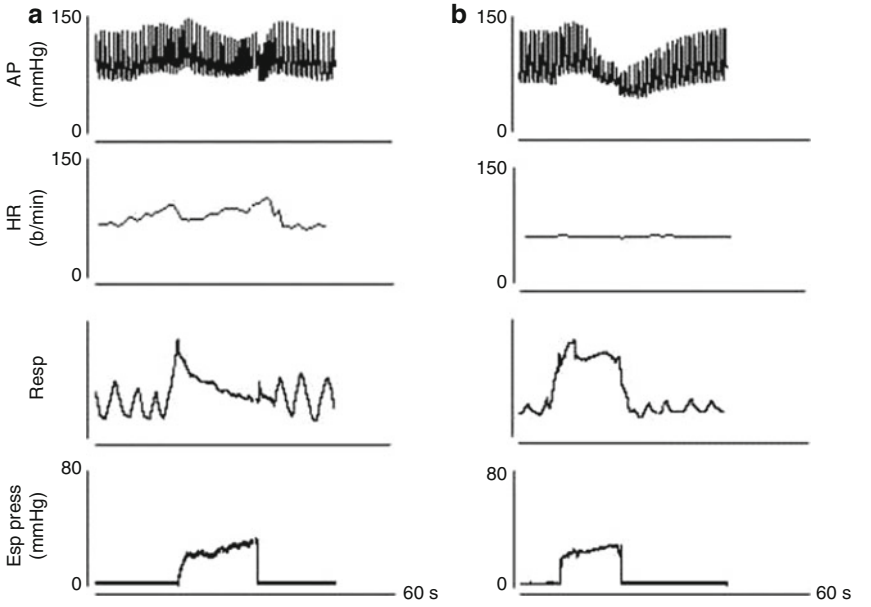

Fig. 12.1 Valsalva maneuver in a healthy subject (*left panel*, **a**) and in a patient affected by dysautonomia (*right panel*, **b**). In (**a**), we observe a transient increase in blood pressure (BP) during phase I, followed by a decrease in BP accompanied by a reflex tachycardia during phase II and phase III; during phase IV, a marked BP overshoot occurs, which in turn triggers a reflex bradycardia. In (**b**), the reflex tachycardia is clearly absent throughout, despite the abnormal BP drop; the rise of BP during phase IV is also blunted. *AP* arterial pressure, *HR* heart rate, *Resp* respiratory activity, *Esp Press* expiration pressure

and cardiovascular changes [10] induced by VM are shown. During phase I, the sudden increase in intrathoracic pressure produced by strained expiration is transmitted to the aorta, causing a transient increase in stroke volume and BP. In phase II, during the maintenance of strained expiration, venous return is reduced and cardiac output falls. This produces a decrease in BP, which in turn causes reflex tachycardia, usually 20–25 bpm above baseline. With the release of raised intrathoracic pressure, BP abruptly falls during phase III. About 5 s later, during phase IV, a marked BP rise, at least 10 mmHg above basal values, occurs. This BP overshoot is the result of an increase in cardiac output that accompanies the rise in venous return to the heart and the residual increase in peripheral vascular resistance due to the reflex increase in sympathoadrenal activity. The increase in stroke volume and BP will in turn trigger a reflex bradycardia.

In patients with sympathetic nervous system dysfunction, the tachycardia of phase II is blunted or absent [10] as well as the rise of BP during phase IV. On the other hand, absent or blunted bradycardia in phase IV suggests selective parasympathetic dysfunction. The Valsalva ratio is an easy and standardized method that is frequently used to evaluate and quantify the response to the VM. The ratio considers the longest R–R interval shortly after the VM to the shortest R–R interval during the

maneuver. Ratios ≥1.4 are considered normal; some authors have considered 1.2 as the lower limit in normal; ratios below 1.1 are clearly abnormal [36].

The VM is altered by many drugs and many disease states, such as congestive heart failure and respiratory diseases; therefore, interpretations of the result may be difficult. Some patients can have difficulties in maintaining expiration, and adequate training should be attempted before making final determinations. Therefore, VM is suggested in selected patients with suspected autonomic failure. Care should be paid to standardization of the maneuver and training of the patient.

Other Tests

Different types of tests are known to increase the sympathetic activity in normal subjects, including mental stress, the application of ice to the neck or hands (cold pressor test), fatiguing muscle exercise (handgrip test), and the administration of adrenergic agonists (phenylephrine test and clonidine test) [10, 13]. These tests are not routinely performed in patients with suspected VVS. Indeed, a combination of these tests is indicated in patients with syncope and suspected dysautonomia to better characterize the ANS defects. As considerable interindividual variation occurs, the interpretation of the results may require some degree of specific expertise. It is usually recommended that these autonomic tests are performed in the setting of a clinical unit or laboratory dedicated to ANS disorders (see Sect. 12.5). These tests can be useful to investigate ANS involvement, for example, a normal cold pressor test indicates a functioning reflex arc with intact sensory nerves, central relays, descending sympathetic pathways, and peripheral sympathetic nerves as well as vascular receptors, while a negative test is consistent with a lesion in one or more of these components, though not diagnostic for a lesion site. Conversely, mental test is more selective. This test stimulates efferent sympathetics without depending upon the afferent inputs. In conjunction with other autonomic tests, it could provide information on the lesion site. For instance, an abnormal Valsalva Manuever, together with a negative mental arithmetic test, suggests a lesion in the brain areas that regulate cardiovascular function, or in the efferent sympathetic nerves, or a defect in vascular responsiveness.

12.3 Predominant Evaluation of Heart Rate

Sinus Arrhythmia

HR has a cyclic variation coupled to respiratory function: during inspiration HR increases, whereas during expiration HR decreases. This arrhythmia, when measured during the R–R interval, is called R–R variation or sinus arrhythmia (SA) [37].

The most routinely used method to analyze SA requires calculation of the expiration–inspiration ratio of the longest to the shortest R–R interval, recorded during deep breathing at a rate of 6 bpm [9]. Continuous ECG and breathing recording is

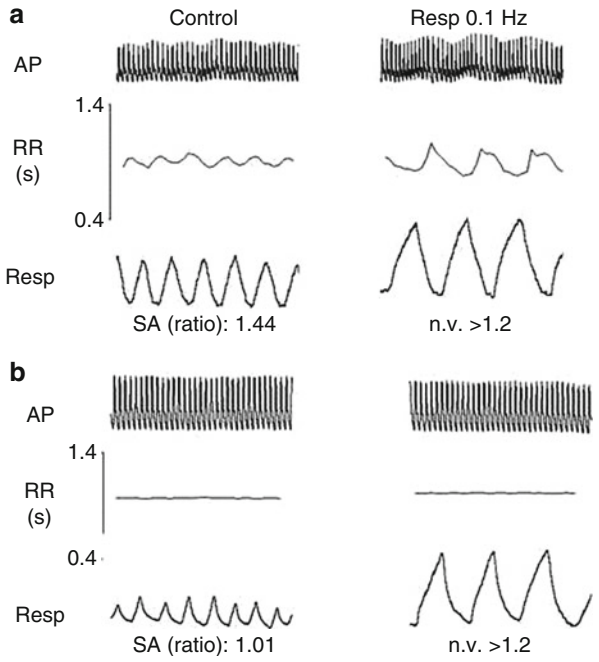

Fig. 12.2 Sinus arrhythmia in a normal subject (*top panel*, **a**) and in a patient affected by dysautonomia (*lower panel*, **b**). In (**a**), the R–R interval variation is clearly coupled to respiratory function. During inspiration, the heart rate increases, whereas it decreases during expiration. SA ratio (the longest to the shortest R–R interval recorded during deep breathing at a rate of 6 bpm) is 1.44. In (**b**), note that the R–R interval variation is blunted and SA ratio is 1.01. Ratios below 1.2 are considered suggestive of dysfunction of the vagus nerve, the thoracic afferent fibers, or the vasomotor center. *AP* arterial pressure, *RR* R–R interval, *Resp* respiratory activity, *SA* sinus arrhythmia, *n.v.* normal values

necessary. Ratios below 1.2 are considered abnormal up to age 40 (the ratio decreases with age) and suggestive of dysfunction of the vagus nerve, the thoracic afferent fibers, or the vasomotor center [10] (Fig. 12.2).

This test should be done in the supine position in the absence of factors affecting HR. The subject should be instructed, and several trials should be tried before final determinations.

The Atropine Test

The use of a cholinergic blocking agent allows to assess the prevailing level of parasympathetic control of HR (see also section "Carotid sinus massage").

During continuous ECG recording, an intravenous infusion of 5 % dextrose, 0.02 mg/kg of atropine sulfate is given over 5 min. Complete parasympathetic blockade is achieved within 5 min, and HR is observed during the following 15 min.

In normal subjects, the HR will increase more than 30 bpm as the result of blocking vagal effects on the sinoatrial node pacemaker. Failure of the HR to increase suggests reduced parasympathetic function. A transient atrioventricular dissociation (usually asymptomatic) can occur during the first minute of administration. The response is more noticeable in young adults, in whom vagal tone is high.

Implantable Loop Recorder

Prolonged ECG monitoring is among the most valuable tools for recognizing the cause of syncope (see Chap. 20). The use of an implantable loop recorder (ILR) can determine the mechanism of syncope directly by the demonstration of an arrhythmia, but can also infer alternative diagnosis documenting no variations of HR at the time of syncope recurrence.

In addition, a strategy based on ILR with the therapy delayed until the documentation of syncope allows a safe, specific, and effective therapy for patients with recurrent suspected VVS [38].

Other Tests

The β-adrenergic agonist isoproterenol is used to test the functional state of the β-adrenergic receptor, while the β-adrenergic blocking agent propranolol is used to determine the prevailing level of β_1 and β_2 receptor activation.

They are both infused intravenously during continuous ECG monitoring. Isoproterenol is administered as a bolus dose of 0.1 μg, followed by a stepwise increase if no response occurs (0.25, 0.5, 1, 2, 4 μg, etc.), until HR increases by 30–35 bpm. Propranolol is infused at 1.1 mg/min for 10 min. At the end of this period, HR is evaluated.

Patients with pure autonomic failure and other conditions associated with reduced catecholamines may show hypersensitivity to isoproterenol. In patients with high level of sympathetic activation, the fall in HR can be exaggerated, while in dysautonomic patients with inadequate baseline sympathetic tone, no HR fall is recorded.

12.4 Predominant Evaluation of Blood Pressure

A number of tests can be performed to directly or indirectly measure the pressor response. They are usually indicated and useful in selected cases, for instance, when a syncope induced by a pheochromocytoma is suspected or to detect the residual function in patients with autonomic failure and history of fainting.

The saline infusion test evaluates the function of buffering cardiovascular reflexes that, under normal conditions, reduce the consequences of an acute volume overload. A 3 L saline solution is infused over 1 h. BP, HR, and urine output (a Foley

catheter must be placed) are monitored. Normally, no more than 10 mmHg increase in BP is recorded together with the extraction of about 6 mL of urine per minute. Extreme caution is needed in elderly patients and in those with reduced cardiac function to avoid acute congestive heart failure.

The cuff occlusion test provides a means of assessing the capability of the cardiovascular system to withstand an acute intravascular volume loss. BP cuffs are placed around the thighs and inflated to a level of 10 mmHg below diastolic BP to occlude venous return (this maneuver maintained for 10 min determines >1 L of blood pooling in the legs [10]). The normal response is no change or slight change (<10 mmHg) in BP. Reduction of BP more than this amount suggests a sympathetic nervous system lesion.

The naturally occurring amine, Tyramine, the α_2-adrenoreceptor antagonist, Yohimbine, and the α-adrenergic blocker, Phentolamine can also be used to test the BP response.

12.5 Plasma Catecholamine Determination

The measurement of plasma catecholamines, epinephrine (Epi) and norepinephrine (NE) (see Chap. 5 for details), represents a useful and widely used method to evaluate sympathetic neural function, though direct recording of sympathetic nerve traffic and NE spillover would represent the desirable approach, due to the precise estimation of the behavior of regional sympathetic neural function [6, 39].

Plasma catecholamines can be determined in basal conditions and during OT or TTT. An intravenous line should be placed 1 h before basal determination. In normal subjects, plasma levels of noradrenaline are increased about twofold with standing [40]. In case of TTT, at the end of the tilting period, a venous sample for catecholamines should be obtained if the test is tolerated. Alternately, blood could be drawn a few moments after the subject develops presyncopal symptoms. During active standing or head-up tilt, plasma NE increases by 80–100 % from basal levels.

To what extent that circulating catecholamines play a role in triggering vasovagal events remains to be established [6] and seems to be different in young and older people [41]. Plasma catecholamine assessment is indicated when an alteration of the autonomic nervous system is suspected. Furthermore, the interpretation of the determinations is strictly related to the proper consideration of associated hemodynamic factors [6].

Conclusions

The European Society of Cardiology Guidelines [4] ensure a methodical and rational approach to patients with syncope and aid in choosing the right patient for the right test. The initial evaluation is basic for the following diagnostic decision-making. Given the complexity of the neural pathways possibly involved in the genesis of the VVS, it is clear that each patient deserves an individually tailored diagnostic procedure. In addition, recently [3], the importance of the neuroautonomic evaluation has been highlighted both in young adults and in

Table 12.2 Example of a protocol in the setting of a clinical laboratory for the evaluation of patients with suspected vasovagal syncope

Instrumentation of the patient	ECG
	Noninvasive BP
	Respiratory activity (±Intravenous line placed 1 h before the test)
Baseline	Recording for 10–15 min at rest
Autonomic tests	Sinus arrhythmia test
	Valsalva maneuver
	Catecholamine determination
Head-up tilt test	Tilt at 60–75° for 20–30 min ± sl tnt
	Catecholamine determination
	Carotid sinus massage

older patients with syncope of uncertain origin. The coexistence of different neurally mediated mechanisms in the genesis of syncope, in particular, in older people, pushes toward a complete autonomic and cardiovascular evaluation in every patient without stopping at the first apparent diagnosis. Tilt test remains a common, noninvasive test modality with great value when undertaken in the correct clinical context. Finally, aging, comorbidities, and polypharmacy are additional variables that can worsen ANS impairment and can be part of the etiopathogenesis of syncope.

A dedicated unit held by a multidisciplinary and multispecialist staff (Syncope Unit) can represent a successful approach for diagnosing and treating patients with syncope. Table 12.2 summarizes an example of a protocol that usually is performed in a Syncope Unit to evaluate a patient with suspected VVS.

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Part IV

Differential Diagnosis

Differential Diagnosis of Vasovagal Syncope

13

Paolo Alboni, Raffaello Furlan, and Pietro Cortelli

Key Points

- Because the clinical presentation of vasovagal syncope (VVS) is extremely variable, the differential diagnosis with other forms of transient loss of consciousness may be difficult.
- The diagnosis of typical VVS is usually easy, but when the presence of a trigger (emotional or orthostatic) is uncertain, the diagnosis becomes uncertain.
- A positive response to tilt testing in patients with severe heart disease and nondiagnostic cardiologic examinations does not allow a diagnosis of VVS because of a potential competing diagnosis with prognostic implications such as ventricular tachyarrhythmia.
- The presence of autonomic symptoms tends to exclude syncope attributable to neurogenic orthostatic hypotension. Tilt testing can differentiate delayed orthostatic hypotension from VVS.

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- Tilt testing and carotid sinus massage with the "method of symptoms" seem to be helpful for the differential diagnosis between unexplained fall and VVS.
- Tilt testing is useful for the differential diagnosis between functional (psychogenic) pseudosyncope and VVS.

The clinical presentation of vasovagal syncope (VVS) may widely vary (see Chap. 11): typical VVS, atypical VVS, unexplained fall, and "sleep syncope." Therefore, the differential diagnosis may sometimes be difficult.

13.1 Differential Diagnosis of Typical Vasovagal Syncope

Typical VVS is a transient loss of consciousness (TLoC) characterized by (1) precipitating triggers such as emotional distress (extreme emotions, fear, severe pain, disgust, blood phobia, medical setting) or orthostatic stress (prolonged standing, particularly in hot and/or crowded places); and (2) symptoms caused by activation of the autonomic system, such as nausea, vomiting, abdominal discomfort, pallor, and sweating. Besides autonomic symptoms, prodromes resulting from cerebral hypoperfusion, such as dizziness, lightheadedness, awareness of fainting, and blurred vision, are commonly reported. There is a consensus that when a TLoC is precipitated by an emotional or orthostatic trigger and is associated with autonomic symptoms, the diagnosis of VVS can be made after the initial evaluation without further investigation [1]. When the emotion is very strong or the upright position is very prolonged (e.g., standing in a long queue), the diagnosis of VVS is generally easy. However, there is a gray area characterized by uncertain triggers. Tolerance to prolonged standing is different among subjects; it mainly depends on the habits of the individual. Therefore, standing can be defined as prolonged by the patient and not by the physician; in this context, an accurate medical history should be undertaken. Sometimes TLoC is preceded by a mild pain, the role of which as a trigger is uncertain. Some potentially emotional circumstances such as religious services, weddings, funerals (not involving close persons), visits to the cemetery, and rock concerts have been reported as syncope triggers [2–5]. In such cases the physician should investigate whether the individual was or was not emotionally involved; in other words, whether a trigger played an effective role. Many patients asking assistance for syncope have mentioned external circumstances which, in their opinion, were important in triggering the syncopal attack, such as hot weather, crowded place, overtiredness, lack of food, menstruation, or saunas [4, 6]. These circumstances, in the opinion of some clinicians, strongly suggest a VVS. Even internal factors such as hypotension, hyperventilation, and straining could be responsible for syncope. However, it is still debated whether these circumstances can be considered

as triggers of VVS or as only predisposing factors. This issue is important because the use of restricted criteria might cause VVS to be underdiagnosed, whereas widened criteria with the inclusion of many other stressors and circumstances that affect blood pressure would increase the sensitivity but decrease the specificity, i.e., the number of patients incorrectly labeled with VVS [7]. Unfortunately, the prevalence of these circumstances has never been compared in patients with VVS and cardiac syncope or other types of TLoC and their diagnostic role remains unsolved.

If the role of a trigger remains uncertain, tilt testing may be indicated, and the diagnosis of VVS can be made only if this test is positive in the absence of a competing diagnosis.

Some subjects report both typical and atypical episodes of VVS; in such cases, the presence of typical vasovagal attacks in the individual's history allows atypical attacks to be accepted as vasovagal.

13.2 Differential Diagnosis of Atypical Vasovagal Syncope

An atypical VVS can be diagnosed if syncope occurs without any identifiable trigger and/or has an otherwise unusual presentation. The clinical features that suggest atypical VVS during the initial evaluation are discussed in Chap. 10, and the clinical presentation in Chap. 11. The diagnosis is based on the reproduction of syncope by means of tilt-table testing and the exclusion of other causes of syncope (e.g., absence of structural heart disease). However, because the tilt test, like the other tests utilized in the diagnosis of syncope, cannot be considered a gold standard and its positivity rate is only 50 %, there is a continuum between atypical VVS and reflex (neurally mediated) syncope. The absence of a clear history and the possibility of multiple etiologies make the diagnosis difficult to establish in some patients. Depending on the clinical features, the differential diagnosis of atypical VVS should be made with other reflex syncopes such as situational syncope and carotid sinus syncope, with orthostatic syncope and cardiac syncope, and with unexplained falls and nonsyncopal TLoCs.

Differential Diagnosis with Situational Syncope

Situational syncope is diagnosed when syncope occurs during or immediately after specific triggers, such as micturition, defecation, swallowing, coughing, and, less frequently, after sneezing, laughing, or playing a brass instrument. Autonomic symptoms are present in about 50 % of patients [3]. There is consensus that when a TLoC clearly occurs during these circumstances, situational syncope can be diagnosed after the initial evaluation without further investigation [1]. Therefore, the differential diagnosis between VVS and situational syncope is generally easy. If the role of a peripheral trigger is uncertain, the patient should undergo further examinations according to the features offered by the initial evaluation. In some individuals, episodes of both VVS and situational syncope are present.

Recently two new forms of situational syncope have been described, the belching syncope and the ejaculation syncope. Kim et al. [8] described a case of situational syncope induced by belching. The patient showed syncopal episodes with high-degree atrioventricular block just after belching. Syncope disappeared after pacemaker implantation. Mozid et al. [9] described a patient reporting several syncopal episodes occurring during sexual intercourse at the point of ejaculation, preceded by prodromal symptoms lasting approximately 10 s. The patient had been diagnosed with prostate adenocarcinoma. Electrocardiographic (ECG) monitoring during sexual intercourse showed a period of sinus tachycardia followed by sinus pauses up to 7 s, which coincided with TLoC. However, it is uncertain whether the trigger was emotional or peripheral, in other words, whether these TLoCs could be diagnosed as typical VVS or situational syncope.

Differential Diagnosis with Carotid Sinus Syncope

Carotid sinus syncope is prevalent in aged males (generally >70 years), being hardly ever seen in the age group younger than 40 years. It is commonly reported that onset of carotid sinus syncope is usually sudden. However, in a study in which the clinical presentation of carotid sinus syncope and atypical VVS was compared, these two types of syncope showed similar clinical features. Indeed, the prevalence of prodromal symptoms, autonomic prodromes, and symptoms during the recovery phase were 62 % versus 76 %, 59 % versus 72 %, and 67 % versus 70 %, respectively (differences not statistically significant) [3]. For this reason, the differential diagnosis between atypical VVS and carotid sinus syncope cannot be made during the initial evaluation. Carotid sinus syncope can be diagnosed only when the carotid sinus massage (CSM) performed with the "method of symptoms" [10, 11] is positive. The technique of performing CSM has greatly evolved over the years. Compared with the technique used before the 1980s, modern CSM involves performing massage in both supine and standing position, usually with the aid of a tilt table, under continuous noninvasive blood pressure monitoring. In addition to yielding a higher positivity rate than the simple supine massage, upright massage has the advantage of enabling a better evaluation of the magnitude of the vasodepressor component, which is amplified by the standing position [10, 12]. Reproduction of syncope is required to diagnose carotid sinus syncope by means of the "method of symptoms." This is the main difference from the traditional method, according to which the induction of asystole >3 s and/or fall in blood pressure >50 mmHg, defined as carotid sinus hypersensitivity (CSH), was considered sufficient for diagnosis. CSH can be observed in 30–40 % of older people without a history of syncope/presyncope and, therefore, cannot be considered diagnostic because of its low specificity [1, 13–15]. CSM performed according to the "method of symptoms" displays high specificity, being positive in only 4 % of subjects without a history of syncope [10]. In its rare "spontaneous" form, carotid sinus syncope is triggered by turning of the head, wearing tight collars, or other accidental mechanical manipulation of the carotid sinuses. However, even in these cases, because of the low

specificity of these triggers, the diagnosis of carotid sinus syncope must be confirmed by a positive response during CSM.

The differential diagnosis between atypical VVS and carotid sinus syncope is based on the varying response to tilt testing and the presence of symptoms during CSM. However, 10–15 % of subjects with syncope of unknown origin after the initial evaluation experienced syncope during both tilt testing and CSM [3, 16, 17]. This form of syncope was defined as "complex neurally mediated syncope" [3]. At the initial evaluation, patients with complex neurally mediated syncope showed clinical features very similar to those of patients with carotid sinus syncope [3]

Differential Diagnosis with Syncope Due to Orthostatic Hypotension

Orthostatic hypotension (OH) results from inadequate sympathetic vasoconstriction during upright standing, which may be responsible for syncope or presyncope. Autonomic failure can be primary, neurogenic, or induced by drugs such as antihypertensives, diuretics, and antidepressant agents (secondary OH).

Orthostatic syncope should be suspected during the initial evaluation (see Chap. 10) when TLoC occurs after standing up, on prolonged standing, or while standing after exercise; in the presence of neuropathy, Parkinsonism or pure autonomic failure (PAF), volume depletion, prolonged recumbency, and physical or gravitational deconditioning; and when there is a significant temporal relationship between the onset of symptoms and the beginning of antihypertensive therapy. A TLoC appearing just after exercise suggests both reflex and orthostatic syncope; in young subjects an atypical VVS/ reflex syncope is more likely to be present, whereas an orthostatic syncope is more likely in the elderly [18].

In patients with neurogenic orthostatic syncope, prodromal symptoms resulting from cerebral hypoperfusion (dizziness, blurred vision, lightheadedness) are present, whereas the autonomic prodromes seen in many reflex syncopes are absent because of systemic autonomic failure. Therefore, the presence of autonomic symptoms tends to exclude a neurogenic orthostatic syncope. A pain in the neck or shoulders at the onset of the attack ("coat-hanger pain"), likely to be caused by chronic ischemia of the muscles in the upper part of the body, strongly suggests orthostatic syncope, and has been rarely reported to be present in reflex syncope [19].

Syncope caused by OH can be diagnosed during the initial evaluation by means of orthostatic testing. In brief, blood pressure is measured in the supine position, after which it is assessed every minute during 3 min of standing. OH is defined as a decrease in systolic blood pressure of at least 20 mmHg and/or diastolic blood pressure $\geq$ 10 mmHg. In patients with supine hypertension, a reduction in systolic blood pressure $\geq$ 30 mmHg may be a more appropriate criterion for OH because the magnitude of the drop in orthostatic blood pressure depends on the baseline blood pressure [20]. Rarely during orthostatic testing a syncope or presyncope is recorded, and in this case orthostatic syncope can be diagnosed without further examination [1].

Of note, patients may present with delayed OH, and in subjects with syncope of unknown origin, delayed OH should be investigated. Delayed OH is characterized by a slow progressive decrease in systolic blood pressure on assuming the upright position. This disorder may be revealed by extending the period of recording blood pressure during orthostatic stress or tilt testing beyond 3 min [20]. The differential diagnosis between orthostatic syncope and VVS is generally easy when using tilt testing. Orthostatic syncope is characterized by progressive decrease in systolic and diastolic blood pressure without the expected increase in heart rate (autonomic failure pattern), whereas in subjects with VVS there is a full compensatory adaptation to the upright position until the onset of the vasovagal reflex (sudden drop in blood pressure with or without bradycardia). However, in some patients delayed OH and VVS may be related. In this case, the tilt test response is characterized by a progressive decrease in blood pressure, followed by the sudden onset of the vasovagal reflex [21].

Differential Diagnosis with Cardiac Syncope

Features enabling a definite diagnosis of cardiac syncope and those which only suggest a cardiac cause of syncope are discussed in Chap. 10. In brief, a cardiac cause of syncope is suggested by presence of heart disease, TLoC during exertion or supine position, chest pain before TLoC, severe pulmonary hypertension, family history of unexplained sudden death and channelopathy, and abnormal ECG [1]. The absence of signs or symptoms of heart disease and a history of arrhythmias during the initial evaluation make a cardiac cause of syncope very unlikely. In this regard, in an Italian multicenter study the absence of heart disease allowed exclusion of a cardiac cause of syncope in 97 % of patients [2]. The presence of heart disease is generally accepted as the best predictor of cardiac syncope. Nevertheless, in the same study [2], 46 % of patients with syncope and mild heart disease (mainly hypertensive heart disease) had atypical VVS/reflex syncope; this limits the utility of this clinical finding in the differential diagnosis. The presence of severe heart disease (dilated cardiomyopathy and previous myocardial infarction) appears to be a better predictor of cardiac syncope [22]. Occurrence of prodromal symptoms caused by autonomic activation is lower in cardiac syncope than in VVS. However, in older patients the autonomic prodromes of VVS are more likely to be short or even absent. Therefore, the clinical features of cardiac syncope and VVS are very similar [23, 24]. When a cardiac syncope is likely after the initial evaluation based on the presence of the previously reported clinical–ECG features, a cardiac diagnostic workup is recommended. This investigation includes echocardiography and one or more of the following examinations: prolonged ECG monitoring, stress testing, and electrophysiologic study. Specific situations are as follows:

- In patients with severe palpitations associated with syncope, ECG monitoring is recommended as a first evaluation step. If this examination does not show evidence of arrhythmia as a cause of syncope, electrophysiologic study can be considered, particularly in patients with ischemic heart disease.

- In patients with chest pain suggestive of ischemia before or after TLoC, cardiac biomarker assessment, stress testing, and eventual coronary angiography are recommended.
- In patients with syncope during or immediately after physical effort, stress testing is recommended as a first evaluation step.

If these examinations are diagnostic, as reported in Table 13.1, cardiac syncope is diagnosed. If cardiac evaluation does not show any cause of syncope, re-evaluation for a neurally mediated syncope is recommended, particularly in patients with recurrent or traumatic fainting. The latter evaluation includes CSM with the "method of symptoms" in patients >40 years and tilt testing. When tilt testing is positive, VVS is diagnosed. However, a positive tilt testing in patients with severe heart disease does not allow one to conclude the workup with the diagnosis of VVS, because a potential competing diagnosis with prognostic implications as ventricular

Table 13.1 Diagnostic criteria of cardiologic examinations, according to the European guidelines for the diagnosis and management of syncope [1]

Diagnostic criteria	*Class*	*Level of evidence*
Echocardiography alone is diagnostic of the cause of syncope in severe aortic stenosis, obstructive cardiac tumors or thrombi, pericardial tamponade, and congenital anomalies of coronary arteries	I	B
Exercise testing is diagnostic when syncope is reproduced during or immediately after exercise in the presence of ECG abnormalities or severe hypotension	I	C
Exercise testing is diagnostic if Mobitz II second degree or third degree AV block develops during exercise even without syncope	I	C
ECG monitoring is diagnostic when a correlation between syncope and an arrhythmia (brady- or tachyarrhythmia) is detected	I	B
In the absence of such correlation, ECG monitoring is diagnostic when periods of Mobitz II or III degree AV block or a ventricular pause >3 s (with the possible exception of young trained persons, during sleep, medicated patients, or rate-controlled atrial fibrillation), or rapid prolonged paroxysmal SVT or VT are detected. The absence of arrhythmia during syncope excludes arrhythmic syncope	I	C
Electrophysiological study is diagnostic, and no additional tests are required, in the following cases:		
Sinus bradycardia and prolonged corrected sinus node recovery time	I	B
BBB and either a baseline HV interval ≥ 100 ms, or II or III degree His-Purkinje block is demonstrated during incremental atrial pacing or with pharmacologic challenge	I	B
Induction of rapid SVT which reproduces hypotensive or spontaneous symptoms	I	B
Induction of sustained monomorphic VT in previous myocardial infarction	I	B

Abbreviations: *ECG* electrocardiographic, *AV* atrioventricular, *SVT* supraventricular tachycardia, *VT* ventricular tachycardia, *BBB* bundle branch block

tachyarrhythmia is present. When the cause of syncope remains uncertain (neurally mediated or cardiac) after complete workup, an implantable loop-recorder should be considered (see Chap. 20).

Recently a new type of syncope without prodromal symptoms characterized by adenosine-mediated paroxysmal atrioventricular block in the absence of heart disease, with normal ECG and without progression to complete atrioventricular block, has been described [25]. The differential diagnosis of this distinct entity in relation to VVS is discussed in Chap. 7.

Tachyarrhythmia Associated with the Vasovagal Reflex

Syncope is a relatively frequent symptom accompanying paroxysmal supraventricular tachyarrhythmias, and has been suggested to be a marker of tachycardia with very high heart rate. This hypothesis is not supported by retrospective studies, which did not find an association between tachycardia cycle length and history of syncope [26, 27]. An alternative mechanism for syncope associated with supraventricular tachyarrhythmia might be an abnormal vasomotor response to the hemodynamic stress of tachycardia. Moreover, intense vagal stimulation can cause atrial fibrillation, and it has been suggested that atrial fibrillation may result from vagal stimulation occurring at the time of VVS [28]. Leitch et al. [29] investigated 22 patients with paroxysmal supraventricular tachycardia; 11 had a history of syncope that mainly occurred in association with palpitations. Tachycardia was induced in the supine position and during 60° head-up tilt. Thereafter, all patients underwent tilt testing during sinus rhythm. The cycle length of tachycardia when upright was shorter than when supine, and mean blood pressure fell to a greater extent after the onset of tachycardia. Mean blood pressure correlated significantly with tachycardia cycle length when supine but not when tilted upright. Syncope occurred in 7 patients during upright tachycardia. These patients had a greater decrease in mean blood pressure than the 15 patients without syncope. Six of the 7 patients with tachycardia-induced syncope also had syncope with tilt testing in sinus rhythm, compared with only 4 of the 15 patients without tachycardia-induced syncope. These results suggest that syncope during upright position in the presence of supraventricular tachycardia is not directly related to tachycardia itself, and is likely associated with vasodepressor syncope. Brignole et al. [30] investigated 40 patients with syncope and atrial fibrillation and 16 control subjects with atrial fibrillation without syncope. Tilt testing was performed during sinus rhythm, and atrial fibrillation was induced on a tilt table at 60° by means of short bursts of atrial pacing. Tilt testing was positive in 66 % of patients and 12 % of control subjects ($p = 0.0004$). The induction of atrial fibrillation in the upright position elicited syncope in 42 % of patients and in none of the control subjects ($p = 0.001$). The correlation between heart rate and systolic blood pressure was weak, and in 5 patients syncope occurred at a heart rate $\leq$130 beats/min. At the time of syncope, heart rate decreased (-12 ± 21 beats/min) in patients with induced syncope, whereas it remained unchanged in patients without induced syncope or slightly increased in control subjects. The positive response

to tilt testing, the onset of syncope after atrial fibrillation was induced, and, above all, the sudden beginning of hypotension associated to slowing of heart rate demonstrate that most patients with paroxysmal atrial fibrillation lose consciousness because of an associated vasovagal reflex. Vasovagal reflex has been postulated to occur because of inappropriate stimulation of ventricular stretch receptors as a result of hypovolemia and vigorous ventricular contractions. The onset of atrial fibrillation reduces left ventricular filling by the loss of atria contraction and shortening of the diastolic filling time. An increase in sympathetic tone is likely to occur at the onset of tachyarrhythmia. Consequently, there may be activation of cardiac mechanoreceptors during atrial fibrillation as a result of diminished ventricular volume and vigorous ventricular contractions. In those patients in whom the induction of atrial fibrillation was unable to cause syncope, atrial fibrillation as a consequence of VVS (vagal stimulation) is a potential mechanism. Both vasovagal reflex induced by atrial fibrillation and atrial fibrillation induced by VVS could explain why about 15 % of patients with syncope and tachyarrhythmia report vagally mediated symptoms (nausea, vomiting) [2]. Therefore, this type of syncope seems to have a "mixed" origin, even if classified as cardiac syncope.

Differential Diagnosis with Unexplained Falls

Falls may be accidental or unexplained. A fall is defined as accidental when there is a clear cause such as slip, trip, or an accidental collision, and as unexplained when there is no evident explanation for the event. If syncope occurs in the upright position, TLoC may lead to a fall; therefore, the clinical presentation of syncope and fall are potentially very similar. In the international guidelines, syncope and falls seem to travel along two different tracks. Indeed, the European guidelines on the management of syncope [1] refer to falling as a nonsyncopal event and provide no discussion on the differential diagnosis. Similarly, the recent international guidelines on the management of falls [31] only mention that unexplained falls could be a manifestation of syncope in patients without prodromal symptoms or with retrograde amnesia. Syncope is due to transient cerebral hypoperfusion, which is responsible for prodromal symptoms, such as dizziness, lightheadedness, and blurred vision. Symptoms caused by activation of the autonomic nervous system may be present. When a patient seeks assistance after a fall of uncertain origin, the first question to answer is whether he or she had symptoms due to cerebral hypoperfusion or activation of the autonomic nervous system. If these symptoms were present, this indicates syncope. If the patient does not remember any prodromal symptoms, a fall should be considered. The patient should be asked to describe every part of the entire incident (Fig. 13.1). If the patient clearly remembers a slip, a trip, or an accidental collision, an accidental fall is indicated. If no such obvious cause is identifiable, the fall can be regarded as unexplained. In such cases, some patients remember the mechanism of the fall, how they lost their balance, and the moment when they hit the ground; thus, a fall can be diagnosed. In the literature, there are no clear data on the percentage of patients suffering from unexplained

falls who are able to remember every part of the event. Often, the description of the event is incomplete or confused. Thus, the question arises as to whether we are dealing with an unexplained fall or with syncope leading to a fall with retrograde amnesia. This diagnostic problem is crucial in older persons, although young and middle-aged subjects are sometimes involved. In such situations, it is not useful to ask patients "Did you lose consciousness?", as they may be suffering from retrograde amnesia. Often the patient states that he or she had a fall, but, in light of the aforestated reasons, this statement should be taken with caution and a thorough history should be taken. Witnesses should be asked whether the patient was unresponsive to external stimuli, particularly acoustic stimuli, during part of the

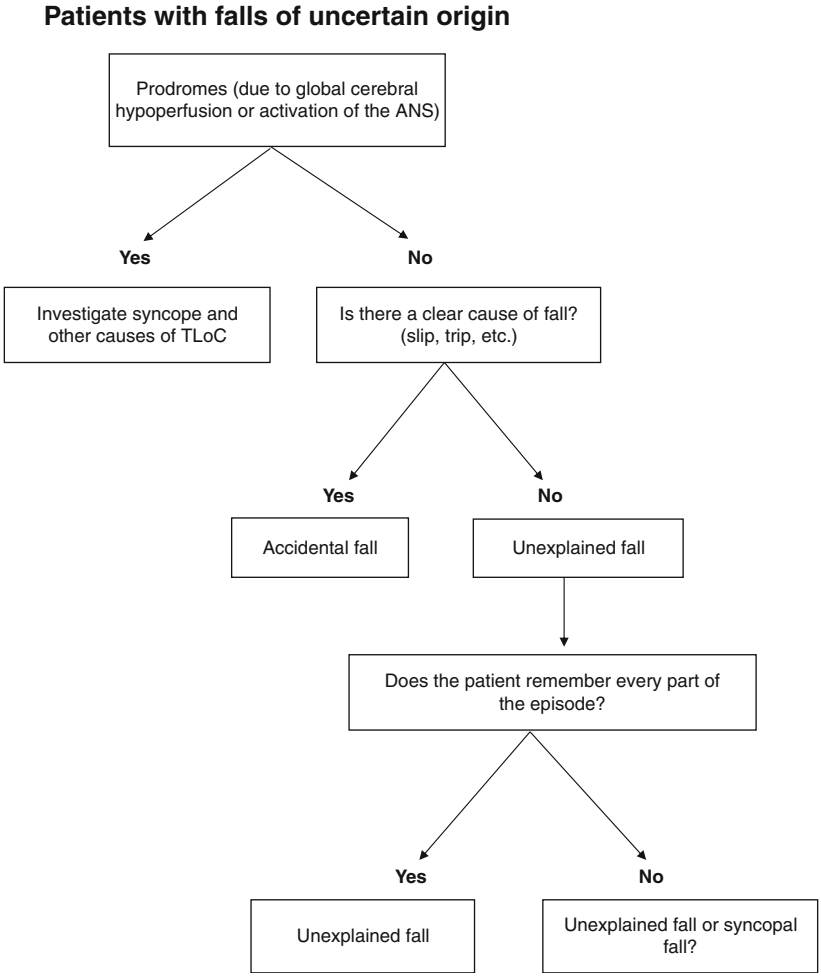

Fig. 13.1 Investigative pathway in patients with falls of uncertain origin. *ANS* autonomic nervous system, *TLoC* transient loss of consciousness

incident, and how this unresponsiveness was established. In the presence of reliable witnesses, the differential diagnosis between syncope and fall can be made. Unfortunately, in 40–60 % of cases, the patients fall in the absence of any witnesses, thus making the differential diagnosis more difficult [32].

What should be done if it is not possible to make a differential diagnosis between unexplained fall and syncopal fall after the patient's history has been taken? There are no evidence-based data. As suggested by the guidelines on falls [31], initial evaluation should be the same as in patients with syncope [1]. This involves taking the patient's history, performing a physical examination, performing supine and standing blood pressure measurement (when not hampered by severe injury), and recording a 12-lead standard ECG. If structural heart disease and/or history of arrhythmias are present, cardiologic investigation should be performed, similarly to patients with suspected cardiac syncope. If a cardiac cause does not emerge, tilt testing and CSM with the "method of symptoms" appear to be the most useful examinations, on the basis of the results of recent studies [33, 34]. Paling et al. [33] performed tilt testing and CSM with the "method of symptoms" on 101 patients with unexplained falls and 179 patients with unexplained syncope (presence of prodromal symptoms). The tilt test/CSM protocol used by Paling et al. [33] was a modification of the commonly utilized test. CSM was performed in the supine position; if syncope/presyncope was induced, the investigation was interrupted. If there was no or insignificant response, subjects were tilted to 70° at head-up position and kept there for 15 min. If there was no response to head-up tilt, they had CSM performed during tilt testing. If there was no response to CSM, they had sublingual glyceryl trinitrate spray and remained in the head-up tilt position for an additional 20 min. Use of this protocol means that not all of the patients underwent both CSM and tilt testing. However, combination of CSM and tilt testing provided a positive response in 67 of 111 patients (60 %) with unexplained falls and in 113 of 179 patients (63 %) with unexplained syncope (difference not statistically significant). These results suggest that many patients with unexplained falls actually have atypical VVS or carotid sinus syncope. Rafanelli et al. [34] performed tilt testing and CSM with the "method of symptoms" on 298 patients with unexplained falls and 989 patients with unexplained syncope. These examinations were performed with the usual sequence [1]. The prevalence of positive tilt test was high (36 %) in patients with unexplained fall, although lower than in those with unexplained syncope (51 %). Carotid sinus syncope showed a similar prevalence in the two groups (14 and 10 %). Overall, both tilt testing and CSM showed a high positivity rate in the group of patients with unexplained falls (61 %), similar to that of the unexplained syncope group (64 %). These results, consistent with those reported by Paling et al. [33], suggest that many unexplained falls are actually cases of atypical VVS/carotid sinus syncope with retrograde amnesia, and that the fall is a consequence of TLoC.

Taken together, these results suggest that patients with falls of unexplained origin after the initial evaluation should undergo tilt testing and CSM (Table 13.2). When tilt testing is positive, VVS could be diagnosed in the absence of any competing diagnosis [35]. The role of an implantable loop-recorder in the diagnosis and

Table 13.2 Cardiovascular management of patients with unexplained falls

Investigation
Supine and standing blood pressure measurement
Any other cardiologic investigation, as appropriate, in the presence of relevant heart disease and/or arrhythmias or conduction disturbances
Carotid sinus massage with the“ method of symptoms”
Tilt testing
Implantable loop recorder?

treatment of VVS with clinical presentation as a fall remains to be determined, even if preliminary data appear to be encouraging [36]. In summary, in some patients the differential diagnosis between unexplained fall and neurally mediated syncope can be obtained by an accurate history; in the remaining patients, tilt testing and CSM appear to be indicated, if a potential cardiac cause of syncope does not emerge after the initial evaluation.

13.3 Differential Diagnosis with Nonsyncopal Loss of Consciousness

In some patients, differential diagnosis should be made between atypical VVS and some forms of nonsyncopal TLoC such as epilepsy, transient ischemic attack (TIA), and hypoglycemia, and with other affections such as functional (psychogenic) pseudosyncope and cataplexy, which mimic a TLoC, even if consciousness is preserved. The clinical features of these disorders, as obtained during the initial evaluation, are reported in Chap. 10. These features are summarized in Tables 13.3 and 13.4.

Epilepsy

In the presence of reliable witnesses, the differential diagnosis between VVS and epilepsy is generally easy (Table 13.3). Involuntary movements can be present in both epilepsy and syncope. In syncope they occur only after the fall, and are considered to be an integral component of the brain’s response to hypoxia. The duration of epileptic movements is longer and they generally last 1 min or more, while in syncope they last only a few seconds. The jerks in epilepsy are coarse, rhythmic, and usually synchronous and violent. They can affect the whole body, whereas those in syncope are usually asynchronous, small, and nonrhythmic. However, synchronous jerks can occur in syncope, though rarely. Complete flaccidity during unconsciousness argues against epilepsy. The only exception is “atonic seizure,” but this is rare and occurs in children with pre-existing neurologic problems. During seizures, the face generally becomes cyanotic, whereas during syncope it is pale. However, facial cyanosis can also be observed in some patients with cardiac syncope. Complex movements or automatisms (eg, lip smacking, chewing, fumbling, head raising)

Table 13.3 Role of history in the differential diagnosis between syncope and epilepsy

	Epilepsy	*Syncope*
Trigger	Rare	Frequent
Prodromal symptoms	Sensorial or somatosensorial aura	Dizziness, blurred vision, nausea, vomiting, abdominal discomfort, sweating
Fall	Generally tonic	Generally flaccid
Skin color	Generally cyanotic	Generally pale
Movements	Tonic-clonic, rhythmic, prolonged (~1 min). Their onset coincides with the beginning of TLoC	Myoclonus, short duration (~15 s), nonrhythmic. They appear late during TLoC
Automatisms	Lip smacking, chewing, fumbling, head raising	Extremely rare
Tongue biting	Frequent	Rare (localized at the tip of the tongue)
Eye deviation	Generally lateral	Generally upward
Symptoms during recovery	Prolonged confusion, aching muscles, headache	No confusion or of short duration (generally < 5 min), nausea, vomiting, pallor, sweating

Abbreviations: *TLoC* transient loss of consciousness

Table 13.4 Signs and symptoms suggestive of nonsyncopal loss of consciousness

Focal neurologic symptoms associated to TLoC	→	TIA
TLoC preceded by tremors and intense sweating in treated diabetic patients	→	Hypoglycemia
Frequent and prolonged TLoCs. Closed eyes during the attack	→	Psychogenic pseudosyncope
TLoC, preceded by an emotional trigger in patients with narcolepsy	→	Cataplexy

Abbreviations: *TIA* transient ischemic attack, *TLoC* transient loss of consciousness

may be observed during an epileptic attack, whereas they are uncommon in syncope and of shorter duration [37]. Eye movements (upward turning, deviation, nystagmus) can take place in both epilepsy and syncope, but in everyday life are often missed by witnesses. Tongue biting, very common in seizures, is highly rare in syncope. Tongue biting tends to affect the side of the tongue in epilepsy and the tip in syncope. After seizures, confusion is prolonged and is often accompanied by aching muscle and headache. By contrast, after syncope, confusion is generally of short duration (up to a few minutes). Head injuries and other traumas, in addition to urinary incontinence, seem to be common in both epilepsy and syncope, and, therefore, are not useful for the differential diagnosis [38]. Sheldon et al. [39] developed evidence-based criteria that distinguish syncope and epilepsy during the initial evaluation. A multivariate regression analysis was performed to identify the variables that were significant predictors. A clinical score was then developed by

Table 13.5 Point scores for the diagnosis of epilepsy

Criteria	*Score*
Loss of consciousness with stress	2
Head turning to one side during loss of consciousness	2
Number of spells >30	1
Unresponsiveness during loss of consciousness	1
Diaphoresis before loss of consciousness	−1
Any presyncope	−2
Loss of consciousness with prolonged standing or sitting	−3

Sheldon et al. [39]
The patient has epilepsy if the score is ≥ 0

assigning points to each of the factors based on the relative magnitude of the regressive coefficient. The points were summed into a score, and a diagnostic threshold was determined using receiver-operating characteristic (ROC) analysis. If the total score is ≥ 0, a diagnosis of epilepsy is made (Table 13.5). This score shows the same limitations of other diagnostic scores (see Chap. 10). However, it appears to be useful for the proper selection of diagnostic method.

In most cases, epilepsy can easily be distinguished from syncope after having collected the clinical features by reliable witnesses. However, in some cases the differential diagnosis can be difficult, particularly in the absence of witnesses or when there are myoclonic jerks. When epilepsy is suspected, the diagnostic workup depends on the patient's history and on the fact that the episode is the patient's first seizure or occurs within the framework of already diagnosed epilepsy. In case the patient has to be evaluated for causes of new-onset epilepsy, is mandatory to exclude several underlying central nervous system conditions that may manifest with epileptic seizure as central nervous system infections, cerebral infarction, mass lesion, systemic metabolic disorders, and substance abuse. The following tests can be helpful in most cases:

- Electroencephalogram (EEG): In adults with epilepsy, 29–56 % will show one or more interictal epileptiform discharges on a single wake EEG. With repeated testing, including sleep recording, an interictal epileptiform discharge is seen in the EEG of 59–92 % of epileptic subjects, but there is minimal additional yield with more than 4 repeats. If the first study revealed nonspecific abnormalities but no interictal epileptiform discharges, there is a higher chance of recording interictal epileptiform discharges on a subsequent EEG. If a wake EEG is followed by a sleep EEG, the sensitivity for interictal epileptiform discharges in some studies is increased from 61 to 81 %. Simply repeating the EEG is not the explanation of this effect. The prevalence of interictal epileptiform discharges in asymptomatic individuals depends in part on the age of the subject and the presence of intracranial disease. Specificity appears to be lower in children; between 1.2 and 6 % of asymptomatic children have interictal epileptiform discharges.

- Blood tests: Some of the useful blood tests include anticonvulsants levels, complete blood count, renal function, electrolytes, glucose, calcium, magnesium, liver function tests, blood gases, blood-clotting measures, and toxicology.
- Lumbar puncture is indicated only when a central nervous system infection is suspected.

Brain imaging should be performed to search for intracerebral lesions. Magnetic resonance imaging (MRI) should include FLAIR imaging to assess for cortical dysplasia. MRI at 3 T is preferred to identify subtle abnormalities of cortical development. The autonomic nervous system is often involved in both focal and generalized seizures, and autonomic changes have been documented interictally, ictally, preictally, and postictally. The immense autonomic disturbances during and immediately after a generalized tonic-clonic seizure are obvious to any onlooker. However, focal seizures also may manifest with autonomic phenomena such as tachycardia and, less often, bradycardia and asystole, pallor, epigastric and cephalic sensations, hypersalivation, respiratory modifications, and pupillary changes [40]. While it is likely that several factors contribute to sudden unexplained death in epilepsy, further study of both ictal respiratory and cardiac changes and the underlying neuroanatomic mechanisms involved in autonomic seizure semiology are likely to provide important data to improve our understanding of the pathophysiology of this devastating condition. Ictal ECG or polygraphic recordings are crucial in detecting these autonomic symptoms and signs. In severe pharmacoresistant epilepsy, a high incidence of significant periods of asystole (20 %) has been documented with extended ECG monitoring over long periods (median, 18 months) by using an implantable loop-recorder.

Transient Ischemic Attack

TLoC during TIA appears to be extremely rare and has been observed only during TIAs involving the vertebrobasilar system. To date, no cases of TLoC have been described during TIA secondary to involvement of the carotid circulation [41]. The differential diagnosis between TIA and syncope is generally easy and is based on the presence during TIA of focal neurologic symptoms such as limb ataxia, oculomotor palsies, loss of balance, difficulty sitting without support, veering to one side, frank vertigo, unilateral hearing loss, dysphagia, laryngeal paralysis, and pharyngeal paralysis. Patients with TIA of the vertebrobasilar system do not have hemiparesis or hemisensory loss. At present, there are no reliable descriptions of a TIA showing up as an isolated TLoC [41]. In patients with syncope, there are no focal neurologic symptoms before and after the attack; however, it must be pointed out that a neurologic symptom, such as paresthesia, is reported by some subjects, mainly women, during VVS [19]. The presence of focal neurologic symptoms is sometimes uncertain and, therefore, a TIA might be only suspected. In such cases, a patient with a recent TIA should be referred to the neurologist, who after neurologic examination may organize testing to exclude occlusive disease of the carotid and vertebrobasilar arteries, cardiac disease, or hematologic disease, in that order.

Angiography of the carotid circulation reveals that 30–50 % of patients with carotid TIA have severe carotid bifurcation disease while the remainder have widely patent vessels. Although angiography is the gold standard to identify carotid disease, it has an approximately 1 % rate of permanent complications, which vary by center. Therefore, screening with ultrasound to select patients with more severe disease for angiography lowers the absolute number of complications. Other noninvasive technologies such as MRI angiography and computed tomography (CT) angiography, capable of identifying carotid bifurcation atherosclerosis, reveal disease prevalence similar to that found with angiography. Transcranial Doppler ultrasound can detect hemodynamic changes distal to a carotid stenosis, which help assess the severity of bifurcation stenosis, improving the selection of patients for angiography.

CT or MRI of the brain is performed in patients with TIA to rule out mass lesions. MRI with diffusion-weighted imaging may be especially useful in patients with TIA, as it may also help clarify the ischemic area and the symptom mechanism. Patients with TIA should preferably undergo neuroimaging evaluation within 24 h of symptom onset. If MRI is not available, head CT should be performed.

In patients with normal or mildly diseased carotid arteries or those at high risk of emboligenic heart disease, cardiology investigation is indicated. Transesophageal echocardiography is more sensitive than transthoracic echocardiography in identifying sources of embolism. Holter monitoring is performed when an emboligenic arrhythmia, such as paroxysmal atrial fibrillation, is suspected.

In patients with negative carotid and cardiac tests, vasculitis tests or specialized coagulation tests (antiphospholipid antibodies and other hypercoagulable states) should be considered, particularly in young patients.

It must be pointed out that in patients with transient TLoC without focal neurologic symptoms, CT or MRI of the brain, EEG, and ultrasound of neck arteries are not indicated.

Hypoglycemia

Hypoglycemia can induce loss of consciousness, which is generally long-lasting and mimics coma. Sometimes, however, loss of consciousness is of short duration, and in this case a differential diagnosis must be made with syncope. TLoC as a result of hypoglycemia should be suspected in diabetic patients under insulin or oral antidiabetic drugs who experience symptoms mainly after a lack of food intake. Symptoms caused by sympathetic activation, such as tremors and intense sweating, are frequently reported. During recovery, prolonged confusion may be present. The diagnosis can be made when glycemia is <60 mg/dl. If glycemia, measured after recovery, shows higher values, a TLoC attributable to hypoglycemia can be only suspected. In this case, caregivers should be instructed to measure glycemia at home during fainting.

Functional (Psychogenic) Pseudosyncope

Functional (psychogenic) pseudosyncope is part of the spectrum of conversion disorder, and is characterized by apparent TLoC that causes major challenges in terms of diagnosis and treatment. As with other functional disorders, a key issue is the absence of pathophysiologic understanding. The similarity between physical signs in functional disorders and those that occur in feigned illness has also raised important challenges for pathophysiologic understanding, and has challenged health professionals' attitudes toward patients with these disorders. It mainly affects women and generally starts at a young age. The patient does not lose consciousness, but because he or she loses postural tone and does not respond to external stimuli, a differential diagnosis with syncope must be made. There are some features that help differentiate this state from true TLoC. In psychogenic pseudosyncope, there are no triggers and the attack often occurs in the presence of other people. In many patients the spells are frequent, sometimes several per day, and are often long-lasting, spanning from a few minutes up to 20 min. During pseudosyncope there are no gross abnormalities except for a lack of responsiveness. The eyes are generally closed, whereas during both syncope and seizures they are commonly open [18, 42]. Lifted limbs that are suddenly released may hesitate in mid-air before falling. Sometimes there are movements consisting of asynchronous convulsion-like movements that resemble epilepsy [42]. Some minor traumas can occur. There is no postictal confusion, but patients often become emotional and cry at the end of the attack. When reliable witnesses are present, the differential diagnosis between functional pseudosyncope and syncope is possible in most cases. Sometimes the clinical features are not clear, and the differential diagnosis should be made mainly with neurally mediated syncope, because patients are young or fairly young women, generally without structural heart disease or ECG abnormalities suggestive of cardiac syncope. Tilt testing is useful for the diagnosis because it has been shown to be capable of inducing the typical attack in about 90 % of patients with functional pseudosyncope [43]. A clinical suspicion of this affection is a recognized indication for a tilt table test in the European guidelines on syncope [1]. During the attack in the tilt table test, characterized by loss of muscular tone with closed eyes, heart rate and blood pressure are normal and are often higher than at baseline [42]. Pallor and sweating are extremely rare (4 and 0 %, respectively) [42]. In a few patients, after a period of apparent TLoC during which blood pressure and heart rate are normal, a VVS can occur; this pattern has been defined as "mixed" [42]. When there are pronounced movements during the spontaneous attack, the differential diagnosis should be made with epilepsy. In these patients, EEG should be recorded during tilt testing, besides blood pressure and heart rate, and the gold standard for functional pseudosyncope is the absence of epileptiform EEG waves during the attack.

Cataplexy

Cataplexy concerns loss of postural control and unresponsiveness to external stimuli without real TLoC. The loss of muscle tone is triggered by emotions, sometimes negative, such as fear and anger, but more often positive, such as laughter or pleasant surprise. There are no autonomic prodromes. In complete attacks, patients slump flaccidly to the ground. Attacks may develop slowly enough to allow the patient to stagger and break the fall before hitting the floor. In the presence of reliable witnesses, this type of fall should not be considered a manifestation of syncope. Cataplexy occurs only in the context of narcolepsy, which is the most important finding for the diagnosis of cataplexy. When cataplexy is predominant and diurnal sleepiness is not disabling, cataplexy should be differentiated by VVS, because it is triggered by an emotion. The type of fall and/or a positive emotion (extremely rare as a trigger of VVS) could suggest cataplexy. In this case, patients should always be asked whether they suffer from diurnal somnolence, because they could not report this symptom.

In patients with suspected narcolepsy-cataplexy, polysomnography helps to document the absence of other disorders that could explain the patient's symptoms, and provides objective confirmation of narcolepsy. Nighttime polysomnography often shows a short sleep latency (<10 min), a short sleep-onset rapid eye movement (REM) (appearing within 15 min after sleep onset), and disrupted sleep with increased stage-1 sleep and frequent arousals. A short sleep-onset REM during nocturnal sleep is a highly specific finding in the absence of other sleep disorders. Human leukocyte antigen typing of Caucasian and Japanese patients with narcolepsy and cataplexy reveals DR1501 and DQB1-0602 antigens in more than 85 %. When the diagnosis is uncertain, a decreased level of orexins in cerebral spinal fluid confirms the diagnosis of narcolepsy.

13.4 Differential Diagnosis of "Sleep Syncope"

Vasovagal syncope is rare in the supine position, with the exception of syncope triggered by venesection or medical procedures, because of the relative preservation of cerebral perfusion. In studies dealing with typical VVS, syncope occurring in the horizontal position was observed only in 5 % of subjects and was always triggered by emotional distress [3, 5]. When syncope occurs in the supine position, a cardiac cause of syncope should first be considered; if a cardiac cause is excluded, other examinations, chosen on the basis of the clinical presentation, should be performed.

Recently the "sleep syncope," a new type of VVS occurring during the sleeping hours while lying down, has been described [44–46]. It has been defined as a "TLoC in a non-toxicated subject occurring during the normal hours of sleeping." The main findings are [44–46]: absence of any trigger; women are mainly involved; history of waking from sleep with abdominal discomfort and an urge to

defecate; other possible symptoms such as sweating, nausea, palpitations, feeling warm, lightheadedness, and myoclonic jerks; symptoms always begin in the supine position, but TLoC occurs in this position only in a third of subjects, whereas in two-thirds it occurs after standing up to go to the bathroom; possible episodes of typical VVS during the day and/or a history of specific phobia(s), mainly blood-injection-injury phobia; bradycardia fortuitously documented in some subjects during TLoC; and basal tilt test positive in about 60 % of subjects.

We believe that "sleep syncope" can be diagnosed after the initial evaluation in subjects without structural heart disease or primary electrical disease and without convulsions during TLoC (in the presence of reliable witnesses), with autonomic prodromes and a history of daytime episodes of typical VVS. When daytime episodes are not reported, a positive tilt test can support the diagnosis. When the nocturnal TLoC does not show the typical aforementioned characteristics, the differential diagnosis should be made with epilepsy, once a cardiac cause has been excluded.

Complex partial, generalized tonic-clonic, and myoclonic epilepsy all occur during sleep and can imitate syncope. The most common form of complex partial seizure originates in the mesial temporal lobes and is frequently heralded by visceral aura [47]. There are a number of related conditions, including "abdominal epilepsy" and Panayiotopoulos syndrome, in which the main associated clinical features are abdominal pain and confusion [48, 49]. Diagnosis may require repeated interictal, sleep, or continuous EEG monitoring. In the absence of EEG evidence, the diagnostic gold standard is a detailed witness account of what happened preceding, during, and after TLoC, particularly the details of the seizure, dystonic posturing, automatisms, postictal confusion, and evidence of tongue biting. Vertebrobasilar migraine can also cause syncopal symptoms (with headache and vomiting), although not usually at night [50]. Sleep paralysis and hypnagogic hallucinations occur in sleep-deprived individuals and narcoleptics, most of whom will have other characteristic features in the history (e.g., daytime somnolence) and abnormal polysomnography. Some unusual abdominal conditions may occasionally present with syncope, and these can be excluded by appropriate tests. For example, systemic mastocytosis, carcinoid, pheochromocytoma, and visceral angioedema can be diagnosed by neuroendocrine assays and imaging. Panic attacks may cause palpitations and gastric disturbances at night, and blood pressure monitoring may be required to demonstrate that symptoms are not secondary to hypotension. In summary, the differential diagnosis for "sleep syncope" is broad and includes epilepsy, migraine, sleep apnea, mastocytosis, panic attacks, besides cardiac arrhythmias, but all of these conditions can usually be excluded by careful history taking and the appropriate investigations. Finally, "sleep syncope" should be differentiated from defecation syncope, which is classified as situational syncope. In "sleep syncope" the prodromal symptoms always begin in the supine position, whereas in defecation syncope they occur during or just after defecation. However, there may be some overlap between these two conditions [45].

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Differential Diagnosis of Vasovagal Syncope: Postural Orthostatic Tachycardia

14

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Key Points

- Postural tachycardia syndrome (POTS) is a syndrome in which an excessive increase in heart rate upon assumption of upright posture, in the absence of orthostatic hypotension, is the final common pathway for multiple overlapping pathophysiologies.
- Presyncopal symptoms in POTS may resemble those in vasovagal syncope (VVS).
- In contrast to the immediate increase in heart rate during upright posture in POTS, there is a delayed, albeit abrupt fall in blood pressure and heart rate with standing in VVS.
- Treatment of POTS includes exercise and medications directed at decreasing sympathetic tone or increasing blood volume.

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14.1 Introduction

Postural tachycardia syndrome (POTS) was first officially described as a syndrome by Schondorf and Low in 1993 [1] and was most recently defined in 2011 [2]. A diagnosis of POTS is currently based on an increase in heart rate (HR) of ≥30 bpm, within 10 min of assuming an upright posture (standing or upright tilt), in the absence of orthostatic hypotension [decrease in blood pressure (BP) > 20/10 mmHg]. In young children, a higher HR threshold (≥40 bpm) should be used, since healthy younger children have a greater physiological orthostatic tachycardia.

The exact prevalence of POTS is not known, with estimates that range from 500,000 [3] to 3,000,000 patients in the United States, and a female:male ratio of 4–5:1. Because POTS usually presents between 13 and 50 years of age, the impact on productivity at work and lifestyle can be devastating [4–6]. The prognosis for adolescents diagnosed with POTS is more favorable for recovery than for newly diagnosed adults [7, 8], but long-term follow-up data is lacking. Patients with a postviral onset may have a better chance of symptom resolution than patients with more hyperadrenergic features, who may require therapy indefinitely [8].

14.2 Differential Diagnosis of POTS

The evaluation of a patient suspected to have POTS first requires a detailed history and physical examination. Known causes of orthostatic tachycardia must be considered and excluded. These include, but are not limited to, acute dehydration, diabetes mellitus, cardiomyopathy, heavy-metal poisoning, Sjögren's syndrome, systemic lupus erythematosus, deconditioning, inappropriate sinus tachycardia, pheochromocytoma, thyrotoxicosis, or manifestations of a paraneoplastic syndrome [2]. Potentially deleterious medications, such as diuretics, anxiolytics, stimulants, and vasodilators, must be taken into account [2, 9].

The tachycardia of POTS is a sinus tachycardia, and an ECG or Holter monitor should exclude the presence of an accessory bypass tract and arrhythmogenic causes of syncope [7]. Structural problems and cardiomyopathy should be ruled out. The chest pains in POTS are almost never due to coronary artery obstruction, but are sometimes associated with electrocardiographic changes in the inferior leads, particularly when upright [10]. Inappropriate sinus tachycardia (IST) can resemble POTS, though IST patients generally have an elevated resting HR (often >100 bpm during daytime rest) [11] in contrast to the high normal heart rates seen in POTS. Whereas patients with IST may benefit from sinus node ablation, this procedure is rarely effective for the orthostatic tachycardia of POTS [8]. In addition to a cardiac consult, a neurologist may be asked to evaluate headaches or dizziness. A gastroenterology consultation may be requested if abdominal pain and nausea are present. Blood tests for serum electrolytes, a complete blood count, liver and thyroid functions, a celiac panel, and vitamin B_{12} are generally normal, but may be useful to rule out other conditions that cause dizziness, fatigue, and gastrointestinal symptoms.

14.3 Clinical Characteristics of POTS

POTS is a chronic condition with symptoms of orthostatic intolerance persisting at least 6 months. Symptoms improve with recumbence [9], and can also be triggered by exercise, heat, or sometimes by food [12]. Patients complain of both cardiac symptoms (palpitations, lightheadedness, chest discomfort, shortness of breath) and noncardiac symptoms (mental clouding, headache, nausea, tremulousness, blurred vision) [9]. Acrocyanosis is apparent in the legs and feet of approximately 50 % of patients. Gastrointestinal complaints are fairly common [12]. Sudomotor testing may be abnormal [12]. Some patients meet the diagnostic criteria for chronic fatigue syndrome [13]. Exercise intolerance exacerbates deconditioning, and the activities of daily life are limited [9, 14].

Significant diurnal variability has recently been reported for the orthostatic tachycardia of POTS [15], with an exaggerated orthostatic tachycardia in the morning compared to that in the evening. The standing HR decreases by late-morning [16]. It is therefore recommended that postural testing be performed in the morning to optimize diagnostic sensitivity for POTS [9].

Patients with POTS frequently have hyperextensible joints [17]. Wallman et al. [18] reported an 18 % prevalence of Ehlers–Danlos syndrome in their POTS population, compared with a 0.02 % prevalence cited for the general population, and 4 % prevalence in their autonomic clinic patients without POTS.

Most patients with POTS complain of fatigue. The prevalence of chronic fatigue in POTS patients has been reported as 48–77 % and of chronic fatigue syndrome (CFS) is 17–23 % [13]. Bagai et al. reported that compared to healthy subjects, POTS patients describe poorer sleep quality, more daytime sleepiness, and greater fatigue [6]. By actigraphy, POTS patients have diminished sleep efficiency [19].

The quality of life for patients with POTS is comparable to chronic obstructive pulmonary disease or congestive heart failure [20], likely due to exercise intolerance, fatigue, and orthostatic symptoms [6, 20]. Physical health domains are primarily affected, while mental health domains are relatively preserved.

14.4 Comparison of Vasovagal Syncope and POTS

Considerable clinical overlap exists between vasovagal syncope (VVS) and POTS. VVS can be diagnosed at any age, though the first fainting episode usually occurs in the second and third decades, also the period during which POTS is often diagnosed. The female predominance is somewhat less in VVS than POTS (60 % vs. 85 %). Many patients with POTS do not have frank syncope, though presyncope may occur daily [9, 21]. Though VVS may also occur with pain, anxiety, and exercise, head-up tilt table testing can be used in the clinic to differentiate between POTS and VVS. In addition to a syncope outcome, the hemodynamic response to upright posture differs between the two disorders.

A series of physiological adaptations occur with standing to maintain BP and cerebral perfusion [5]. The characteristic hemodynamic patterns of VVS and

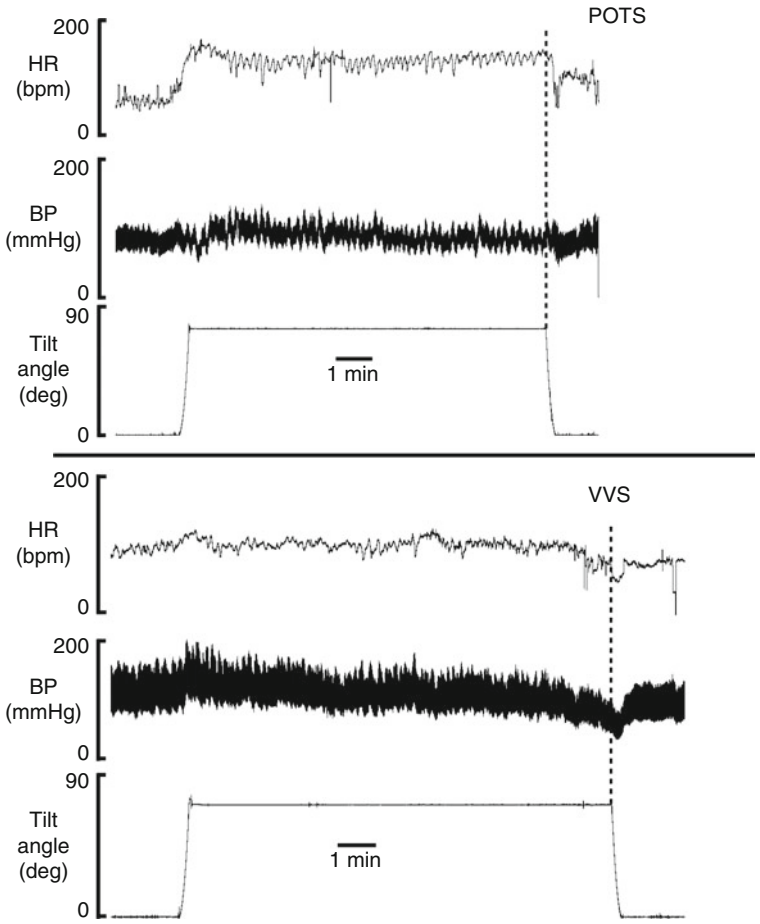

Fig. 14.1 Traces from head-up tilt table tests for a patient with POTS (*top*) and with VVS (*bottom*). For POTS, there is an early and sustained increase in heart rate and a slight increase in blood pressure with tilt. For VVS, heart rate and blood pressure increase slightly at the tilt onset, but are maintained at levels close to the baseline, until abrupt falls just before the tilt table is lowered

POTS result from failures of these physiologic compensatory mechanisms (Fig. 14.1). In patients with POTS, venous return remains inadequate in the face of enhanced plasma volume shifts from the vascular space to the interstitial space, sympathetic tone increases vigorously, and orthostatic tachycardia is exaggerated with BP unchanged (or even increased) [5]. Patients may complain of symptoms throughout the tilt test, but do not faint. On the other hand, in VVS, upright posture is associated with a generally delayed but abrupt decrease in stroke volume and cardiac output with bradycardia and hypotension [22], and resultant cerebral hypoperfusion leading to a sudden loss of consciousness [23] (Fig. 14.1).

14.5 Pathophysiological Mechanisms in POTS

POTS is not a single disease. POTS should be considered as a "final common pathway" for a number of overlapping pathophysiologic processes. Thus, POTS is a heterogeneous syndrome with multiple contributing causes.

Hyperadrenergic POTS

Many POTS patients have excess sympathoneural tone. While supine plasma norepinephrine (NE) is often normal in POTS, a significantly increased upright plasma NE (>3.55 nmol/L and sometimes >5.91 nmol/L) can be seen in many POTS patients [4]. Patients have an exaggerated sympathetic pressor response during the recovery and overshoot phases of the Valsalva maneuver [5, 9]. These hyperadrenergic patients may increase their BP with standing and complain of tremor, anxiety, and cold, sweaty extremities [8]. Yet, the correlation between hyperadrenergic symptoms and a high plasma NE remains to be established [12].

Though elevated sympathetic tone is usually secondary to another pathophysiological mechanism in POTS, it may also be the primary problem. Shannon et al. [24] reported a family with a loss-of-function genetic mutation causing NE transporter (NET) deficiency and POTS in the proband. NET is a clearance transporter, which leads to increased synaptic NE when defective. While this mutation is not common, many drugs act through NET blockade and can worsen tachycardia in POTS [25].

Furlan et al. [26] evaluated the sympathetic tone in patients with POTS using microneurographic recording from the peroneal sympathetic nerve, plasma norepinephrine, and spectral analysis of BP and HR variabilities. Sympathetic drive to vessels and the heart was enhanced in the supine position. During upright tilt, however, the increase in sympathetic drive to vessels was blunted in patients, whereas sympathetic modulation of HR was maintained or enhanced. These results might indicate a central nervous system cause of a hyperadrenergic state in some patients with POTS [26].

Hypovolemic POTS

Blood volume is frequently low in patients with POTS [27–29]. Raj et al. reported significant deficits in total blood, plasma, and red cell volume in POTS when patients were controlled for sodium intake and withdrawn from medications prior to testing [27]. Chronic hypovolemia could contribute to a hyperadrenergic state. An expected compensatory response for hypovolemia is activation of the renin–angiotensin–aldosterone system to promote sodium and volume retention, but some POTS patients with hypovolemia have inappropriately low standing plasma renin activity and aldosterone compared with the controls [4, 30]. These can be accompanied by high circulating angiotensin II levels [31] without a parallel increase in its

metabolite, angiotensin (1–7), suggesting that angiotensin-converting enzyme 2 abnormalities might contribute to the plasma volume deficit in POTS [9, 32].

Neuropathic POTS

Up to 50 % of POTS patients may have a preferential denervation of sympathetic nerves in the lower limbs [33], as first shown by diminished NE spillover [34]. The inability of the peripheral vasculature to maintain sufficient constriction during upright posture allows blood pooling in the splanchnic vasculature [35, 36] and lower extremities [8]. A partial dysautonomia in POTS has also been indicated by impaired sudomotor function [37], excessive venous pooling in standing patients [38], and reduced intraepidermal nerve fiber density [33].

Mast Cell Activation Disorder

Some POTS patients report severe flushing in association with their tachycardia and may have a mast cell activation disorder. These patients often have a hyperadrenergic appearance, with orthostatic tachycardia and hypertension, as well as dramatic BP overshoots in phase 4 of the Valsalva maneuver. It has not been determined whether the sympathetic activation induces mast cell degranulation or if mast cell activation causes the release of vasoactive mediators and sympathetic activation compensates for the ensuing vasodilation [39]. Measuring urinary methylhistamine levels around a spell can make the diagnosis.

Autoantibodies

A diagnosis of POTS following a virus-like syndrome in some patients has stimulated a quest for autoantibodies that affect autonomic functions in POTS. Rare cases are associated with a low titer of an antibody targeting the ganglionic acetylcholine receptor [12]. Recently, Li et al. found evidence of functional autoantibodies to α-adrenergic receptors (AR) and β-AR in POTS patients, with much lower activity in the control subjects [40]. This is an emerging area of POTS research.

14.6 Treatment of POTS

Nonpharmacological Treatment of POTS

The initial step in the care and treatment of patients with POTS is education about behaviors and medications that can precipitate symptoms. Patients must be examined for any existing illnesses, which could be causing their POTS. Medications that might contribute to POTS should be discontinued or reduced.

Patients should be advised to avoid extreme heat and activities that lead to dehydration. In an effort to increase intravascular volume, they should be encouraged to drink water 2–3 L/day, while increasing their sodium intake to >200 mEq/day. Intravenous saline (1–2 L) can quickly expand blood volume and curb tachycardia in POTS patients [41], but this treatment is associated with an increased risk of vascular access complications (including infections) when used chronically.

Venous pooling as a result of upright posture in POTS appears to occur primarily in the splanchnic region [36], and abdominal compression to inhibit pooling may improve stroke volume and cardiac output. Elastic waist-high support hose or body-shaper garments may be effective at increasing venous return.

Patients with POTS complain of significant exercise intolerance [9, 42]. Deconditioning contributes to the limited ability to exercise, which then exacerbates the deconditioning. A 3-month aerobic exercise program coupled with resistance training improves orthostatic tachycardia, symptoms, and quality of life [28, 43].

Raj et al. found that POTS patients were mildly depressed, which may reflect unhappiness about living with a chronic illness [44]. Behavioral approaches, such as yoga and biofeedback, to help patients cope with their disorder can be important components of the treatment of POTS [7].

Pharmacological Treatment of POTS

Randomized placebo-controlled trials are lacking for this patient population [9, 14, 42]. Given the heterogeneity of POTS, the success of a medication may be influenced by the POTS subtype, though Thieben et al. reported no difference in the symptomatic improvement of different subtypes of POTS to a variety of medications [12].

A hyperadrenergic phenotype with POTS might respond better to agents that decrease sympathetic tone. Low doses (10–20 mg) of the nonselective β-AR antagonist propranolol can acutely control HR and orthostatic symptoms without causing fatigue [45]. A 4-week trial of long-acting propranolol decreased standing HR without improving the quality of life [28]. Central sympatholytics (e.g., clonidine and methyldopa) can decrease the sympathetic nervous system tone, but need to be used carefully to avoid undesirable side effects such as drowsiness and worsening of the mental clouding [9]. Pyridostigmine can also restrain HR in POTS [46]. It inhibits acetylcholinesterase and raises parasympathetic tone by increasing the availability of acetylcholine at both the autonomic ganglia and the peripheral muscarinic receptors. It has led to long-term symptom improvement in approximately 50 % of patients with POTS, though increased gut motility may lead to discontinuation in 20 % of patients [47].

Ivabradine is a novel agent approved for the treatment of angina in many parts of the world, but not yet in the United States. It slows HR by inhibiting the pacemaker funny channel current in the sinoatrial node and does not affect BP. A retrospective case series found decreased tachycardia in 60 % of POTS patients [48]

Midodrine, an α1-AR agonist, can be used to increase peripheral resistance by stimulating vasoconstriction. It not only improves the symptoms and orthostatic

tachycardia, but can also be associated with the unpleasant sensations of scalp-tingling and goose bumps [41].

Fludrocortisone, an aldosterone analog, increases sodium reabsorption in the distal tubules of the kidney, and should thereby increase sodium retention and volume expansion. Fludrocortisone also stimulates potassium excretion, making it necessary to monitor potassium levels, and it can also worsen migraine headaches [9, 21].

The vasopressin analog, desmopressin (DDAVP), can also increase volume and reduce tachycardia and symptoms [49]. It can lead to hyponatremia, as only free water is retained. Erythropoietin may also be used to increase blood volume, via increasing red cell mass, and may cause vasoconstriction as well [8], but its side effects, cost, and need for injection make it a less attractive option [7].

NET inhibitors, or serotonin-norepinephrine reuptake inhibitors (SNRIs), may worsen tachycardia in POTS [25]. In contrast, selective serotonin reuptake inhibitors (SSRIs) such as sertraline do not worsen tachycardia or orthostatic symptoms in POTS patients [50]. Studies on its benefit related to coping with the POTS syndrome have not been conducted.

Conclusion

POTS is a heterogeneous disorder, related to multiple, overlapping pathophysiological mechanisms. The hallmark clinical trait is an excessive increase in HR upon assumption of the upright posture, in the absence of orthostatic hypotension. Unlike VVS patients, POTS patients do not generally faint, though a number of cardiac and noncardiac symptoms may be triggered within a few minutes of standing and persist until recumbence in POTS. Presyncopal symptoms in VVS may resemble those in POTS, but their appearance is delayed in VVS (often for several minutes after standing), and they are associated with an abrupt fall in BP and HR. Exercise training is an important therapeutic strategy in POTS. Pharmacological treatments are second- line approaches that often target specific pathophysiological features.

Conflicts of Interest None

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Differential Diagnosis of Vasovagal Syncope: Sick Sinus Syndrome

15

Paolo Alboni and Nelly Paparella

Key Points

- Sick sinus syndrome can be diagnosed only when there is a clear correlation between symptoms and sinus node (SN) dysfunction. In the absence of such correlation, the mechanism of undocumented intermittent symptoms such as syncopal spells in patients with permanent mild sinus bradycardia remains uncertain.
- Some clinical data suggest that a reflex mechanism is likely to be involved in many patients with syncope and sinus bradycardia.
- The results of some clinical studies, where head-up tilt testing and carotid sinus massage with the method of symptoms were performed in patients with syncope and sinus bradycardia, seem to confirm a reflex mechanism as the cause of syncope in most cases. However, a depressed SN automaticity, expressed by much prolonged SN recovery time, suggests a role of SN dysfunction in the origin of syncope.
- Patients with syncope and permanent mild sinus bradycardia, without much prolonged SN recovery time, should be managed as the patients with syncope and normal sinus rate.

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15.1 Sick Sinus Syndrome

The sick sinus syndrome (SSS) is a descriptive term that refers to a constellation of signs and symptoms defining sinus node (SN) dysfunction in a clinical setting. SSS is extensively described in Chap. 22. Summarizing, the most frequent electrocardiographic (ECG) sign is persistent sinus bradycardia (sinus rate <50 beats/min), but even sinoatrial block, sinus pauses, or alternating bradyarrhythmias and tachyarrhythmias can be present. Though bradyarrhythmias are required for the diagnosis, supraventricular tachyarrhythmias, mainly atrial fibrillation and flutter, are present in 40–50 % of patients with SSS requiring hospital assistance [1]. Episodes of alternating bradyarrhythmias and tachyarrhythmias are known as bradycardia–tachycardia syndrome. There is evidence that atrial fibrillation and flutter can lead to remodeling of the SN (besides that of the atria), with subsequent further dysfunction of this node [2, 3]. The factors that disrupt the SN function can be intrinsic or extrinsic. Intrinsic causes of SSS include degenerative fibrosis of the sinoatrial node, ion channel dysfunction, and remodeling of the SN. Historically, the most common intrinsic cause is thought to be age-related, idiopathic degenerative fibrosis of the SN [4]. Recent research and understanding of familial and congenital SSS, however, have shown that an inherited dysfunction of ion channels within the SN also plays a significant part in age-related SSS [3, 5–7]. Remodeling of the SN occurs in heart failure and in atrial fibrillation, and this appears to play a role in the development of SSS for some patients [2, 3, 8]. Extrinsic factors that can mimic or exacerbate SSS include physical training (sports), the use of certain pharmacological agents, metabolic disturbances, and autonomic dysfunction.

Sinus bradycardia can be entirely asymptomatic in young healthy individuals or during sleep. The main physiologic effect of bradycardia is to decrease cardiac output. As long as the changes in stroke volume compensate for the decrease in heart rate, patients with profound bradycardia can remain completely asymptomatic. However, SSS tends to be progressive. Patients with more advanced disease can present with symptoms and signs of end-organ hypoperfusion. Easy fatigability and reduced exercise capacity are common in persistent bradyarrhythmia. In older patients, profound sinus bradycardia may be responsible for the symptoms of heart failure [9]. Subtle symptoms such as irritability, lassitude, inability to concentrate, apathy, confusion, forgetfulness, palpitations, and dizziness are frequent in patients with SSS. Intermittent symptoms such as syncope or presyncope are present in about half of the patients affected by SSS requiring hospital assistance [10, 11]. The diagnosis of SSS requires the presence of ECG abnormalities and clinical symptoms clearly related to SN dysfunction; marked bradycardia, including sinoatrial pauses, are not diagnostic of SSS in the absence of symptoms.

SSS can impair the quality of life; however, it is a relatively benign condition, because total survival and the risk of sudden death of patients with established sinoatrial disorder (irrespective of the symptoms) appear to be similar to that of the general population [12–18]. Moreover, there is no evidence that cardiac pacing prolongs survival in patients with SSS [14, 18]

15.2 Syncope in Patients with Sinus Bradycardia

Though persistent clinical manifestations of bradycardia (due to consequent reduction in cerebral and peripheral perfusion) such as reduced exercise capacity, fatigue, and other subtle symptoms can be expected, it is more difficult to explain the intermittent symptoms such as syncope or presyncope, and the etiology of these symptoms in subjects with persistent mild (40–50 beats/min) sinus bradycardia is uncertain. Theoretically, there are three possible causes of intermittent severe bradyarrhythmia in patients with SSS: (1) exhaustion of intrinsic SN function, (2) an abnormal neural reflex, and (3) prolonged sinus pause, following termination of tachycardia in the bradycardia–tachycardia syndrome. No trial specifically addressed the prevalence of these settings during spontaneous syncope. Some clinical data suggest that a reflex mechanism is more likely to be involved: the course of syncope is very variable from patient to patient; syncope does not recur in more than half of unpaced patients with SSS during a 4-year follow-up. Moreover, not uncommonly, the syncope represents an isolated manifestation [11–13, 19]; syncope recurs in up to 20 % of SSS patients during long-term follow-up, despite adequate pacing [10]; the prognosis does not appear to be different between SSS patients with and without neurologic symptoms [14].

Two studies have specifically evaluated the relationship between syncope and abnormal reflexes in patients with sinus bradycardia [20, 21]. Brignole et al. [20] performed head-up tilt testing (HUT) and carotid sinus massage (CSM) with the method of symptoms in 35 patients with sinus bradycardia and syncope, and compared the results with those obtained in 35 patients with normal sinus rate who were affected by syncope of uncertain origin. The percentage of positive HUT in the subjects with sinus bradycardia was high (54 %), higher than that recorded in the subjects with syncope of uncertain origin (26 %). The percentage of positive CSM in the subjects with sinus bradycardia was also high (60 %) and similar to that observed in patients with syncope of uncertain origin (63 %). Brignole et al. [20] hypothesized that an abnormal neural reflex plays a major role in causing syncope in subjects with SSS. In their study, however, it was not defined whether a SN dysfunction can enhance the cardioinhibitory efferent reflex and therefore predispose to the positivity of these tests (i.e., whether in patients with SSS, "false-positive" responses may occur). For this reason, Alboni et al. [21] studied two groups of patients, group 1 with sinus bradycardia and syncope (25 patients) and group 2 with sinus bradycardia without neurologic symptoms (25 patients). The patients underwent HUT, CSM with the method of symptoms, Holter ECG monitoring, and electrophysiologic study. Age (71 ± 12 and 67 ± 16 years) and prevalence of structural heart disease (76 % and 84 %) did not significantly differ between the two groups of patients. Resting sinus rate, evaluated by standard ECG (44 ± 4 and 46 ± 3 beats/min), corrected SN recovery time (CSNRT), evaluated during the electrophysiologic study (966 ± 947 and 670 ± 674), and Holter monitoring data did not differ significantly. The patients with sinus bradycardia and syncope had a higher prevalence of positive response to HUT (60 % vs. 12 %, $P = 0.001$) and CSM (44 % vs. 24 %, not significant) than those without syncope; overall, 76 % of the patients with

Table 15.1 Prevalence of positive response to carotid sinus massage with the method of symptoms and to head-up tilt testing in patients with sinus bradycardia, with and without the history of syncope [21]

	Sinus bradycardia and syncope (25 pts)	Sinus bradycardia without syncope (25 pts)	*P*
Positive CSM response			
Total positive responses	11 (44 %)	6 (24 %)	NS
Cardioinhibitory or mixed response	11 (44 %)	6 (24 %)	NS
Vasodepressor response	0	0	
Positive HUT response			
Total positive responses	15 (60 %)	3 (12 %)	<0.001
Cardioinhibitory or mixed response	10 (40 %)	2 (8 %)	<0.05
Vasodepressor response	5 (20 %)	1 (4 %)	NS
Positive CSM or HUT response	*19 (76 %)*	*9 (36 %)*	*<0.01*

Abbreviations: *CSM* carotid sinus massage, *HUT* head-up tilt testing, *pts* patients

syncope had at least one positive test versus 36 % of those without syncope ($P=0.01$) (Table 15.1). In the patients with sinus bradycardia and no neurologic symptoms, positive HUT response occurred in 12 %, an incidence slightly higher than that reported in control subjects without syncope (approximately 7 %) [22–28]. In the patients with sinus bradycardia without the history of syncope, a positive CSM with the method of symptoms occurred in a rather high proportion (24 %). During this test, the receptors are stimulated directly, whereas in HUT they are stimulated indirectly. In other studies, where CSM was performed with the method of symptoms, a positive response to this test was observed only in 4 % of control subjects with normal sinus rhythm and no history of syncope [29]. Therefore, the results we obtained in patients with sinus bradycardia and no neurologic symptoms suggest that a SN disorder can predispose to cardioinhibitory responses. However, the incidence of positive response to HUT was much higher in the patients with sinus bradycardia and syncope. The results of the present study, together with those reported by Brignole et al. [20], suggest that in subjects with persistent mild sinus bradycardia, syncope is mainly related to an abnormal neural reflex and that the diseased SN plays a marginal facilitating role in the development of a cardioinhibitory reflex, with the possible exception of the minority of patients with a very prolonged CSNRT time, suggestive of a major depression of SN automaticity [30]. In other words, these results suggest that when in the general population an asymptomatic subject with sinus bradycardia experiences a neurally mediated syncope, he/she is commonly diagnosed as a SSS patient, even if there is not any documented correlation between loss of consciousness and SN dysfunction.

A reflex mechanism of syncope fits well with the unpredictable natural history of syncopal recurrences in subjects with sinus bradycardia and can explain why neurological symptoms have no prognostic relevance in patients with SN dysfunction.

However, another possible mechanism of syncope must be considered, that is, a prolonged pause following the termination of atrial tachyarrhythmias in patients with bradycardia–tachycardia syndrome. We do not know the prevalence of this mechanism of syncope, and a prospective study utilizing the implantable loop recorder should be carried out, but the earlier-mentioned data suggest that a reflex mechanism should be more frequent.

15.3 Syncope and Sinus Bradycardia: What Is the Diagnosis?

Though persistent symptomatic bradycardia clearly defines SSS, the meaning of intermittent severe sinus bradycardia or sinus arrest is less clear. Often, the same event (i.e., intermittent symptomatic sinus arrest) may be diagnosed by one physician as primary cardiac arrhythmia (SSS) and by another as cardioinhibitory reflex syncope. The problem is further complicated by the fact that the diagnosis of intermittent severe bradycardia is often only presumed but not documented by ECG.

From a nosological point of view, "syndrome" is defined as the association of signs and symptoms that have a pathophysiological correlation. Both signs and symptoms are necessary to define a syndrome. Thus, "sick sinus syndrome" should be diagnosed only when intermittent symptoms are clearly correlated with severe bradycardia/asystole, secondary to a diseased SN (cause–effect relationship). In bradycardia patients in whom syncope is the only symptom, the diagnosis of SSS can be made in a minority of patients who show ECG documentation of prolonged pause/s following the termination of a tachycardia or prolonged CSNRT (>800 ms) [18, 30, 31]. In the other cases, the causal relationship between syncope and persistent sinus bradycardia is very weak, and bradycardia might be an unrelated comorbidity accompanying a reflex syncope. In these cases, if HUT or CSM are abnormal, the most appropriate diagnosis appears to be "reflex syncope (vasovagal or carotid sinus syncope) with associated sinus bradycardia" [31].

15.4 Practical Implications

Distinguishing *sick sinus syndrome from vasovagal syncope or carotid sinus syncope with associated sinus bradycardia* has a practical value in the selection of candidates for cardiac pacing. While cardiac pacing is an effective therapy in patients with SN dysfunction and persistent symptoms, its value is more questionable in the latter cases. The effect of cardiac pacing on the incidence of syncope has been investigated in the THEOPACE study, where 107 patients with SSS were randomized to no treatment (control group), oral theophylline, or dual-chamber rate-responsive pacemaker therapy [11]. Twenty-three percent of the patients in the control arm, 17 % in theophylline arm, and 6 % of the pacemaker arm had syncope during a mean follow-up period of 19 months. In patients assigned to pacemaker therapy, the incidence of syncope was lower than in control patients ($P = 0.02$).

However, the observed 17 % absolute reduction in syncope is very low because of the low incidence of syncope in the no-treatment group.

From a practical point of view, subjects with sinus bradycardia and syncope, without other symptoms attributable to SN dysfunction, should undergo autonomic tests (HUT potentiated with nitroglycerin and CSM with the method of symptoms) and electrophysiologic study to assess, as far as possible, the mechanism of syncope. In the presence of depressed SN automaticity (CSNRT > 800 ms), pacemaker implantation could be indicated [18, 30]. If CSNRT is not prolonged and the HUT is positive, the patient should be managed as the patients with reflex syncope and normal sinus rate (see Chaps. 20 and 21). As a general rule, the implantation of a loop recorder could be indicated. While cardiac pacing is rather effective when a reflex asystolic pause is documented at the time of syncopal recurrence, there is no rationale for the use of pacing in patients with dominant vasodepressive syncope [32]. Therefore, also in patients with *reflex syncope with associated sinus bradycardia*, without other symptoms attributable to persistent sinus bradycardia, an attempt to document a spontaneous event should be made before embarking upon permanent cardiac pacing. In any case, it must be underlined that the decision to implant a pacemaker needs to be kept in the clinical context of a benign condition [14], the intention being to avoid intermittent symptoms and not to prolong survival or prevent cardiovascular events.

In the recent 2013 European guidelines on cardiac pacing [18], it is asserted that many syncopal episodes in patients with permanent mild (40–50 beats/min) sinus bradycardia could be due to an abnormal reflex. In patients with SSS, pacemaker implantation is a class I indication, only when there is a clear relationship between the symptoms and SN dysfunction. In patients with intermittent symptoms as syncopal spells, without persistent symptoms attributable to SN dysfunction, autonomic tests and electrophysiologic study are recommended to assess the mechanism of syncope.

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Differential Diagnosis of Vasovagal Syncope: Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome

16

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Key Points

- Fatigue is a frequent symptom in the general population, being reported by up to 50 % of the respondents to large-scale surveys.
- Much of the common symptoms observed in myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS) could be attributed to a dysfunction of the autonomic nervous system.
- Due to sympathetic hyperactivation and/or parasympathetic dysfunction, the body is no longer able to respond to different stressors, which can explain the fatigue, stiffness, pain, exercise intolerance, or sleeping problems.
- The pathophysiological mechanisms of orthostatic intolerance (up to syncope) underlying CFS include hypovolemia, venous pooling, hyperadrenergic states, and lower limb adrenergic neuropathies.
- Cognitive and emotional factors, including behavioral conditioning and amplification, may play a key role.
- CFS and orthostatic intolerance can be managed by a combination of patient education, volume restitution, physical countermaneuvers, graded exercise training, and pharmacotherapy.

16.1 Introduction

Fatigue is a frequent symptom in the general population, being reported by up to 50 % of the respondents to large-scale surveys [1, 2]. It is attributable to underlying systemic diseases such as diabetes, cardiopulmonary disease, or rheumatoid

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arthritis, but may also accompany psychiatric conditions such as depression, panic disorder, or somatization.

The etiology of isolated fatigue or fatigue associated with the symptoms of other minor illnesses is often undiagnosed and poorly treated. The word "fatigue" can have various meanings, including exhaustion, a perceived decrease in the ability to undertake mental or physical activities, delayed recovery after demanding physical exertion, or weariness due to unrefreshing sleep. Self-reported fatigue is typically transient, self-limiting, and explained by prevailing circumstances, but a small minority of subjects experience persistent and debilitating fatigue.

When fatigue cannot be explained by a medical condition such as depression, cancer, infections, or inflammatory disorders, it may be due to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), a clinical diagnosis without any distinguishing physical or routine laboratory findings [3–5]. Attempts have been made to establish whether its etiology is infectious, immunological, neuroendocrinological, psychiatric, or sleep- or malignancy-related, but no definite conclusion has yet been reached, and it seems likely that it is a heterogeneous illness that reflects a common pathway of various pathophysiological abnormalities that manifest themselves with similar symptoms [6–9].

16.2 ME/CFS Diagnostic Criteria

A clinical diagnosis of ME/CFS can only be made when all other possible etiologies of fatigue have been excluded. The Centers for Disease Control and Prevention (CDC) published specific criteria for diagnosing in 1988, which were mainly based on physical symptoms because it was believed that CFS was primarily a viral illness. The definition was broadened in 1994, and the revised CDC criteria have been the most widely accepted ever since [6] (Table 16.1).

In 2003, a Canadian Expert Consensus Panel introduced a case definition of ME/CFS with the compulsory criteria of postexertional malaise, and neurological, neurocognitive, neuroendocrine, autonomic, circulatory, and immune manifestations [7].

The new International Consensus Criteria (ICC) for ME published in 2011 laid down postexertional neuroimmune exhaustion as compulsory [10, 11] (Table 16.2), and proposed abolishing the criterion of chronic fatigue and the name CFS in favor of ME, which refers to the underlying pathophysiology of widespread inflammation and multisystemic neuropathology without mentioning symptoms.

However, there is evidence that the CFS criteria of Fukuda et al. [6] define a heterogeneous population of subjects with chronic fatigue of whom ME patients are a subset. On the basis of the findings of Nacul et al. [12] and Peckerman et al. [13], it is estimated that 40–60 % of subjects with CFS fulfill the stricter ME criteria.

Table 16.1 Centers for Disease Control's Criteria for chronic fatigue syndrome

Clinically evaluated, unexplained, persistent, or relapsing fatigue that is:
Of new or definite onset
Not a result of ongoing exertion
Not alleviated by rest
Results in a substantial reduction in previous levels of occupational, social, or personal activity
Four or more of the following symptoms that persist or recur during six or more consecutive months of illness and that do not predate the fatigue:
Self-reported impairment of short-term memory or concentration
Sore throat
Tender lymph nodes
Muscle pain
Multijoint pain without swelling or redness
Headaches of a new type, pattern, or severity
Unrefreshing and/or interrupted sleep
Postexertion malaise (a feeling of general discomfort or uneasiness) lasting more than 24 h
Exclusion criteria:
Active, unresolved, or suspected disease that is likely to cause fatigue
Psychotic, melancholic, or bipolar depression (but not uncomplicated major depression)
Psychotic disorders
Dementia
Anorexia or bulimia nervosa
Alcohol or other substance misuse
Severe obesity

Officially defined by CDC in 1988 and revised in 2001 (CDC 2001)

All in all, though some authors still prefer to use the looser definition of CFS, others prefer the stricter criteria based on postexertional malaise [5, 13, 14].

16.3 Prevalence of ME/CFS

It has been estimated that the prevalence of ME/CFS in the United States has been relatively stable at 0.4 % over the last 10 years [15–17], which means that it affects more than 1.3 million people, who not only have a quality of life that is similar to that of patients with congestive heart failure (CHF) [18], but are also unlikely to recover after they have had the illness for more than 3 years [19].

ME/CFS often coexists with conditions such as irritable bowel syndrome (IBS), and temporomandibular disorder (TMD) and fibromyalgia (FM) [20, 21], a syndrome characterized by widespread pain and somatic symptoms [22]. It seems that 20–70 % of FM patients meet the criteria for ME/CFS [23, 24], and that 35–70 % of the subjects with ME/CFS-like illnesses also have FM [25, 26].

Table 16.2 Myalgic encephalomyelitis: International Consensus Criteria

Myalgic encephalomyelitis is an acquired neurological disease with complex global dysfunctions. Pathological dysregulation of the nervous, immune, and endocrine systems, with impaired cellular energy metabolism and ion transport are prominent features.
Although signs and symptoms are dynamically interactive and causally connected, the criteria are grouped by regions of pathophysiology to provide general focus
A patient will meet the criteria for postexertional neuroimmune exhaustion (A), at least one symptom from three neurological impairment categories (B), at least one symptom from three immune/gastrointestinal/genitourinary impairment categories (C), and at least one symptom from energy metabolism/transport impairments (D)
A. *Postexertional neuroimmune exhaustion (Compulsory)*
1. Marked, rapid, physical, and/or cognitive fatigability in response to exertion
2. Postexertional symptom exacerbation
3. Postexertional
4. Recovery period is prolonged
5. Low threshold of physical and mental fatigability (lack of stamina) results in a substantial reduction in pre-illness activity level
B. *Neurological impairments*
At least one symptom from three of the following four symptom categories:
1. *Neurocognitive impairments*
(a) Difficulty processing information
(b) Short-term memory loss
2. *Pain*
(a) Headaches
(b) Significant pain
3. *Sleep disturbance*
(a) Disturbed sleep patterns
(b) Unrefreshed sleep
4. *Neurosensory, perceptual, and motor disturbances*
(a) Neurosensory and perceptual
(b) Motor
C. *Immune, gastrointestinal, and genitourinary impairments*
At least one symptom from three of the following five symptom categories:
1. *Flulike symptoms* may be recurrent or chronic and typically activate or worsen with exertion
2. *Susceptibility to viral infections* with prolonged recovery periods
3. *Gastrointestinal trac*t
4. *Genitourinary*
5. *Sensitivity to food, medications, odors, or chemicals*
D. *Energy production/transportation impairments: At least one symptom*
1. Cardiovascular
2. Respiratory
3. Loss of thermostatic stability
4. Intolerance of extremes of temperature

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16.4 Causes of ME/CFS

Though considerable progress has been made, there is still no unifying construct concerning some of the major pathogenetic mechanisms of ME/CFS. Its probably complex etiology is unclear and may involve multiple interacting factors, leading to various subcategories of the illness. These and the presence of many psychiatric comorbidities have led some experts to question whether it has any organic etiology at all, and current research is investigating the involvement of the immune and adrenal systems, genetics, stress-related syndromes, and impaired neuropsychological functions.

As many of the symptoms are the same as those of viral infections, some physicians have hypothesised a postinfectious etiology: one theory is that it is caused by chronic Epstein–Barr virus infection, but there is no concrete evidence of any association with specific viruses [27].

Genetic susceptibility is supported by the findings of one study showing that patients with exercise-induced CFS differently express certain genes that play a role in metabolism and immune responses [28], and another study has shown an association between specific gene mutations, ME/CFS and some viral infections associated with CFS [29].

The fact that ME/CFS is often associated with depression has led many physicians to believe that it is a purely somatic illness [30], but there is no evidence supporting this conclusion.

The risk of developing ME/CFS may be increased as much as six times by a childhood trauma, which may reduce resilience and also increase the risk of adrenal system dysfunction [31]. It is also important to note that social support systems tend to be less reliable in the case of subjects with CFS [32], the treatment of which is less likely to be successful in the socially maladjusted children [33].

One study has found that cortisol levels are about 5 μg/dL (137.94 nmol/L) less in CSF patients than in patients without CFS [34]. This is probably due to an impairment in adrenal cortex responsiveness to adrenocorticotropic hormones rather than to hypothalamopituitary dysfunction [35], but it is not clear if this is caused by infection, genetics, or a childhood trauma, or a combination of these and possibly still unknown factors.

Patients with ME/CFS often have vascular abnormalities or impaired autonomic nervous system regulation of the vascular system, particularly in response to standing [36, 37], which explains the frequent association of CFS and dysautonomia: 29 % of CFS patients have postural orthostatic tachycardia syndrome (POTS), and almost 50 % of patients with POTS experience fatigue.

ME/CFS may be considered one of the so-called central sensitivity syndromes (CSS), an overlapping group of similar syndromes related by the common mechanism of central sensitization (CS), that is, the hyperexcitation of central neurons as a result of various synaptic and neurotransmitter/neurochemical activities [38, 39] that manifests itself in the form of hypersensitivity to various noxious (e.g., pressure and heat) and nonnoxious stimuli (e.g., touch). It is therefore possible that specific peripheral fatigue and pain pathways in ME/CFS patients are sensitized by still

unknown mechanisms (infections, and physical and/or psychological stressors) [40–42], continuous inputs from which maintain the state of chronic fatigue and chronic widespread pain.

There is a close link between chronic fatigue and what is known as Gulf War illness (GWI). More than 25 % of the 697,000 veterans who served in the 1990–1991 war in the Persian Gulf and 15 % of nondeployed personnel have developed a symptom complex of widespread pain, fatigue, headache, and gastrointestinal, bladder, and other "functional" nociceptive and interoceptive complaints [43]. These veterans were exposed to a wide variety of substances (binary nerve agents, acetylcholinesterase inhibitors, organophosphates, other pesticides, and herbicides) that may have given rise to their symptoms [44]. The condition was initially called chronic multisymptom illness (CMI), and defined as the presence of two or more symptoms of fatigue, and musculoskeletal or mood/cognitive dysfunctions, for more than 6 months. In one study [44], all of the veterans who met the CMI criteria also met the criteria for CFS (odds ratio 40.6), and 52 % met the criteria for FM (odds ratio 2.32), thus indicating extensive symptom overlap.

Impaired neuropsychological function [45] and abnormal brain MR scans [46] in CFS patients without a concomitant psychiatric illness suggest the brain as the target organ producing fatigue. Various brain imaging studies have shown that blood flow is reduced in the frontal, parietal, temporal, subcortical, and periventricular regions of the brain [47, 48], and, though the significance of these findings is unknown, these regions may play a role in modulating fatigue and pain.

16.5 Clinical Examinations and Differential Diagnosis

Patients with chronic fatigue should have their history taken and undergo a physical examination aimed at identifying the most bothersome symptoms, or symptoms that may indicate a more serious underlying illness on the basis of the guidelines of the National Institute for Health and Clinical Excellence (NICE) [49]. They should also undergo an evaluation of their mental status, including an investigation of depression, which is present in 39–47 % of CFS patients.

Laboratory tests cannot be used for diagnostic purposes, but they can rule out other conditions that preclude a diagnosis of CFS [50]. The CDC recommends an initial urinalysis, complete blood count, a comprehensive metabolic panel, and the measurement of phosphorus, thyroid-stimulating hormone, and C-reactive protein levels [50]. NICE also recommends using immunoglobulin, endomysial antibodies to screen for celiac disease and, if indicated by the patients' history or physical examination, urine drug screening, and rheumatoid factor and antinuclear antibody testing [49]. Determining viral titers is not recommended unless the patient's history suggests an infectious process, because they neither confirm nor exclude a diagnosis of ME/CFS.

ME/CFS and Chronic Orthostatic Intolerance

Orthostatic intolerance is defined as an inability to remain upright without experiencing severe signs and symptoms such as hypotension, tachycardia, lightheadedness, pallor, fatigue, weakness, and syncope, and may take the form of overt dysautonomia, presyncope symptoms, vasovagal syncope, or orthostatic tachycardia [51]

Patients with ME/CFS often show clinical features such as increased sweating, pallor, sluggish pupillary responses, gastrointestinal symptoms, and more frequent micturition [52, 53]. It has been found that neurally mediated syncope and POTS are prevalent in adults and children with CFS, and suggested that the hemodynamic mechanisms underlying these autonomic conditions play a role in the pathophysiology of ME/CFS.

POTS, which has a female:male ratio of 5:1 and is one of the most frequent forms of chronic orthostatic intolerance in the general population, is a disabling condition characterized by excessive tachycardia and symptoms upon standing that are greatly improved by lying down, but may also be accompanied by sometimes chronic and overwhelming nonorthostatic symptoms such as fatigue. There is a substantial overlap between POTS and ME/CFS [54–57]: it has been found that the prevalence of POTS in CFS patients ranges from 19 to 70 %, and that the prevalence rates of chronic fatigue and ME/CFS are respectively 48–77 % [58] and 17–23 % [59, 60]. It has also been suggested that the pathophysiological mechanisms underlying both conditions include increased sympathetic activation and low blood volumes [61–63].

One characteristic of all chronic fatigue disorders is persistent activation of the sympathetic nervous system [64, 65] revealed as organ-specific catecholamine spillover [66–68], muscle sympathetic nerve activation [67], and high plasma catecholamine levels [68]. Sympathetic activation during exercise is also increased [69]. Tests of autonomic function suggest that patients with ME/CFS show reduced vagal and sympathetic responsiveness to standardized laboratory stimuli (paced breathing, standing up) and a walking test [55, 70], and that these alterations are inversely related to their overall fitness [71]. Fatigued patients also show reduced autonomic responsiveness (an increase in sympathetic drive and a decrease in vagal modulation) to standardized mental stressors [72]. These findings highlight the fact that patients with ME/CFS have a diminished cardiac response to exercise [73], which may contribute to their physical fatigue and inactive lifestyles [74], though similarly reduced autonomic cardiac responsiveness can also be detected in other illnesses such as arterial hypertension or myocardial infarction. Generally, most patients with unexplained chronic fatigue seem to present with resting sympathetic hyperactivity and reduced vagal modulation [75].

There are different ways for evaluating autonomic function. One is measuring heart rate variability (HRV), that is, analyzing the variability of time between successive R waves (R–R interval analysis). [76–79].

In a recent study by Mees et al. [80], 16 case–control studies were included, 10 comparing FM patients to controls and 6 comparing CFS patients to controls. Methodological quality was moderate to good. Both time domain and frequency

domain measurements were used. The majority of the researchers observed lower HRV in FM patients compared to healthy control persons, as well as increased sympathetic activity and a blunted autonomic response to stressors. Resistance physical training improved HRV in FM patients. In ME/CFS patients, HRV was only reduced during sleep.

A variety of published papers concerning the relationship between chronic orthostatic intolerance and ME/CFS have recently been reviewed by Van Cauwenbergh et al. [81] and Martinez-Martinez et al. [82].

A multitude of studies have described the responses to a head-up tilt test. La Manca et al. [83] found that CFS patients had a higher heart rate and smaller pulsative systolic area at baseline, and that 11 out of 39 showed an abnormal tilt response. Timmers et al. [84] also found a higher heart rate in ME/CFS patients, 10 of 36 of whom showed an abnormal tilt response. When these patients were divided on the basis of their tilt responses, La Manca et al. [83] observed lower pulse pressure and a smaller pulsative systolic area in the ME/CFS patients with an abnormal response, and Timmers et al. [84] observed an albeit nonsignificantly higher number of patients with ME/CFS with orthostatic intolerance. A one-way comparison during the supine baseline phase of a study by Yamamoto et al. [85] revealed only a smaller mean respiration rate interval in patients with ME/CFS, whereas during the tilt, the respiration rate interval and its standard deviation, the amplitude of low-frequency component, and the aperiodic fractal spectral components were all reduced. However, comparison of the baseline and posttilt findings in the two groups showed that only the aperiodic fractal spectral components were significantly decreased in the patients with ME/CFS.

Naschitz et al. [86, 87] observed no differences between patients with ME/CFS and controls in the supine position, but, during the tilt, there were between-group differences in diastolic and systolic blood pressure, heart rate, respiration rate per minute, and end-tidal CO_2; furthermore, the patients, but not the controls, reached the predefined end points [86]. At the end of the tilt, the patients with ME/CFS had systolic, diastolic blood pressure, and heart rate significantly higher [87]. De Becker et al. [88] found no differences during the supine phase, but the patients had higher heart rates, and showed greater changes in heart rate and low-frequency power in the tilt position. The study of Duprez et al. [89] found significantly lower supine BP variability (total, low-frequency, and high-frequency variances) in ME/CFS patients, but these differences disappeared in the standing position; analysis of RR interval variability did not reveal any major alterations in autonomic function among the ME/CFS patients. Schondorf et al. [54] identified a higher resting heart rate, but no other differences: 60 % of the patients with ME/CFS did not have orthostatic intolerance, and the female controls had a lower diastolic blood pressure. Jones et al. [90] found no differences in orthostatic instability between their ME/CFS patients.

There is therefore good evidence that patients with CFS have a higher heart rate in the tilt position, but the lack of consistency between studies makes it difficult to draw any firm conclusions regarding the other parameters.

Yataco et al. [91], Bou-Holaigah et al. [56], and Razumovsky et al. [92] all used isoproterenol infusions to study the autonomic nervous system of ME/CFS patients

and found that most of them had abnormal responses. Yataco et al. [91] found differences in heart rate, heart rate variability and in patients with positive tilt between the supine position and the first 5 min and 10–15 min at the end of the upright tilt. They concluded that heart rate variability indices do not indicate any difference in autonomic function between patients and controls. Bou-Holaigah et al. [56] found a slower heart rate and lower systolic and diastolic blood pressure only at the end of the tilt, and concluded that ME/CFS is closely associated with neurally mediated syncope, which could have important implications for the management of ME/CFS. Razumovsky et al. [92] found that patients with ME/CFS had a higher heart rate at baseline and during the tilting phase, which also led to the appearance of symptoms of orthostatic intolerance, including syncope. In comparison with baseline, there was a greater increase in the pulsatility index and cardiovascular resistance, and a decrease in cerebral blood flow velocity (CBFV).

All three studies showed a different heart rate and decreased blood pressure at the end of the tilt test [81].

Some studies have used other autonomic tests such as rhythmic deep breathing and the Valsalva maneuver. The results showed no differences in rhythmic deep breathing between patients with ME/CFS and healthy controls. Sisto et al. [93] found a higher vagal power with a lower breathing rate in both sitting and standing positions, which followed the same decrease for patients with ME/CFS as controls. This decrease was lower in patients with ME/CFS, with the exception at a rate of 18 breaths/min in the standing position. Jones et al. [90] showed a higher diastolic blood pressure in the supine position in the ME/CFS group, a lower diastolic blood pressure in neural mediated syncope patients after immediate standing, in comparison with postural orthostatic tachycardia and subjects with normal tilt tests. In the study by Hoad et al. [36], maximum heart rate on standing was significantly higher in the CFS/ME group, compared with the controls. Of the CFS/ME group, 27 % (16/59) had POTS compared with 9 % in the control population ($P=0.006$). This difference was predominantly related to the increased proportion of those in the CFS/ME group whose heart rate increased to >120 beats/min on standing ($P=0.0002$). Increasing fatigue was associated with increase in heart rate ($P=0.04$). Hollingsworth et al. [94] found a higher rate of loss of consciousness, positive tilt tests and POTS, and higher Orthostatic Grading Scale (OGS) scores in the ME/CFS group. OGS scores were higher in the subgroup of patients with an "abnormal left ventricular work index" than in those with a "normal left ventricular work index." Soetekouw et al. [95] observed higher diastolic and systolic blood pressure in the ME/CFS group when implementing the Valsalva maneuver; the handgrip and cold pressor tests did not lead to any significant difference in systolic or diastolic blood pressure, but the latter did lead to an increase in the maximal heart rate that approached significance. The mental arrhythmic test led to a smaller increase in heart rate (i.e., difference between maximal and minimal heart rate) in the ME/CFS group.

The results of these studies showed no differences in rhythmic deep breathing between patients with CFS and healthy controls, but provide moderate evidence that patients with ME/CFS are more likely to experience excessive orthostatic tachycardia on standing.

Two studies have measured autonomic function during sleep in CFS patients. Boneva et al. [96] found a significantly increased HR ($P<0.0004$), a shorter mean RRI ($P<0.0004$), reduced HRV, and higher norepinephrine levels ($P=0.05$). Burton et al. [97] found significantly lower HRV ($P<0.006$). There is therefore moderate evidence that patients with ME/CFS have reduced values of HRV during sleep.

Natural History

It is not surprising that patients with such a debilitating disease frequently ask whether their symptoms are likely to improve with time, but little is known about the natural history of fatigue and the other symptoms affecting subjects with ME/CFS. In a recent study, Jones et al. [98] evaluated the symptom assessment instruments available in 2005 and 4 years later (2009) for 74 % of ME/CFS patients. Fatigue impact scale (FIS), hospital anxiety (HAD-A), and depression scale (HAD-D) scores significantly improved during follow-up, whereas Epworth sleepiness scale (ESS) and orthostatic grading scale (OGS) scores remained stable. FIS improved in 29⁄74 subjects (39 %), and by ≥10 points in 19 individuals (26 %); it worsened by ≥10 points in 33⁄74 subjects (45 %). Multivariate analysis showed that the independent predictors of current fatigue were FIS in 2005, HAD-D in 2009, and OGS in 2009. Current fatigue was independently associated with the current autonomic symptom burden, current depression, and change in anxiety during follow-up. These findings may have implications for targeted symptom management in patients with ME/CFS.

Comorbidities

Patients with ME/CFS are frequently diagnosed as having concomitant postural tachycardia syndrome (POTS), a finding that suggests a shared pathogenesis [99]. ME/CFS and POTS comorbidity (CFS–POTS) was observed in 33/306 patients (11 %), who were significantly younger ($P<0.001$), had a shorter illness duration ($P=0.034$), experienced greater task difficulty ($P=0.002$), and were able to stand for significantly shorter periods than the patients with CFS alone ($P<0.001$). They also had significantly lower baseline diastolic blood pressure ($P=0.002$), a significantly higher heart rate, and lower pulse pressures at each standing measurement. The hemodynamic and demographic differences between the two groups of patients suggest that those with POTS form a distinct subgroup of the ME/CFS population.

Another study has also clearly identified the subgroups of patients with ME/CFS alone or with POTS [100]. The latter were younger ($P<0.0001$), less fatigued ($P=0.002$), less depressed ($P=0.01$), and experienced less daytime hypersomnolence ($P=0.02$); they also showed greater orthostatic intolerance ($P<0.0001$) and autonomic dysfunction. A combination of an ESS scale score of ≤9 and an OGS score of ≥9 accurately identified the patients with POTS with 100 % positive and negative predictive values.

Conclusions

ME/CFS is a heterogeneous, disabling disorder, characterized by persistent or relapsing unexplained fatigue, accompanied by characteristic physical, constitutional, and neuropsychological symptoms lasting for >6 months [6, 11, 101, 102]. Its etiology and pathophysiology remain unknown, but it has been suggested that autonomic nervous system abnormalities play a role. Patients often show clinical features of autonomic dysfunction such as orthostatic intolerance (up to a loss of consciousness), increased sweating, pallor, sluggish pupillary responses, gastrointestinal symptoms, and frequent micturition. It has been found that neurally mediated syncope leading to loss of consciousness and POTS are prevalent in both adults and children with ME/CFS, and it has been suggested that the hemodynamic mechanisms underlying these autonomic conditions play a role in the pathophysiology of ME/CFS and contribute to its symptoms.

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Differential Diagnosis of Vasovagal Syncope: Fibromyalgia

17

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Key Points

- Fibromyalgia (FM) can be considered a mixture of symptoms due to genetic predisposition, stress-related factors, and alterations in various parts of the central nervous system, including the pain-processing pathways (centralized pain), the hypothalamic–pituitary–adrenal axis, and the autonomic nervous system.
- Many FM patients complain of symptoms like palpitations and fatigue and frequently describe the inability to stand for prolonged times without symptoms.
- FM is a sympathetically maintained pain syndrome showing relentless sympathetic hyperactivity.
- FMs are more likely than matched controls to exhibit vasovagal syncope with vasoinhibition when tilt table testing is performed.
- Although FM syndrome is defined by chronic widespread pain, tenderness, and disabling fatigue, additional symptoms, including dizziness, lightheadedness, and vasovagal syncope are often reported.

17.1 Introduction

Fibromyalgia (FM) syndrome is a complex and challenging condition for healthcare systems worldwide. A chronic disease of unknown etiology, it is characterized by widespread pain and symptoms that may include fatigue, sleep disturbances, bowel and bladder disorders, mood disorders, neurocognitive impairment, presyncope, and syncope [1].

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It can develop at any age, and is similarly prevalent in different countries, cultures, and ethnic groups with a significant predominance of women. The recorded population prevalence rates range from 2 to 8 %, depending on the diagnostic criteria used [2, 3].

Emerging evidence indicates that increased pain processing within the central nervous system plays a primary pathophysiological role. Recent studies have identified distinct FM subgroups on the basis of their clinical, neurochemical, and neuroendocrinological abnormalities, including increased cerebrospinal fluid levels of substance P and excitatory amino acids, and functional anomalies in the hypothalamic–pituitary–adrenal (HPA) axis and the sympathoadrenal (autonomic nervous) system [4].

17.2 Diagnosis of Fibromyalgia

Originally called fibrositis and generally defined as widespread pain [5], Yunus et al. called it fibromyalgia in 1981, and proposed a set of diagnostic criteria including tender points and the presence of various symptoms [6]. In 1990, the American College of Rheumatology (ACR) published the first criteria differentiating FM and other chronic widespread pain syndromes (widespread pain for at least 3 months and the presence of 11 out of 18 tender points) [7], but these were research classification criteria and never intended to be used in clinical practice, although they have been extensively used as such (Table 17.1).

Twenty years later, new and presumably improved ACR preliminary FM criteria were published [8] in response to criticisms that the presence of different tender points cannot be an objective assessment of whole-body pain [9].

FM was therefore defined as a complex multidimensional pain disorder [10] with the inclusion of symptoms such as fatigue, stiffness, depression, and cognitive problems. Syncope may be present. Given newer diagnostic criteria, the disease was characterized by a female:male ratio of 2:1, similar to other chronic pain conditions.

The new 2010 ACR criteria [11] are entirely symptom-based and simplified the clinical diagnosis by removing the need for a tender point evaluation, thus leading to the recognition of a female:male ratio of 2:1, which is similar to that of other chronic pain conditions. Nonetheless, the items were further modified in 2011 in order to allow their complete self-administration and create a questionnaire suitable for epidemiological studies, although some authors believe that these criteria will lead to an overestimate of FM diagnoses. These criteria include a self-report survey concerning the locations of pain that is administered using a single piece of paper [1], and the patients are also asked about the presence and severity of symptoms such as fatigue, sleep disturbances, memory difficulties, headaches, bowel habits, and problems of mood.

Table 17.1 The 1990 criteria for the classification of fibromyalgia*

1. *History of widespread pain*
Definition. Pain is considered widespread when all of the following are present: pain in the left side of the body, pain in the right side of the body, pain above the waist, and pain below the waist. In addition, axial skeletal pain (cervical spine or anterior chest or thoracic spine or low back) must be present. In this definition, shoulder and buttock pain is considered as pain for each involved side. "Low back" pain is considered lower segment pain
2. *Pain in 11 of 18 tender point sites on digital palpation*
Definition. Pain, on digital palpation, must be present in at least 11 of the following 18 sites:
Occiput: Bilateral, at the suboccipital muscle insertions
Low cervical: Bilateral, at the anterior aspects of the intertransverse spaces at C5-C7
Trapezius: Bilateral, at the midpoint of the upper border
Supraspinatus: Bilateral, at origins, above the scapula spine near the medial border
Second rib: Bilateral, at the second costochondral junctions, just lateral to the junctions on upper surfaces
Lateral epicondyle: Bilateral, 2 cm distal to the epicondyles
Gluteal: Bilateral, in upper outer quadrants of buttocks in anterior fold of muscle
Greater trochanter: Bilateral, posterior to the trochanteric prominence
Knee: Bilateral, at the medial fat pad proximal to the joint line
Digital palpation should be performed with an approximate force of 4 kg. For a tender point to be considered "positive" the subject must state that the palpation was painful. "Tender is not to be considered 'painful'"

Reproduced with permission from [7]
*For classification purposes, patients will be said to have fibromyalgia if both criteria are satisfied. Widespread pain must have been present for at least 3 months. The presence of a second clinical disorder does not exclude the diagnosis of fibromyalgia [7]

17.3 What Causes Fibromyalgia?

The causes of FM are unknown [12] and can vary widely. The most likely environmental factors are certain types of infections (e.g., Epstein-Barr virus, Lyme disease, Q fever, viral hepatitis), traumas (road accidents) [13, 14], and psychological stress [15], but patients are also likely to have a history of headaches, dysmenorrhea, temporomandibular joint disorder, chronic fatigue, irritable bowel syndrome and other functional gastrointestinal disorders, interstitial cystitis/pain, full-bladder syndrome, endometriosis, and other regional pain syndromes (especially back and neck pain) [1].

FM can be considered a mixture of symptoms due to genetic predisposition [16], stress-related factors, and alterations in various parts of the central nervous system (CNS), including the pain-processing pathways (centralized pain), the HPA axis, and the autonomic nervous system (ANS) [4].

"Centralized pain" is the term now used to describe any CNS dysfunction or pathology that may contribute to the development or maintenance of chronic pain, including the psychosocial aspects of pain perception [1, 4, 17]. It refers to a process in which pain, primarily due to peripheral nociceptive inputs, is subsequently amplified by central factors, and so predisposed individuals feel more pain than would normally be expected [13]. There is increasing evidence that the characteristics often attributed to FM actually represent a broader "pain-prone phenotype": being female, an early-life trauma, a personal or family history of chronic pain, a personal history of other centrally mediated symptoms (insomnia, fatigue, memory problems, mood disturbances) and cognitions (such as catastrophizing) are common to subsets of subjects with any chronic pain state, and predict those who are more likely to develop chronic pain [13].

Family members of FM patients may also have a history of chronic pain [18], and it is known that the genes associated with a greater or lesser frequency of chronic pain or pain sensitivity regulate the breakdown of pain-sensitivity-modulating neurotransmitters [19].

17.4 Relevant Features of Fibromyalgia

Pain

Pain is a defining feature of fibromyalgia [20, 21]. About two-thirds of the patients state that they "hurt all over"; this symptom has been found to be useful in differentiating FM from other conditions [22].

Pain may be described as any combination of burning, tingling, shooting, stabbing, deep aching, sharp and feeling bruised all over [23]. Some authors, using an adapted McGill Pain Questionnaire, found that pain in FM had a greater spatial distribution and involved a greater number of pain descriptors compared to other pain syndromes [24].

Fatigue

Fatigue is quite common in FM; it is generally worse in the morning and patients often awaken feeling more exhausted than when they went to bed. Moderate or severe fatigue occurs in about 75–90 % of patients [25, 26]. Patients will typically describe their fatigue using the expression, "I'm always tired." Other descriptors for fatigue include exhaustion, tiredness, lack of energy, and sometimes, a global feeling of general weakness.

Nonrestorative Sleep

About 75 % of patients describe sleep disturbances that may include early, middle, or late insomnia; hypersomnia; frequent awakening; light sleep with irregular diurnal

rest; or reversed or chaotic sleep rhythms. Poor sleep may aggravate pain and may also contribute to disturbed sleep. There is a relationship between poor sleep and pain, and sleep disturbances are important in the genesis of tender points [27, 28].

Neurocognitive Disturbances

Impaired concentration and short-term memory consolidation, reduced performance speed, inability to multitask, distractibility, and cognitive overload are all present. Complaints of cognitive "fog" (fibro-fog) or simple confusion, linguistic performance impairment, dyslexia when fatigued, and difficulty with writing, reading, mathematics, word retrieval, and speaking are especially common. It is easy for patients to lose track of things and to forget many things [29, 30].

Psychiatric Disorders

Several studies provide evidence that psychiatric disorders occur at significantly higher rates in subjects with FM compared with other pain patients or healthy controls. Studies examining psychiatric comorbidity in community samples of subjects with FM found elevated levels of psychopathology [31, 32], although psychiatric illness is not a necessary factor in the etiopathogenesis of FM.

Autonomic and Neuroendocrine Manifestations

Cardiac arrhythmias, dizziness, light-headedness, vertigo, syncope, sicca syndrome, temperature instability, heat or cold intolerance, and intestinal and bladder motility disturbances may characterize fibromyalgia [33].

17.5 Ortostathic Intolerance (OI) and Fibromyalgia

Orthostatic intolerance (OI) refers to a variety of symptoms that occur upon standing. It physiologically occurs in humans because standing up is a fundamental stressor that requires rapid and effective circulatory and neurological compensation in order to maintain blood pressure, cerebral blood flow, and consciousness. The main complaint is light-headedness, dizziness or presyncope, but other increasingly recognized symptoms include headache, fatigue, visual disturbances, and cognitive impairment [2].

OI characterizes different types of dysautonomias such as those associated with orthostatic hypotension (in diabetic and alcoholic neuropathies, Parkinson's disease, Systemic Multiple Atrophy) and the postural orthostatic tachycardia syndrome (POTS) [34], which, conversely, is connected to normal blood pressure values during standing.

POTS is by far the most common form of OH in the young. There are daily symptoms, which last for several months. HR shows an exaggerated increase with the upright position [35].

Symptoms in POTS patients include light-headedness, shortness of breath, palpitations, tremulousness, chest discomfort, headache, visual disturbances, mental clouding ("brain fog"), and nausea which are shared by FM.

Notably, patients with POTS may meet diagnostic criteria for fibromyalgia syndrome. For example, similarly to POTS patients (~30 %) only a minority of fibromyalgia patients complain of frank vasovagal syncope, although daily or almost daily presyncope occurs. Chest pain is common, but almost never due to coronary artery obstruction in both diseases. Significant exercise intolerance and extreme fatigue, particularly during daily activities are common to both disorders.

17.6 Fibromyalgia and Vasovagal Syncope

Many FM patients complain of symptoms like palpitations and fatigue and frequently describe the inability to stand for prolonged times without symptoms [36]. Such symptoms point to excessive heart rate increments on standing and are related to abnormalities of the ANS [37].

Different groups of investigators have described sympathetic nervous system dysfunction, potentially leading to syncope, in patients suffering from FM. From the literature review, a clear pattern of sympathetic abnormalities in FM emerges: basal sympathetic hyperactivity accompanied by blunted sympathetic response to different types of stressors.

The suggestion that FM is a sympathetically maintained pain syndrome is based on controlled studies showing relentless sympathetic hyperactivity in FM patients, and that their pain is submissive to sympathetic blockade and rekindled by norepinephrine injections.

Most studies looking for autonomic performance in FM have used heart rate variability (HRV) analysis as a probing instrument [38].

Martinez-Lavin [39] used a tilt table to test 19 FM patients, and found a lower increase in the low-frequency component of HRV that was interpreted as indicating a diminished sympathetic response. In a further study [40] he found that SDNN, SDANN, and pNN50 (but not MSSD) were reduced in comparison with controls, thus indicating a reduction in vagally mediated HRV; the patients also lost the circadian variation seen in the controls, and showed no nocturnal increase in the high-frequency components but a continuous predominance of low-frequency band oscillations [40]. The authors concluded that patients with FM have a combination of circadian sympathetic hyperactivity and a lack of additional sympathetic responses to stress.

Another "functional" measure of the integrity of the autonomic nervous system is to perform tilt table testing. Several groups have demonstrated that patients with FM are more likely than matched controls to exhibit vasovagal syncope with vasoinhibition when tilt table testing is performed. Bou-Houlaigh et al. [41]

demonstrated an abnormal response to 45 min of 70° tilt in 60 % of patients and none of the controls. After administration of isoproterenol infusions, this rate increased to 95 % in patients and 40 % in controls.

In another study [42] that used a similar tilt table testing paradigm, but did not administer an iso-proterenol infusion, Clauw et al. demonstrated that 19 % of the patients with FM had a positive tilt table test, as compared with 9 % of controls.

Based on direct recordings of the post-ganglionic sympathetic fibers activity (muscle sympathetic nerve activity, MSNA), Furlan et al. [43] suggested that patients with FM had an overall increase of sympathetic activity and a reduction of cardiac vagal modulation in recumbent position, compared with healthy controls. Moreover, these authors showed that the indices of baroreflex modulation of heart rate and muscle sympathetic nerve activity were similar in patients and controls at rest suggesting that the enhanced sympathetic activity of the heart and vessels observed in FM is unlikely to be due to a failure of the inhibitory modulation exerted by arterial baroreceptors, but rather it seems to be the result of a primary increase of central sympathetic drive. Notably, FM patients showed a higher rate of vasovagal syncope during tilt compared to healthy controls. This was attended by a lack of increase of MSNA and LFSAP (low-frequency component of systolic arterial pressure variability, an index of vascular sympathetic modulation) during tilt, suggestive of an insufficient vasoconstrictor drive to the vessels during the upright position.

A recent study evaluated nocturnal HRV parameters as potential FM biomarkers [44]. Nocturnal HRV indices indicative of sympathetic predominance were significantly different in FM women when compared to healthy individuals. In FM patients, these HRV parameters correlated with several symptoms including pain severity.

A microneurography study by Elam et al. [45] found no differences in muscle sympathetic nerve activity (MSNA) between FM patients and healthy controls in the recumbent position or during cold pressor stimulation, whereas the results of other studies indicate increased sympathetic activity on the grounds that a selective sympathetic blockade induced by guanethidine reduced pain and the number of tender points [46].

In a recent paper, a group of patients with VVS were evaluated for FM symptoms; 16 % had concomitant fibromyalgia. Significantly, all fibromyalgia cases were female [47]. This subgroup of fibromyalgia subjects had more secretomotor complaints (mainly dry eyes and dry mouth) and more bowel constipation than the remainder of the group. Also in this subgroup of fibromyalgia subjects, several significant associations were found between age, blood pressure, number of syncopal episodes, constipation, insomnia, pupillomotor impairment, and disability. In contrast, no correlations were found in the subgroup of fainters without FM.

Conclusions

Although FM syndrome is defined by chronic widespread pain, tenderness, and disabling fatigue, additional symptoms, including dizziness, light-headedness and vasovagal syncope are often reported. In FM, a dysfunction of the ANS is thought to be the underlying etiopathogenetic mechanisms accounting for the symptoms arising during postural changes including an excessive rate of vasovagal syncope.

POTS is the most common form of orthostatic intolerance without associated orthostatic hypotension. It can be frequently detected in FM patients and is often associated with fatigue, sleep abnormalities, and migraine headaches.

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Part V

Prognosis and Treatment

Risk Stratification and Prognosis of Vasovagal Syncope in the Emergency Department

18

Matthew J. Reed and Giorgio Costantino

Key Points

- ED assessment of possible syncope patients follows a three-step approach: Syncope should be confirmed via a detailed history, underlying causes should be identified and treated, and finally risk stratification should take place using clinical judgment, a risk score, or a clinical decision rule.
- Uncomplicated vasovagal syncope is suggested when there are no features that suggest an alternative diagnosis and no features suggestive of a cardiac cause. Posture, provoking factors, and prodromal symptoms are most predictive of vasovagal syncope.
- Most ED diagnostic problems are caused by patients with atypical vasovagal syncope (i.e., patients without any trigger or prodrome), and patients with symptoms suggestive of vasovagal syncope but with other concerning comorbidities.
- Atypical vasovagal syncope can be defined as a TLoC, not preceded by an evident trigger, positive tilt test, and absence of any competing diagnosis.
- After reassurance, it must be explained to patients diagnosed with vasovagal syncope that their prognosis is good, the mechanisms causing their syncope, possible trigger events, and avoidance strategies.

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18.1 Risk Stratification in the Emergency Department (ED): Who Comes to the ED?

While most patients who have an episode of syncope either do not seek any medical attention (18.1–39.7 syncope events per 1,000 patient-years [1]) or present to their General Practitioner (GP) or family doctor (9.3 syncope visits per 1,000 patient-years [1]), attendance at an Emergency Department (ED) probably only accounts for around 0.7 syncope visits per 1,000 patient-years [1]. The populations who attend the ED are likely to represent the more extreme end of the syncope severity spectrum. The majority of patients who either do not seek medical attention or who visit their GP are likely to have had an episode of vasovagal syncope.

18.2 Assessment of the Suspected ED Syncope Patient – Step 1

It is now well established that there are three main steps in the assessment of the suspected syncope patient attending the ED. "Step 1" involves identifying patients who may have had syncope. There have been some recent attempts to look at the role of the ED triage personnel to assess for suspected syncope in patients presenting to the ED and to risk stratify them; however, in most EDs, this initial step is performed by the treating Emergency physician, or clinician (as some EDs now employ nursing staff in advanced practitioner roles). This might seem like a fairly simple task; however, there are many syncope mimics that can make it difficult for the inexperienced clinician to establish a diagnosis of syncope. For a small minority of patients, it may be difficult in the ED to decide that a patient has had an episode of syncope, the main differential being seizure. For this reason, the European Society of Cardiology has identified a more generic term to include the undifferentiated patients who present to the ED with suspected syncope or seizure, namely Transient Loss of Consciousness (abbreviated to TLoC).

While this term is useful for those patients in whom there is diagnostic uncertainty, a diagnosis of syncope can usually be made in the ED. When UK ED clinicians were asked to recruit syncope patients to the ROSE study [2], a study looking at the risk stratification of syncope in the ED, of the 1,100 patients who were recruited by these ED clinicians, only 12 patients (1.1 %) were diagnosed with a possible seizure after inpatient and outpatient investigation. The definition of syncope used in this study was "a transient loss of consciousness with an inability to maintain postural tone that is followed by a spontaneous recovery without need for therapeutic or electrical intervention."

18.3 Syncope Differentials

During "Step 1" of initial ED assessment, the ED clinician must consider the following possible diagnoses:

Neurological seizure. It is important to identify features in the history that may point to neurological seizure activity, the most important of which is the presence of a post-ictal phase. While confusion may be present immediately after syncope, this should not last for more than a minute [3]. Other discriminators such as tonic–clonic activity, incontinence, and tongue biting may help to diagnose neurological seizure. These in isolation thought do not rule out syncope if a period of cerebral anoxia has occurred [4]. Seizure activity that is thought not to be primarily due to a period of cerebral anoxia (i.e., epilepsy) should not be classified as syncope.

Vertigo. Here a careful history is vital. The term "dizzy" is commonly used amongst both patients and less-experienced ED clinicians to describe the feeling that patients have prior to an episode of TLoC. The ED clinician should explore the patient's symptoms carefully to determine whether they are rotational, that is, a feeling of the room spinning around them, which might point to either a peripheral (e.g., vestibular neuritis) or central (e.g., posterior circulation cerebrovascular accident; CVA) cause of vertigo.

Disequilibrium. Here the patient again might describe "dizziness"; however, a sensation of loss or lack of equilibrium or stability is more commonly associated with this symptom. The patient, when pressed, might describe a feeling similar to standing on a moving boat, with walking being difficult due to the floor apparently moving underneath them. Causes of this symptom are similar to the causes of peripheral vertigo.

Presyncope. Also described as near-syncope, this syndrome is again commonly described as "dizziness;" however, the key here is that the patient does not lose consciousness. They may feel "lightheaded" but will not be witnessed to blackout. A bystander description is vital here, as patient with both syncope and presyncope are both very unreliable as to whether they lost consciousness. This is important from a prognostic point of view, with presyncope being more benign [5].

Mechanical Fall. It can sometimes be difficult to elucidate a history of a trip from a patient – however, if reliable, means further TLoC investigations can be deferred.

Collapse Query Cause. This term is commonly used to describe any patient who has had an undifferentiated collapse – however, should be reserved for those patients, commonly elderly, who have had a fall without loss of consciousness, usually secondary to chronic medical problems and leg weakness. It should not be used to describe undifferentiated TLoC.

Syncope. This is a TLoC due to cerebral hypoperfusion. It is transient, of rapid onset, short duration, and associated with spontaneous recovery.

18.4 Assessment of the Suspected ED Syncope Patient – Step 2

"Step 2" of ED assessment involves ruling out causes of syncope that may lead to a rapid clinical deterioration. Here, other important symptoms prior to the syncopal event must be looked for as these may suggest an alternative serious cause. Symptoms such as chest pain (which might suggest acute coronary syndrome, aortic dissection, or pulmonary embolus), sudden onset of headache (suggestive of subarachnoid hemorrhage), dyspnea (acute coronary syndrome, aortic dissection, or pulmonary embolus), palpitations (arrhythmia), back pain (aortic dissection), focal neurological deficits (aortic dissection or subarachnoid hemorrhage), and abdominal pain (ectopic pregnancy or ruptured abdominal aortic aneurysm) must be ruled out. A focused examination focusing on the cardiovascular and neurological system must be carried out. Patients are unlikely to present with vasovagal syncope and a serious underlying cause. Occasionally, underlying conditions such as malignancy or anemia may increase the likelihood of a vasovagal syncopal episode; however, in the main, the cause of syncope in patients with a serious underlying condition is due to a period of hypoperfusion secondary to cardiovascular compromise. This tends to be more prolonged and it is rare for a patient with a serious underlying cause for their syncopal episode to improve back to baseline, an exception possibly being subarachnoid hemorrhage.

18.5 Assessment of the Suspected ED Syncope Patient – Step 3

"Step 3" of ED assessment involves stratifying the patient with syncope according to their risk of serious future adverse outcome. This part of the ED assessment presumes that the ED clinician is confident that the patient has had a true syncopal event and that they do not have an obvious underlying cause.

There are three main diagnostic groups that should be considered for patients at this step of the ED assessment:

- Cardiac syncope, which accounts for the cause in around 10 % of patients presenting to the ED. Underlying conditions include malignant arrhythmias such as sinus pause, atrioventricular block, ventricular tachycardia, supraventricular tachycardia, acute coronary syndrome, aortic stenosis, and pulmonary embolism [6]. A cardiac cause should be considered in any patient who has palpitations related to their syncope, associated chest pain, exertional symptoms, new or unexplained breathlessness, family history of sudden death in people aged younger than 40 years, previous history of VT/VF/cardiac arrest, a systolic heart murmur, physical signs or symptoms of heart failure, or an abnormal electrocardiogram (ECG) [7]. Patients with these features should be admitted or referred for urgent specialist cardiovascular assessment. Syncope without prodromal symptoms should also warrant a high level of suspicion.

- Postural or orthostatic hypotension responsible for about 25 % of presentations.
- Vasovagal (also termed neurocardiogenic or reflex) syncope, which is the diagnosis in about 40 %.

If the actual underlying diagnosis or diagnostic group is not clear, a process of stratification aims to use aspects of the patient's history, examination, and ECG findings to place the patient in one of three risk groups (high, medium, or low risk), which are then able to guide investigation and discharge decisions. High-risk patients are those with features that could be suggestive of a cardiac cause. Low-risk patients are those with features more likely to be associated with either postural hypotension or vasovagal syncope.

There are several ED syncope risk stratification rules that aim to stratify ED syncope patients based on historical, examination, and ECG findings. These are summarized in Table 18.1.

18.6 Diagnosing Vasovagal Syncope in the ED

The diagnosis of uncomplicated vasovagal syncope in the ED is suggested when there are no features that suggest an alternative diagnosis (see Sect. 18.4), when there are no features suggestive of a cardiac cause, and when features are present that are suggestive of uncomplicated vasovagal syncope (see Sect. 18.5).

For ease of recall, it has been suggested that these should be categorized as the three "Ps" [13]:

1. *Posture* (prolonged standing, or similar previous episodes that have been prevented by lying down)
2. *Provoking* factors (such as pain or a medical procedure)
3. *Prodromal* symptoms (such as diaphoresis or a feeling of warmth before the episode)

The ESC guidelines suggest that the presence of precipitating events such as fear, severe pain, emotional distress, instrumentation, or prolonged standing associated with typical prodromal symptoms, suggest a certain diagnosis of vasovagal syncope. These criteria have been shown to have a sensitivity of 98 % and a specificity of 100 % for vasovagal syncope, although this was in a selected population of patients [14].

The ESC guidelines also suggest that vasovagal syncope is *highly likely* in the absence of cardiac disease; a long history of syncope; after an unpleasant sight, sound, smell, or pain; after prolonged standing or a crowded, hot place; associated nausea or vomiting; during the absorptive state after a meal; and after exertion. These criteria have a sensitivity of 98 % and a specificity of 95 % for vasovagal syncope [15].

One subset of vasovagal syncope is "situational" syncope, which traditionally refers to reflex syncope associated with a clear and consistent provocation such as straining during micturition (usually while standing), coughing, or swallowing.

Table 18.1 ED syncope risk stratification rules

Rule	Features
SFSR [8]	Abnormal ECG
San Francisco Syncope Rule	Anemia (hematocrit <30 %)
Pneumonic = CHESS	A complaint of shortness of breath
	Systolic hypotension (<90 mmHg)
	History of congestive cardiac failure
	Each characteristic scores one. High risk is any present.
OESIL score [9]	Age >65
	History of cardiovascular disease
	Absence of prodromal symptom
	Abnormal ECG.
	Each characteristic scores one. High risk >1
ROSE [2]	*Admit if any of the following are present*:
Risk Stratification of Syncope in the ED	BNP level ≥ 300 pg/ml
Pneumonic = BRACES	Bradycardia ≤50 in ED or prehospital
	Rectal examination showing fecal occult blood (if suspicion of gastrointestinal bleed)
	Anemia – Hemoglobin ≤90 g/l
	Chest pain associated with syncope
	ECG showing Q wave (not in lead III)
	Saturation ≤94 % on room air
EGSYS [10]	Palpitations preceding syncope (4pts)
	Heart disease and/or abnormal ECG (3pts)
	Syncope during effort (3pts)
	Syncope while supine (2pts)
	Precipitating or predisposing factors (warm, crowded place/ prolonged orthostasis/fear/pain/emotion) (1 pt)
	Autonomic prodromes (nausea/vomiting) (1 pt)
	Each characteristic scores one. High risk of 2 year mortality/cardiac cause >2
BOSTON [11]	*High risk if any of the following are present:*
	Signs and symptoms of acute coronary syndrome
	Worrisome cardiac history
	Family history of sudden death
	Valvular heart disease
	Signs of conduction disease
	Volume depletion
	Persistent (>15 min) abnormal vital signs in the ED without the need for concurrent intervention such as oxygen, pressor drugs, or temporary pacemakers
	CNS

(continued)

Table 18.1 (continued)

Rule	Features
Martin [12]	Abnormal ECG
	History of congestive heart failure
	History of ventricular arrhythmia
	Age >45 years
	Each characteristic scores one. High risk >1

18.7 Use of Vasovagal Clinical Decision Rules

There are two decision rules that have been devised specifically for vasovagal syncope. The Sheldon (2006) rule [16] was derived by administering a 118-item historical questionnaire to 418 patients with syncope and no apparent structural heart disease. Vasovagal syncope was defined as a positive tilt table test and the prevalence of each of the 118 items was compared between the 235 patients with a positive tilt table test and putative vasovagal syncope and those with syncope of other causes (88 patients). Sheldon et al. derived the following scoring system, which states that TLoC episode is classified as a vasovagal syncope if the total symptom score is −2 or more, calculated by summing the following if present:

Presyncope or syncope with pain or medical procedure	(+3)
Sweating or warm feeling before TLoC	(+2)
Presyncope or syncope with prolonged sitting or standing	(+1)
Remembers something about the TLoC	(−2)
Age at first TLoC at least 35 years	(−3)
Blue color noted by bystander	(−4)
Any one of bifascicular block, asystole, supraventricular tachycardia, and diabetes +	(−5)

+ None of these must be present in order to have a diagnosis of vasovagal syncope

Sheldon et al. found the rule able to classify 90 % of patients correctly, diagnosing vasovagal syncope with a sensitivity of 89 % and a specificity of 91 %. These criteria have subsequently been shown to have a sensitivity of 87 % and a specificity of 31 % for vasovagal syncope in an external validation study [17].

The Graf (2008) study [18] enrolled 317 consecutive patients and undertook a standardized workup (history, examination, ECG) followed by carotid sinus massage and head-up tilt test. The authors derived a risk score, which reported a sensitivity of 84 % (64–95) and a specificity of 50 % (34–66) in their validation cohort for the diagnosis of vasovagal syncope or psychogenic pseudosyncope.

Symptom Score = 2 x B – C – A + 2

A) Age:
   - 1 for age 45 years and below
   - 2 for age over 45 and below 65 years
   - 3 for age over 65 years

B) Number of prodromes:
   - Score 0 for 1 or 0 symptoms
   - Score 1 for 2 or more symptoms

C) ECG P-wave duration:
   - Score 0 for duration below 120 ms
   - 1 for duration 120 ms and above or nonsinus rhythm.
   - A score ≥0 classified patients as suffering from vasovagal or psychogenic pseudosyncope. A score <0 classified patients as non vasovagal/psychogenic pseudosyncope.

18.8 Vasovagal Mimics in ED

There are several other types of syncope that deserve special mention and can present in a very similar fashion to vasovagal syncope. "Carotid sinus" syncope can be triggered by mechanical manipulation of the carotid sinuses in its rare spontaneous form. In the more common form, no mechanical trigger is found and it is diagnosed by carotid sinus massage (CSM) [7]. CSM is diagnostic for carotid sinus hypersensitivity and should be performed if neck movements or pressure on the neck may have precipitated syncope. It is important to first exclude the presence of a carotid bruit and to be aware of the risk of precipitating a prolonged sinus pause or an episode of hypotension.

While most vasovagal syncope occurs with a prodrome and is precipitated by a trigger, there are some cases that can occur without any triggers or prodrome. This type of vasovagal syncope is termed "atypical." The diagnosis then rests less on history-taking and more on the exclusion of other causes of syncope and on reproducing symptoms on tilt testing [19].

Atypical vasovagal syncope can be defined as a TLoC not preceded by an evident trigger, positive tilt test, and absence of any competing diagnosis. However, since tilt test, like the other tests utilized in the diagnosis of syncope, is not a gold standard, there is a continuum between atypical vasovagal syncope and reflex (neurally mediated) syncope.

A vasovagal mechanism can also be present in many other disease and patients, as in aortic stenosis or pulmonary embolism. Most problems in the ED related to diagnosing vasovagal syncope are caused by patients with atypical vasovagal syncope (i.e., patients without any trigger or prodrome), and patients with symptoms suggestive of vasovagal syncope but with other concerning comorbidities.

Since vasovagal syncope is the most common type of syncope and also just as prevalent with increasing age as in the young, it is still more probable than any other etiology. However, the first aim of the physician, particularly in the ED, is to exclude more worrisome causes for a patient's syncope.

There are a few tools that can help the physician here. Mostly the diagnostic strategy should rely on accurate history-taking, admission, and ECG monitoring. Some advice on managing these two different kinds of patients is suggested in the following:

(a) Patients with atypical vasovagal syncope

Most patients with atypical vasovagal syncope are older, but atypical vasovagal syncope can present also in young patients. The problem arises if syncope occurs without any prodrome or triggers. Most of these patients will have had an episode of vasovagal syncope, but the concern is more serious pathologies such as catecholaminergic polymorphinc ventricular tachycardia (CPVT) or arrhythmogenic right ventricular dysplasia (ARVD). These are difficult conditions to pick up in the ED. The best way to manage these patients should be a period of monitoring, an echocardiogram and referral to a syncope specialist or to a syncope unit. Unfortunately, there is no evidence-based recommendation as to how many hours these patients should be monitored. We suggest between 3 and 12 h.

(b) Patients with typical vasovagal syncope but with important comorbidities.

Unlike the previous patient group, these patients are usually older with comorbidities and on multiple medications. However, their syncope has some characteristics of being benign and suggestive of vasovagal syncope. In particular, they may have a prodrome or trigger. Many of the ED risk stratification tools would consider this patient at high risk, while most patients would probably be at low risk of adverse syncope outcome. Since we cannot easily exclude that syncope could have been provoked by more than one cause, we suggest monitoring this group in the ED and referring them for urgent syncope specialist or syncope clinic evaluation. A tilt test may reproduce syncope in a laboratory setting and may reproduce symptoms of previous syncopal episodes. Of course, this approach does not exclude the coexistence of another syncope cause.

As alluded to earlier, it must also be remembered that different causes of syncope can coexist in the same patient as the following case example illustrates:

Case Example

- 60, male.
- Known dilated cardiomyopathy, has Automated Internal Cardiac Defibrillation (AICD) in place for Ventricular Tachycardia.
- Was walking along the beach when he had 2–3 s of prewarning, then transient loss of consciousness for 1 min during which his AICD fired.
- Patient had had many previous transient loss of consciousness episodes, most of which were after food, associated with 2–3 min of prewarning symptoms, and which had been diagnosed as vasovagal syncope.

18.9 Biomarkers

There have been some attempts to diagnose low-risk syncope with the use of biomarkers such as high sensitivity Troponin [20] and Brain Natriuretic Peptide [21]. However, while high sensitivity Troponin shows promise both at ruling out serious outcome in ED syncope patients and diagnosing vasovagal syncope in the ED [20], more work is needed.

18.10 Prognosis of Vasovagal Syncope

Despite a lifetime prevalence of at least 20–40 %, much remains to be learned about vasovagal syncope [22]. In particular, we have little sense of its natural history, information that might prove helpful to patients and physicians alike. A search of PubMed using the terms vasovagal syncope, prognosis, and cohort study retrieved only 100 articles, only a few of which focus on prognosis.

The main source of vasovagal syncope prognostic information comes from the Framingham study [23]. This study of 312 patients showed that vasovagal syncope (including orthostatic syncope, medication-related syncope, and syncope due to other infrequent causes) was not associated with an increased risk of major outcome during a mean follow-up of 8.6 years [23]. Many authors also maintain that vasovagal syncope is a nonpathological advantageous stress response [24].

Although there may be a selection bias resulting from the small number of patients who seek medical advice (particularly hospital advice) after a syncopal event [7], it does seem that vasovagal syncope is a benign condition not associated with increased mortality. Even subjects with prolonged asystole during tilt testing have a good prognosis [25]. This is important as many physicians, including specialists, are concerned by this finding often suggesting unnecessary pacemaker insertion. Vasovagal syncope is however associated with some morbidity, mainly associated with traumatic injuries, particularly in patients with repeated episodes.

18.11 Morbidity and Risk of Recurrence

While almost 30 % of people will have a syncopal spell during the course of their lifetime, just 30 % of these will have a recurrence. The median age of a first syncopal event is less than 20 years [22], but recurrences can occur over decades, and many seek medical advice late [22]. The number of recurrences is very varied, the most important risk factor being the number of previous episodes [26]. At present, there is no well-validated tool that can be used clinically to recognize patients at risk of recurrence.

Recurrence, in particular that which occurs early, can markedly influence a patient's quality of life [27]. This impact ranges from effects on education in the young, through impaired social life and ability to drive in adolescence, curtailed career opportunities in adult life, and risk of fractures and other injuries in later years [19, 28]. Perceived quality of life can also be severely impaired [28, 29].

Unfortunately, therapeutic options for patients with severe vasovagal syncope are limited (see therapeutics chapter) leading to many being advised that a cure may not be a feasible goal. A more comprehensive strategy aimed at education, reassurance, and prognostication should therefore be employed once the clinician is confident in the diagnosis [22].

18.12 What to Do for These Patients in the ED

Once vasovagal syncope has been identified in the ED, it is very easy for the ED clinician to relax, happy that a benign diagnosis has been made. However, while patients might be at very low risk of serious outcome, they can still be quite upset and anxious after an episode of vasovagal syncope that has caused them to end up in the ED. Although the ED can be a very busy and frantic place, it is therefore very important to spend some time to reassure the person that their prognosis is good. The ED clinician should also explain the mechanisms causing their syncope and advise patients on possible trigger events and strategies to avoid them.

If episodes are frequent, it can be useful to ask them to keep a record of their symptoms, when they occur and what they were doing at the time, which they can present to their GP or family doctor in order to help understand trigger events. If patients experience further episodes, particularly if they are different from their presenting episode, then they should again seek further advice from their family doctor.

Finally, the patient can be directed to websites containing information sheets for patients with vasovagal syncope, such as the STARS website (www.stars.org.uk).

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Treatment of Vasovagal Syncope: Counseling, Drugs, and Counter-Pressure Maneuvers

19

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Key Points

- Education, reassurance, and explanation of the benign nature of the syncopal spells is the first-line therapy in all patients with vasovagal syncope (VVS).
- Hydration should be recommended to all patients with VVS.
- Physical counter-pressure maneuvers are effective when loss of consciousness is preceded by prodromal symptoms.
- Drugs do not seem to be very effective in the prevention of VVS recurrences; only midodrine seems to be somewhat effective, particularly in patients with arterial hypotension.

Transient loss of consciousness is a common symptom in the general population; it is estimated that approximately 40 % individuals will faint at least once in their lifetime. Vasovagal syncope (VVS), characterized by paroxysmal reflex-mediated hypotension associated with bradycardia, is the most common of the neurally mediated syncopal syndromes. The neurally mediated vasovagal reflex is caused by a rapid increase in vagal tone, which results in bradycardia or asystole, associated with hypotension, caused by the reduction in peripheral sympathetic activity, leading to systemic vasodilation with consequent global cerebral hypoperfusion and loss of consciousness.

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The vasovagal reflex is commonly precipitated by various physical or psychological triggers. The most common triggers are:

- Prolonged standing or upright sitting
- Standing up quickly
- Violent coughing
- Sight of blood
- Micturition
- Any painful or unpleasant stimuli
- Watching or undergoing medical procedures (e.g., venipuncture)
- Lack of sleep
- Dehydration
- Being exposed to high temperatures
- Use of certain drugs that influence blood pressure (BP)
- Psychological stress

Even if VVS is benign, it might be recurrent, in some patients may cause significant injury, and may affect the quality of life. Therefore, every therapeutic strategy can improve the quality of life but does not influence the survival rate [1, 2]. Several strategies are available for the treatment of neurally mediated syncope.

19.1 Education and Reassurance

Treatment of VVS involves a tailored approach starting with patient education about the benign nature of the episode, patient reassurance and instruction; in two words "patient counseling" may suffice to prevent syncopal recurrences.

This first step treatment approach is particularly indicated in those patients who present with single or infrequent episodes of VVS, or in the presence of specific triggers, or when warning symptoms are present and are sufficiently prolonged to allow the patient to implement counter-pressure maneuvers.

On the other hand, a more structured therapeutic approach is suggested when VVS:

- Is recurrent
- Impairs the quality of life with subsequent substantial changes in daily lifestyle
- Or is associated with severe injuries (present in about 5 % of patients)

In clinical practice the following treatment strategies have been proposed:

- Patient education, reassurance, and instruction to prevent and counteract the vasovagal reflex
- Increase sodium and fluid intake to increase blood volume, when possible
- Adopt counter-pressure maneuvers
- Tilt training
- Pharmacologic therapy
- Pacing

Table 19.1 summarizes the European Society of Cardiology (ESC) 2009 guidelines for the treatment of VVS [3]. Education, reassurance, and explanation of the benign nature of VVS is considered a first-line therapy (Class IC). A simple and clear explanation to the patient that VVS is a benign condition, that this syncope is not responsible for increased mortality, and that the syncopal spells are not related to any specific cardiac or neurologic disease, may help the patient and relatives feel more confident with this disorder and reduce the number of recurrences.

The second step is to explain to the patient the mechanism of the vasovagal reflex. The knowledge of what really happens during the reflex can help the patient recognize the early symptoms and prodromes, when present, so that he or she may adopt all the measures useful in avoiding or delaying the loss of consciousness.

For example, patients who experience a tilt-induced syncope are more aware of the role of the vasovagal reflex, and this might explain the reduced recurrences of syncope after tilt test.

The next step is to try to identify the triggers of the vasovagal reflex. Many different triggers are able to activate the vasovagal reflex and sometimes it is possible to identify the specific trigger for each patient. If there are specific triggers, every effort should be made to avoid such situations, which may be helpful in preventing recurrences.

Table 19.1 Recommendations of the task force on the management of syncope of the European Society of Cardiology [3]

Recommendations	Class[a]	Level[b]
Explanation of the diagnosis, provision of reassurance, and explanation of risk of recurrence are indicated in all patients	I	C
Isometrics PCMs are indicated in patients with prodrome	I	B
Cardiac pacing should be considered in patients with dominant cardioinhibitory CSS	IIa	B
Cardiac pacing should be considered in patients with frequent, recurrent reflex syncope, age >40 years, and documented spontaneous cardioinhibitory response during monitoring	IIa	B
Midodrine may be indicated in patients with VVS refractory to lifestyle measures	IIb	B
Tilt training may be useful for education of patients but long-term benefit depends on compliance	IIb	B
Cardiac pacing may be indicated in patient with tilt-induced cardioinhibitory response with frequent, recurrent unpredictable syncope and age >40 after alternative therapy has failed	IIb	C
Cardiac pacing is not indicated in the absence of a documented cardioinhibitory reflex	III	C
β-Adrenergic blocking drugs are not indicated	III	A

Abbreviations: *CSS* carotid sinus syndrome, *PCM* physical counter-pressure maneuvers, *VVS* vasovagal syncope

[a]Class of recommendation

[b]Level of evidence

Table 19.2 Counseling for patients with vasovagal syncope

The patient should be informed about:
1. The benign nature of the VVS
2. The cardiovascular mechanism underlying the vasovagal reflex and related symptoms for an aware and appropriate self-management
3. How to avoid the possible triggers that can activate the vasovagal reflex
4. How to better recognize the prodromal symptoms (if present)
5. How to promptly apply the physical maneuvers to counteract the reflex

Table 19.3 Recommendations for patients to prevent the vasovagal reflex and syncope recurrences

Avoid the everyday situations that can potentially trigger the vasovagal reflex (generally the patient knows what is dangerous for himself/herself)
At the beginning of prodromal symptoms, the patient should lie down
Assume hypotensive medication with caution and consider its removal
In case of susceptibility to a postprandial syncope, it is better to lie down for a while at the end of the meal
Increased intake of fluids and dietary salt
Wear elastic stockings
For men:
Urinate seated to avoid the postmicturition syncope
Be aware that orthostatic hypotension is facilitated by the intake of alpha-antagonist agents used for prostatic hypertrophy

In patients assuming medications which can potentially facilitate a vasovagal reflex (such as diuretics, vasodilators, alpha-antagonist agents, hypotensive drugs), one should consider removing such medications when possible.

Table 19.2 summarizes the counseling for patients with VVS and Table 19.3 reports what the patients should avoid and/or adopt to prevent and counteract the vasovagal reflex and syncope recurrence.

However, some of these recommendations do not have strong evidence to support the efficacy. For example, increased hydration alone can be helpful for short periods and high salt intake may improve orthostatic intolerance, but this may not be advisable in patients with renal failure, heart failure, or hypertension [4]. Few data support the efficacy of wearing elastic stockings for the prevention of VVS, and often patients do not tolerate such measures for long periods of time.

When recurrent, VVS may be associated with a negative psychosocial impact. Often the patient lives in fear of the next syncopal episode. This psychosocial impairment predicts a failure of the other treatments for VVS. In these patients, psychotherapeutic support may be taken into account.

19.2 Physical Counter-Pressure Maneuvers

The ESC guidelines [3] recommend physical isometric counter-pressure maneuvers as a Class I indication (level of evidence B). There is a wide variety of physical maneuvers that are effective in counteracting the hypotensive component of the vasovagal reflex. To lie down at the onset of prodromes appears to be the simplest, most common, and effective maneuver. There are no evidence-based data to support this recommendation, but this maneuver appears to be highly effective in preventing syncope and consequent injuries. Squatting, hand-grip, leg crossing, limb and/or abdominal musculature contraction while standing up, isometric arm counter-pressure maneuvers (i.e., contraction of a rubber ball with the dominant hand), gripping one hand with the other and abducting both arms at the same time, knee flexion, and marching on the spot [5, 6] are all maneuvers able to counteract the vasovagal reflex, especially when applied at the beginning of symptoms when BP starts to fall. These maneuvers are able to increase cardiac output and BP.

The Physical Counterpressure Maneuvers Trial (PC Trial) [7] is a randomized controlled study that investigated the potential efficacy in aborting the vasovagal reflex when adding physical maneuvers to conventional therapy (106 patients) compared with conventional therapy alone (117 patients). The results of this study demonstrated a 39 % relative risk reduction in syncopal recurrence in the group trained to perform physical maneuvers; however, this therapeutic strategy failed in 35 % of patients. This failure could be explained by the absence or short duration of the warning symptoms.

19.3 Pharmacological Treatment

If all these conservative measures fail in preventing syncope recurrences, pharmacologic therapy may be considered.

Several pharmacologic treatments have been used for VVS (Table 19.4). Although some data have been encouraging in small, uncontrolled trials, at the moment there are no pharmacologic treatments for VVS that have demonstrated effectiveness in large randomized trials.

Many drugs have been investigated for the prevention of VVS [21, 22]: beta-blockers (atenolol, metoprolol, propranolol), alpha-agonist agents (etilefrine, midodrine), anticholinergic agents (scopolamine), theophylline, fludrocortisone, disopyramide, serotonin reuptake inhibitors (SSRIs), and angiotensin-converting enzyme inhibitors (enalapril).

Several studies that have tested different beta-blockers [11–13], with or without control groups and with different end points, have provided little convincing evidence for their effectiveness in preventing VVS. The most important beta-blocker trial, The Prevention of Syncope Trial (POST), which assessed the efficacy of metoprolol in VVS, failed to show benefit in the prevention of recurrence of syncope

Table 19.4 Drugs tested in the vasovagal syncope prevention. Controlled studies

Reference	Drug	Patients	Results
[8]	Disopyramide	21	Ineffective
[9]	Scopolamine	60	Ineffective
[10]	Etilefrine	126	Ineffective
[11]	Atenolol	22	Ineffective
[12]	Atenolol	50	Ineffective
[13]	Metoprolol propranolol	56	Effective
[14]	Metoprolol	208	Ineffective
[15]	Midodrine	16	Effective
[16]	Midodrine	61	Effective
[17]	Midodrine	20	Ineffective
[18]	Fludrocortisone	20	Ineffective
[19]	Paroxetine	68	Effective
[20]	Paroxetine	96	Ineffective

[14]. However, metoprolol might be prescribed in older patients with VVS and comorbid hypertension.

Fludrocortisone is another drug tested that has given conflicting results. Scott et al. [23] reported that children had a lower recurrence rate of syncope and presyncope while taking fludrocortisone. On the contrary, Salim et al. [18], in a randomized, double-blind study, found more symptoms in children in therapy with fludrocortisone than in the control group. In a multinational, randomized, controlled clinical trial, the Second Prevention of Syncope Trial (POST 2), Sheldon et al. [24] reported that after 1 year, syncope recurrence was indeed lower in the fludrocortisone group than in the control group in both the intention-to-treat and on-treatment analyses, but the difference was not statistically significant.

Studies using SSRIs have fared not much better than other drugs. In a double-blind, placebo-controlled study, Di Girolamo et al. [19] showed reduced syncope recurrence by daily administration of 20 mg paroxetine. By contrast, Theodorakis et al. [20] reported that fluoxetine was not superior to placebo.

Midodrine, an alpha-1 adrenergic receptor agonist, was shown to be more effective than placebo in preventing VVS in more than one trial [15, 16], whereas Romme et al. [17] reported negative results. Despite these results, midodrine is the only pharmacologic agent recommended in the ESC guidelines [3] when the patient is refractory to the lifestyle measures (Class IIb indication, level of evidence B). An ongoing randomized study, the Prevention of Syncope Trial 4 (POST4) [25], with results expected in 2017, will provide some insights on the effectiveness of midodrine in the prevention of VVS. Some limitations related to midodrine include compliance with therapy (3-times daily dosage) and possible side effects, such as hypertension and urinary retention in older males. At present, midodrine appears to be indicated in patients with recurrent VVS and hypotension. Disopyramide, transdermal scopolamine, and etilefrine did not show any efficacy in the prevention of VVS recurrence in randomized controlled studies [8–10].

At present, there is no clear evidence from large-scale, blinded, randomized trials that drugs have long-term benefit in the prevention of VVS. For this reason, pharmacologic therapy is not recommended as a first-line choice for the prevention of VVS recurrences [3]. However, the vast majority of patients with VVS can be adequately controlled with nonpharmacologic approaches and do not require pharmacologic treatment.

19.4 Orthostatic Training

Tilt training was proposed as a treatment for the prevention of VVS recurrence [26–29]. Starting from the observation that recurrent tilt testing on consecutive days leads to a decrease in positivity, the treatment is based on the hypothesis that consecutive tilt tests could lead to a training effect enhancing the peripheral sympathetic activity. Repeated daily tilt tests were performed during the in-hospital stay until syncope did not occur after 3–8 sessions. On the basis of these encouraging results, an orthostatic training (standing against a wall for 30 min, 1–2 times per day) was proposed to the patients followed in the outpatient clinic. However, the data of these studies are not conclusive and not always positive. The limitation of this strategy is the poor compliance of the patients, which might reduce its efficacy.

Conclusions

Counseling on VVS physiology and its prognosis is the first line of treatment for prevention of syncopal recurrences. Therapy is not indicated if syncope is not recurrent. When therapy is indicated, an increased fluid and salt intake should be recommended. Patients with prodromal symptoms should be encouraged to lie down or assume a squatting position. Physical counter-pressure maneuvers should be well known and promptly applied by the patient at the early stage of the prodromal symptoms. If this conservative treatment is ineffective, a drug such as midodrine can be prescribed, but not to patients with hypertension or urinary disorders. Home orthostatic training can be prescribed to motivated patients.

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Role of Loop Recorder and Pacemaker Implantation in Vasovagal Syncope

20

Franco Giada and Antonio Raviele

Key Points

- Implantable loop recorder (ILR) monitoring showed that in selected patients with recurrent neurally mediated syncope, about half of the spontaneous syncopal episodes were asystolic in nature. However, the prevalence of spontaneous asystolic episodes has not been investigated in subjects with typical vasovagal syncope.
- Among selected patients with recurrent atypical vasovagal syncope (tilt positive), an asystolic pause during ILR monitoring was present in more than 80 % of patients with asystolic response and in about 50 % of those with no -asystolic response during tilt-induced syncope.
- Open studies showed a marked reduction of vasovagal syncope recurrence with dual-chamber pacing. However, placebo-controlled studies (pacemaker on versus pacemaker off) could not reproduce these results.
- Recent data showed that a pacemaker was effective in patients with neurally mediated syncope and ILR-documented asystolic pauses. However, this therapeutic strategy remains to be clearly defined.

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Given that vasovagal syncope is characterized by a benign prognosis, therapy should be aimed at preventing associated trauma and improving quality of life rather than prolonging life expectancy. An important aspect of the natural history of vasovagal syncope is its cyclic course. Syncope relapses tend to cluster, that is, there are periods characterized by an excessive rate of syncope onset and others without symptoms. This periodicity raises the questions of whether, when, and how long the patient has to be treated.

Medical advice on the benign nature of the disorder together with appropriate reassurance may result in a clinical improvement with a decline in syncope relapse. Therefore, according to the European guidelines, only selected patients should be treated: patients suffering from highly recurrent vasovagal syncope, individuals in whom syncope onset is not preceded by prodromal symptoms or recognized triggers, those suffering from associated severe trauma, and persons engaged in risky jobs (pilots, professional drivers, etc.) [1].

20.1 Role of Implantable Loop Recorder

In current clinical practice, the implantable loop recorder (ILR) is used as diagnostic tool to evaluate transient loss of consciousness of possible arrhythmic origin, in particular unexplained syncope. Indeed, in patients with syncope that remains unexplained after the initial clinical evaluation, long-term electrocardiographic recording is considered the diagnostic gold standard [1–3]. Thus, when syncope is clinically relevant (i.e., recurrent, accompanied by reduced quality of life and/or trauma) and/or when there is a high probability of an arrhythmic cause (i.e., the patient is suffering from heart disease), long-term monitoring by means of ILR is often necessary.

Several studies have shown that in both older and pediatric patients with unexplained syncope, with or without structural heart disease, using an ILR yields a more complete diagnosis than does conventional testing [4, 5]. Moreover, Krahn et al. [6] showed that a strategy of primary monitoring is more cost-effective than conventional testing in establishing a diagnosis in recurrent unexplained syncope. The European Society of Cardiology (ESC) guidelines on the management of syncope [1] and the European Heart Rhythm Association guidelines on the use of implantable and external electrocardiographic loop recorders [3] provide a class I indication for the use of ILRs in patients with infrequent (i.e., with less than monthly frequency) unexplained syncope of possible arrhythmic origin, or in high-risk patients when all other investigations prove inconclusive. However, early use of ILR in the diagnostic workup can be safely adopted, provided that patients at high risk of life-threatening arrhythmic events are excluded. The ISSUE 3 study recently suggested the use of ILR to selected patients with recurrent vasovagal syncope and asystolic response, before embarking on pacemaker (PM) implantation [7]. In this regard, we know from ILR experience that when the device is implanted in selected patients with recurrent neurally mediated syncope, about half of the spontaneous syncopal episodes are asystolic in nature. However, the prevalence of spontaneous

asystolic episodes has not been investigated in subjects with typical vasovagal syncope. Recent data showed that among patients with atypical vasovagal syncope (tilt positive), an asystolic pause during ILR monitoring was present in 86 % of patients, with asystolic response and in 48 % of those with non-asystolic response during tilt-induced syncope [8].

20.2 The Role of the Pacemaker

In vasovagal syncope, PM therapy is aimed at overcoming bradyarrhythmias produced by reflex vagal hyperactivity including severe sinus bradycardia, sinusal pauses, and atrioventricular blocks associated with prolonged asystole. Studies dealing with the therapeutic effects of a PM in syncope patients can be classified as follows: (1) investigations that have identified PM-suitable patients based on their bradycardic response during tilt-induced syncope; (2) The ISSUE-3 study, where PM-suitable patients were screened on the basis of a bradyarrhythmic spontaneous syncope as assessed by ILR recording [7].

Patients' Selection Based on the Hemodynamic Changes Observed During Tilt-Induced Syncope

While single-chamber VVI-mode pacing has proved to be ineffective in the treatment of vasovagal syncope [9], several nonrandomized studies [10–12] have shown a significant decrease in syncope recurrence in patients who have undergone dual-chamber pacing. Subsequently, three randomized studies revealed the efficacy of dual-chamber PM implantation in decreasing relapses in patients with recurrent vasovagal syncope. The Vasovagal Pacemaker Study (VPS) [13] demonstrated the effectiveness of DDD pacing with rate-drop response (RDR) in patients affected by vasovagal syncope who were positive on tilt testing and presented a variable cardioinhibitory component. The VASIS study [14], on the other hand, showed the effectiveness of DDI pacing with hysteresis in patients with vasovagal syncope and positive tilt testing with a marked cardioinhibitory component. Finally, the SYDIT study demonstrated the superiority of DDD with RDR pacing with respect to drug therapy [15].

However, as these studies were noncontrolled (patients randomized to the control arm did not receive a PM), the benefit observed might have been due to the placebo effect of the PM. Indeed, the more recently published VPS II trial [16] and SYNPACE trial [17], two randomized, double-blind, placebo-controlled studies in which all enrolled patients underwent PM implantation after which they were randomized to active pacing or inactive pacing, were unable to show any statistically significant superiority of PM treatment over placebo. The main finding of the SYNPACE study [17] is that active cardiac pacing is not more effective than inactive pacing in preventing syncopal recurrences in patients with severe vasovagal syncope: neither the number of patients with syncopal recurrence nor the time to the

first syncopal recurrence significantly differed between PM-on and PM-off patients. Even the incidence and number of presyncope were similar between patients with active pacing and those with inactive pacing. Moreover, in the SYNPACE study the presence of a marked cardioinhibitory component during tilt-induced syncope was not able to identify patients who were likely to benefit from permanent pacing.

Patients' Selection Based on Heart Rate Changes Addressed by ILR Recordings During Spontaneous Syncope

The ISSUE-3 study is a double-blind, randomized, controlled multicenter trial that for the first time showed the effectiveness of cardiac pacing with an RDR algorithm in reducing syncope recurrence in patients who suffered from a spontaneous syncope with documented asystole or bradyarrhythmias by means of ILR recording [7]. Of note, all patients suitable to be enrolled underwent PM implantation and were subsequently randomized to PM-on or PM-off.

According to ISSUE-3 authors, the discordant results obtained by previous studies about the efficacy of PM therapy in preventing syncope recurrence could be explained by the major differences in the hemodynamic patterns characterizing tilt-induced syncope and spontaneous syncope. In patients with vasovagal syncope, ILR may document severe bradycardia or asystole, as a result of cardioinhibitory vagal mediated reflexes, but cannot reveal the possible concomitant presence of vasodepression, which conversely may be quite easily unveiled during a tilt-induced syncope, particularly if continuous blood pressure monitoring is performed. On the other hand it is possible that, based on the simple heart rate response during tilt-induced syncope, in previous studies a PM had been implanted in patients in whom a prevalent vasodepressive vasovagal syncope was actually present. By contrast, in the ISSUE-3 study, a PM was implanted only in those patients characterized by bradycardia or asystole, as assessed by ILR recording; that is, in individuals who were assumed to be the most likely responders to cardiac pacing.

The ISSUE-3 study is characterized by several weaknesses. There is no screening log for patients with vasovagal syncope, so the number of individuals who actually need the proposed therapeutic strategy is unclear. In addition, there are no follow-up data concerning those patients in whom ILR recording was not associated with a loss of consciousness, i.e., the large majority of the population investigated. This information would have been of pivotal importance to compare the clinical outcome of patients who did not undergo specific treatment with the clinical outcome characterizing individuals who underwent PM implantation. In addition, the primary outcome was the time at first syncope recurrence; conversely, syncope burden, i.e., the number of syncopes over time, would have been a more convincing piece of information. Data about potential changes in the quality of life of the patients are lacking, and the number of PM interventions is not reported. Importantly, the RDR algorithm may lead to inappropriate enhancement of heart rate, which may induce palpitations and negatively affect the patient's quality of life. Finally, the strategy of ISSUE-3 is somewhat complicated, time consuming, and costly. Indeed, to avoid a single syncopal episode

in 23 treated patients (number needed to treat = 23), an ILR had to be placed in 511 patients who were followed up for a year. In conclusion, from the methodological standpoint ISSUE-3 is an elegant and well-planned study that suggests the possibility of effectively using a PM in patients with recurrent vasovagal events.

20.3 Future Perspectives

One of the most important limitations of pacing in vasovagal syncope is the timely detection of the onset of the neuromediated reaction and subsequent triggering of pacing. RDR, like the other algorithms used in the studies mentioned herein, is a sensing modality based on reduction of heart rate. It is possible that the use of different sensing modalities, such as those based on cardiac contractility [18] or respiratory changes [19], might trigger cardiac pacing in an earlier phase of neuromediated reaction and yield better results in preventing syncopal relapses.

Conclusions

Given that a PM is an invasive treatment, the use of pacing in reducing recurrences of vasovagal syncope deserves additional comments. Indeed, there might be a mismatch between the theoretical approach and the real clinical world. Indeed, as a general consideration, the risk of complications following PM implantation has long been recognized in both the short and long term. This aspect is crucial for patients characterized by a long life expectancy, such as young individuals with vasovagal syncope. Thus, additional caution in pacing indication is mandatory. In the ISSUE-3 study, pacing proved to be ineffective in a remarkably high percentage (23 %) of patients in whom syncope relapse was observed despite PM activity. This finding indirectly suggests the crucial role played by the vasodepressive component underlying the vasovagal reflex that is unaffected by cardiac pacing. Moreover, in previous studies where the effects of cardiac pacing were evaluated acutely during tilt testing, a PM proved to be ineffective in reducing tilt-induced syncope, although prodromal symptoms lasted longer and frank syncope frequently turned out to be presyncope. Of note, during tilt-induced vasovagal syncope the intravenous administration of phenylephrine, a powerful short-acting vasoconstrictor agent, was found to be effective in counterbalancing the reflex hypotension and abolishing syncope [20], despite a further decrease in heart rate because of the arterial baroreflex control of heart rate (Fig. 20.1). Taken together, these findings highlight the pivotal role played by reflex hypotension in producing loss of consciousness, and point to the ancillary role carried out by the cardioinhibition in the genesis of the vasovagal event. Indeed, in the large majority of the cases, the cardioinhibitory component of the vasovagal reflex, if present, is delayed and seems to be "less important."

ESC guidelines on syncope [1] and cardiac pacing [21] identify a class IIa indication for PM implantation in vasovagal syncope patients older than 40 years, with recurrent and unpredictable syncope and documented symptomatic pause(s)

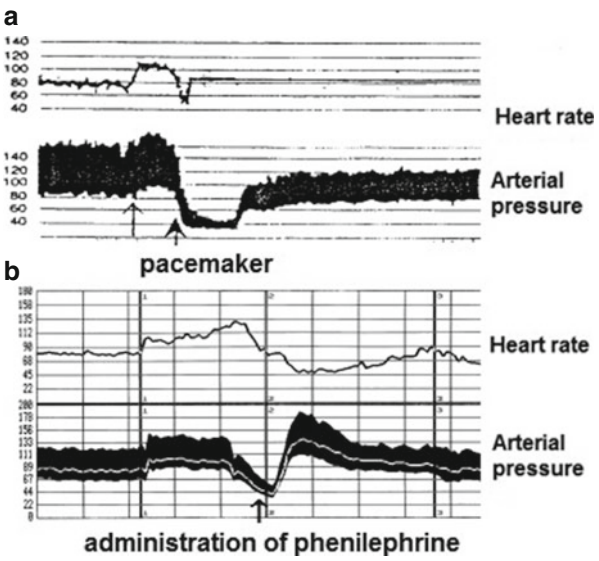

Fig. 20.1 Effects of a pacemaker (**a**) and intravenous administration of phenylephrine (**b**) during tilt-induced syncope. A pacemaker counteracts bradycardia, but is not effective in the prevention of hypotension and syncope. Phenylephrine prevents syncope by increasing blood pressure despite the decrease in heart rate

attributable to sinus arrest or atrioventricular block. However, guidelines acknowledge that "in patients with reflex syncope, cardiac pacing should be the last choice and should be given to highly selected patients, i.e. those with relatively old age, affected by severe forms of reflex syncope, with a history of recurrent syncope and frequent injuries, probably due to lack of prodromal symptoms. The fact that pacing is effective in some patients with reflex syncope does not mean that it is also always necessary. It must be emphasized that the decision to implant a PM needs to be undertaken in the clinical context of a benign condition (in terms of mortality), which frequently affects young patients."

We believe that pacing should be used in aged individuals, in whom vasovagal syncope often overlaps with sick sinus syndrome and carotid sinus hypersensitivity, disorders that may lead to falls, consequent fractures, and impaired quality of life.

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Therapy: Conclusive Remarks

21

Paolo Alboni and Raffaello Furlan

The course of vasovagal syncope (VVS) is benign, but when it is recurrent, it may be highly symptomatic, leading to significant deterioration of quality of life with psychological, driving, and employment implications [1]. Therefore, every treatment can be addressed only to improve quality of life and not to prolong survival. Patients seeking medical assistance after experiencing an episode of VVS often undergo costly diagnostic examinations and are anxious and concerned about the possibility to be at increased risk of dying or suffering from a myocardial infarction or stroke. Therefore, priority should be given to patient's reassurance about the benign nature of VVS. There are no evidence-based data on the effects of such a reassurance, but clinical experience suggests that a convincing advice often improves the quality of life of patients with recurrent VVS. Conventional therapy of VVS includes lifestyle modification, pharmacological treatment, and cardiac pacing.

21.1 Pharmacological Treatment

Many drugs have been tested in the treatment of VVS but results have been rather disappointing. The list includes beta-blockers, dysopiramide, scopolamine, etilefrine, midodrine, clonidine, fludrocortisone, and serotonin reuptake inhibitors. While results have been satisfactory in uncontrolled or short-term controlled trials, several long-term placebo-controlled trials have been unable to show consistent

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beneficial effects of the active drug over placebo. Beta-blockers have been advocated in VVS based on presumed lessening of ventricular mechanoreceptor activation owing to their negative inotropic effects. This assumption has not been supported by the results of one major clinical trial (POST) [2], where metoprolol was not superior to placebo in the prevention of syncopal recurrences. Alpha-adrenergic agonists are potent vasoconstrictors that could ameliorate the reduction in peripheral resistance responsible for venous pooling and vasodepression. Etilefrine was the first alpha-agonist tested for treatment of VVS. The VASIS study [3], a large, multicenter, placebo-controlled double-blind study, did not show any significant differences in the recurrence of syncope between etilefrine and placebo. Midodrine, a specific alpha-1-agonist, was initially tested in patients with orthostatic hypotension. A few clinical trials and a recent meta-analysis assessed the efficacy of midodrine in patients with recurrent VVS [4–9]. One study reported negative results [9], but in the other studies midodrine proved to be beneficial on symptoms frequency, symptoms during a tilt testing [4–6], and quality of life [4, 5]. A recent meta-analysis of six randomized trials evaluating alpha-agonists for the treatment of VVS included 329 patients [8]. This study reported a large positive effect in favor of midodrine compared with placebo (odds ratio 0.21; 95 % confidence interval 0.06–0.77; $P=0.01$). Weighted mean percentage of responders for midodrine (76 ± 7 %) was significantly higher than that for etilefrine (65 ± 15 %; $P<0.001$). The observations reported by this meta-analysis are questionable because of methodological flaws. Nonetheless, there seems to be a significant treatment effect when midodrine is administered and this hypothesis is currently being tested in a large randomized trial (POST4), with results expected in 2017 [10]. Midodrine is not recommended in patients with hypertension or heart failure. Potential weaknesses of midodrine therapy include long-term compliance because of the frequent dosing (two to three times daily) and side effects such as hypertension and urinary retention that might limit its utility in older patients. Fludrocortisone is a corticosteroid with marked mineral corticoid activity that increases sodium and fluid retention and, consequently, intravascular volume. Fludrocortisone has been shown to be ineffective in a small, randomized double-blind trial carried out in children [11]. Recently, it has been investigated in adults in the POST 2 trial, where 213 patients were randomized to fludrocortisone or placebo [12]. The primary outcome of the study was the time to first recurrence of syncope, which was not significantly reduced by fludrocortisone. Further analysis of POST 2 population may identify subgroups that could benefit from this therapy. Serotonin is known to modulate central nervous system regulatory activity on blood pressure and heart rate. Based on that, investigators have attempted to use selective reuptake inhibitors (SSRIs) to raise serotonin level in the nervous system. Paroxetine was shown to be effective in one placebo-controlled trial, which included highly symptomatic patients from one institution [13]. These results have not been confirmed by another study [14]. Notably, SSRIs may be useful in patients with associated anxiety and panic disorders. Recently, ivabradine, an I(f) current blocker acting on the sinus node to slow heart rate, was tested in 25 subjects with episodes of VVS preceded by palpitations and showing sinus tachycardia before syncope during tilt testing [15]. At follow-up, 72 % of patients reported marked clinical improvement or complete resolution of symptoms. The results of this pilot study appear to be

Table 21.1 Recommendations and treatments of vasovagal syncope

Prevention of the vasovagal reflex	*Treatment of the impending vasovagal reflex*
Avoidance of potential triggers	Assumption of supine position
Hydration, salt intake	Physical counterpressure maneuvers
Moderate exercise training	Pacemaker implantation
Tilt training	Cardioneuroablation
Psychotherapy	
Paroxetine	
Lower limb compression	
Withdrawal of vasodilator agents	

encouraging, but a randomized controlled trial should be carried out before utilizing this drug in the clinical setting.

In conclusion, pharmacological treatment of VVS does not appear to be very effective, in spite of a few promising results. This is because the mechanism of VVS is quite complex and still elusive. Our knowledge on the afferent part of the vasovagal reflex (i.e., the step from the trigger to the autonomic control and central processing) is very limited. In contrast, the efferent part of the reflex is quite certain: hypotension and bradycardia are due to the transient inhibition of the sympathetic and activation of the vagal functions, respectively.

It has to be pointed out that a VVS treatment can act on the neural afferent pathway, which means prevention of the vasovagal reflex or on the efferent pathways, which means treatment of the impending/activated inhibitory reflex [16]. For example, midodrine exerts its effects on alpha-1 adrenergic receptors of the arteriolar and venular vascular smooth muscles, producing vasoconstriction and venoconstriction, respectively. Midodrine may therefore play a therapeutic role by promoting venoconstriction, which reduces venous pooling, thereby preventing the vasovagal reflex, and/or by promoting vasoconstriction. This latter could counteract the fall in blood pressure when the reflex is already activated. The mechanism of action of this drug is not clear, although the first hypothesis, that is, a venoconstriction, appears to be more likely. In this regard, a mix of recommendations and treatments is often prescribed to patients with VVS. From a conceptual point of view, prevention and therapy represent two different approaches. However, with regard to the treatment of VVS, there is some confusion in the current literature. In the present chapter, we report separately the therapeutic interventions aimed at preventing the vasovagal reflex and those aimed at treating the impending reflex (Table 21.1).

21.2 Prevention of the Vasovagal Reflex

Avoiding Potential Triggers

Identifying and potentially avoiding known triggers such as prolonged standing, hot and/or crowded environments, volume depletion, venipuncture, distressing emotions, etc., should be useful in reducing syncopal recurrences, even if this aspect has never been investigated in clinical trials.

Hydration and Salt Intake

An increase of the intake of dietary salt and water is thought to result in a clinical improvement in the vast majority of patients with VVS [1]. Plasma volume expansion ameliorates orthostatic tolerance in patients with recurrent VVS [17–20]. Patients should attempt to accomplish a daily dietary intake of at least 2 g of sodium, assuming salt tablets two to three times daily [19, 20]. The increase in dietary sodium should be accompanied by increase in fluid intake up to 2–2.5 L per day (in adults). Beneficial effects are reported in most subjects within 1 week, particularly in subjects with low dietary salt intake [21]. Patients with hypertension should avoid increasing salt intake. Rapid water ingestion may prevent VVS recurrence [22]. Previous studies have reported that this intervention is effective in preventing orthostatic intolerance and postprandial hypotension in patients with autonomic failure [23–25]. Recent reports suggest that water drinking can also be applied to improve orthostatic tolerance in healthy subjects [26–28]. The rapid onset of the effects of water drinking and its sustained effect support the use of this simple intervention as a preventive measure that can also be used during particular situations that trigger VVS [29]. Although the evidence supporting this strategy is rather weak, it is probably a cost-effective and safe strategy that should always be used as first-line therapy.

Moderate Exercise Training

Physical training has been proposed as a useful strategy in the management of patients with VVS. In nonrandomized studies, moderate physical training appeared to be effective in reducing susceptibility to VVS [29, 30]. Moderate exercise induces an increase in blood volume and muscle tone, contributing to optimization of venous return, a desirable effect in VVS patients [30, 31]. However, it should be underlined that intense physical training may lead to a decrease in orthostatic tolerance [32].

Tilt Training

This treatment strategy was developed after the observation that the rate of positive tilt test tended to decrease by repeating tilt testing. The purpose of tilt training was to reset baroreceptor reflexes, improving gravitational stress response by leading to more efficient vasoconstriction [33]. Ector et al. [34] performed repeated daily tilt tests until vasovagal responses improved and the patient tolerated the full duration of the test, which they found would happen after 3–8 tilt-training sessions. Unfortunately, in most clinical environments this treatment is not feasible. Therefore, attempt was made to shift orthostatic training (standing against a wall for 30 min, one to two times per day) to outpatient setting. Results obtained with home training were heterogeneous [35–38] and inefficacy of the treatment appeared to be related,

at least in part, to a low compliance of the patients. Therefore, this treatment should be proposed to highly motivated young subjects with recurrent VVS triggered by orthostatic stress.

Lower Limb Compression

The aim of this treatment is to reduce the venous pooling in the legs, thus preventing thoracic hypovolemia, and, consequently, the onset of the vasovagal reflex. Twenty unselected patients with clinical diagnosis of VVS and positive tilt test were included in a placebo-controlled randomized crossover study [39]. Patients underwent two consecutive tilt tests, at 1 h interval, with and without legs compression by pneumatic compression boots (positive pressure = 30 mmHg). The treatment appeared to be effective since tilt test was positive in 13 (65 %) of the patients in the control group and only in 2 (10 %) of the patients who underwent legs compression ($P < 0.0001$). It remains to be determined whether this treatment is effective in the prevention of spontaneous VVS.

Psychotherapy

Heterogeneous groups of patients with recurrent VVS report high rate of anxiety (~30 %) and depression (~15 %) [40, 41]. Individuals who are nonresponders to conventional therapies proved to be significantly more anxious and depressed [42]. It is unclear whether anxiety and distress arise as a direct consequence of the symptoms of VVS, hence leading to nonresponse, or those with high levels of anxiety are destined to be nonresponders. It has been demonstrated that both possibilities can occur in different patients [43, 44]. In nonrandomized studies, behavioral psychotherapy techniques such as applied relaxation and applied tension [45–47] and psychiatric drug treatment [48] reduced syncope recurrences in patients with anxiety and/or depression, besides improving the psychiatric symptoms.

Withdrawal of Vasodilator Agents

A drug-related vasovagal reflex has been inferred in some patients, who after oral administration of short-acting nitrate preparations developed hypotension and bradycardia [49]. In a case-control randomized trial, Gaggioli et al. [50] demonstrated that chronic vasodilator therapy enhances susceptibility to vasovagal reaction during tilt testing. Patients with positive tilt testing were randomized to continue the same vasodilator therapy they were taking or to discontinue it. The tilt testing performed at the end of the study period was positive in 85 % of patients who continued the treatment, but only in 52 % who discontinued vasodilator therapy ($P = 0.02$). Thus, a drug-related mechanism, alone or in combination with other mechanisms, should be considered in the evaluation of patients with VVS. However, whether the

response to acute testing also predicts the outcome of spontaneous syncope remains to be established. As for midodrine, it is very likely that the withdrawal of vasodilator agents exerts its effect by increasing venoconstriction, which reduces venous pooling, thereby preventing the vasovagal reflex, but it is also possible that it reduces the fall in blood pressure when the reflex is already activated.

21.3 Treatment of the Impending Vasovagal Reflex

Physical Counterpressure Maneuvers

In younger patients, VVS is usually preceded by prodromal symptoms. Their prompt and appropriate recognition provides enough time to start counterpressure maneuvers (CPMs). Isometric CPMs of the legs (leg crossing) or arms (hand grip and hand tensing) may induce a significant blood pressure increase during the phase of impending VVS [51–54]. This effect seems to be mediated by an increase in sympathetic vasomotor activity which counteracts the withdrawal of sympathetic system characterizing VVS. The Physical Counterpressure Maneuvers Trial was a randomized trial that assessed the effects of adding CPMs to conventional therapy in VVS patients [54]. Results indicated a 36 % relative risk reduction for syncope onset, but 35 % of patients did not experience prodromal symptoms lasting for sufficient time to use counterpressure maneuvers. Notably, this relative risk reduction is among the largest seen in a randomized trial of any VVS therapy. CPMs are rather effective, feasible, safe, and well-accepted by patients in daily life and should be advised as first-line treatment in younger patients presenting with VVS and recognizable prodromal symptoms. CPMs appear to be less effective in older patients because of diminished muscle strength and slower response time. Depending on the age and the clinical characteristics of the patient, another recommendation that could be given is to lie down at the onset of the prodrome. Although there are not any data supporting this recommendation, it appears to be highly effective for preventing loss of consciousness and injury.

Cardiac Pacing

The role of cardiac pacing in the treatment of VVS is controversial. Previous nonplacebo-controlled trials showed a marked reduction in syncopal recurrences with dual-chamber pacing [55–57]. However, placebo-controlled trials in which all patients received a dual-chamber pacemaker and were randomly assigned to pacemaker-on or pacemaker-off, could not reproduce these positive effects [58, 59]. A meta-analysis of all studies suggested a nonsignificant 17 % reduction in syncopal recurrences from the double-blinded studies, and 84 % reduction in the studies where the control group did not receive an inactive pacemaker [60]. In conclusion, the results of initial trials have overrated the beneficial effects of

pacemaker treatment due to a lack of blinding of both physicians and patients. In contrast, blinded trials suggest that the apparent effect is due to a strong expectation response to pacing.

Implantable loop-recorder (ILR) may identify patients with severe cardioinhibitory VVS and hence a better detection rate may identify responders more accurately. In the recently published ISSUE-3 study [61], a double-blind, randomized placebo-controlled trial, 511 patients (mean age 63 years) who had experienced > 3 syncopal episodes in the previous 2 years, received an ILR; 89 of these had documentation of syncope with ≥ 3 s asystole or ≥ 6 s asystole without syncope and met criteria for pacemaker implantation; 77 of 89 patients were randomly assigned to dual-chamber *pacing on* or *pacing off*. The 2-year estimated syncope recurrence rate was 57 % with pacemaker off and 25 % with pacemaker on ($P = 0.039$). The observed 32 % absolute and 57 % relative reduction in syncope recurrence support this invasive treatment even if the results were not excellent, since 25 % of patients of pacemaker on arm had syncopal recurrences, likely because of concomitant hypotension. The results of ISSUE-3 trial suggest that the use of ILR improves the selection of patients who could benefit from a pacemaker, but this strategy is limited by the large number of ILRs to be implanted to identify a small number of patients who will then potentially benefit from cardiac pacing. An on-treatment analysis, which included even the nonrandomized patients followed-up in the ISSUE registry, showed that 5 ILRs had to be implanted to find one patient who finally had a pacemaker to be inserted [62]. A subanalysis of the ISSUE-3 trial showed that among the patients with ILR-documented asystolic episodes, cardiac pacing was much more effective in the patients who had negative response to tilt testing than in those with positive response [63]. Indeed, 52 patients, 26 tilt positive and 26 tilt negative, with ILR-documented asystolic pause received a pacemaker. At 21-month follow-up, the estimated product-limit syncope recurrence rates were 55 % and 5 %, respectively ($P = 0.004$). Therefore, the highest efficacy of cardiac pacing seems to be present in patients with spontaneous asystolic pause (ILR-documented) and negative tilt testing. This result was largely unexpected and seems to suggest that a vasodepressive mechanism is dominant in tilt positive patients, while a cardioinhibitory mechanism is dominant in tilt negative patients. However, this result needs to be confirmed by other trials since it was obtained in a small study group and a type II error cannot be excluded. While the use of ILRs may help to identify the most suitable patients for pacemaker therapy, this approach is still characterized by weakness, namely the high rate of nonresponders and the exceeding number of ILRs to be implanted to find out patients who will really benefit from that therapy. At present, it is not possible to draw definite conclusions on the indications to cardiac pacing in patients with certain or suspected VVS. Implantation of a loop-recorder is a possible strategy. An alternative possibility is pacemaker implantation in patients with asystolic response during tilt testing. In this regard, Brignole et al. [63] reported that an asystolic response during tilt testing predicted a similar asystolic form during ILR monitoring with a positive predictive value of 86 %. Even if cardiac pacing seems to be less effective in patients with positive tilt testing, a fourfold longer median time to syncope recurrence was observed in asystolic than in

nonasystolic tilt positive patients on pacemaker treatment (8 vs. 2 months) [63]. The same finding was observed in the SYNPACE trial [59], in which the time to the first syncope recurrence was much longer on pacemaker therapy than on placebo in patients who had shown an asystolic response during tilt testing.

Dealing with pacing therapy and VVS, the most important issue appears to be the patient selection. The fact that pacing is effective does not mean that it is always necessary. It must be emphasized that the decision to implant a pacemaker needs to be undertaken in the clinical context of a benign condition (in terms of cardiovascular events), which frequently affects young subjects. Thus, cardiac pacing should be the last choice in highly selected patients with recurrent syncopal episodes, injuries, and/or deteriorated quality of life because of syncopal spells. In this regard, the "oculobradycardic reflex" should be mentioned [64], which we described some years ago after the "oculostenotic reflex," which might potentially lead to overutilization of pacemaker therapy if patients who undergo implantation of loop-recorder are not rigorously selected.

At present, there are no data on the cardiovascular treatment of patients with VVS with clinical presentation as unexplained fall (see Chaps. 11 and 13). In a pilot study, the use of ILR in these patients appears to be encouraging, but larger studies are needed [65].

Cardioneuroablation

Recently, endocardial vagal denervation of the left atrium, also defined as cardioneuroablation, has been proposed to treat VVS [66–69]. The purpose of this procedure is to destroy the efferent vagal pathways to abolish the cardioinhibitory component of the vasovagal reflex. Therefore, this treatment does not prevent the vasovagal reflex, but acts on the efferent vagal cardiac pathway without affecting the sympathetic vasomotor control. The spectral study of endocardial potentials during sinus rhythm reveals two types of myocardium. The first one, the compact myocardium, is characterized by high amplitude, isotropic conduction, and a smooth spectrum, whereas the second one, the fibrillar myocardium, has low amplitude, anisotropic conduction, and a segmented spectrum. Several observations have demonstrated a close relation between the fibrillar myocardium and the cardiac innervation interface. Through online real-time spectral mapping technique, it is possible to reveal the fibrillar muscle type in order to guide radiofrequency catheter ablation. Consequently, most of the post-ganglionic parasympathetic neurons of the left atrium may be destroyed and should not recover, whereas the sympathetic and sensory terminal fibers usually recover with a time course spanning from weeks to months. Pachon et al. [68] performed cardioneuroablation in 43 patients (mean age 32 years) with recurrent VVS and important cardioinhibition at tilt testing. During a mean follow-up period of about 2 years, only three patients (7 %) had syncopal recurrences. During post-ablation tilt testing, only four patients (10 %) showed partial cardioinhibitory response. Yao et al. [69] utilized this procedure in ten patients (mean age 50 years) with recurrent episodes of VVS. After a mean follow-up period of 30 months, no patient had any recurrence of syncope, but five patients (50 %) had episodes of presyncope. This treatment could be an alternative to pacemaker

implantation, but a larger patient cohort is needed to confirm the safety and efficacy of the procedure. It could be potentially indicated in highly selected patients with recurrent, disabling VVS, and with relevant cardioinhibition response who are refractory to conventional treatment.

21.4 Choice of Treatment

Education/reassurance is an important first step in all patients with VVS, independently of the severity of this condition. As a general rule, the patient should be reassured about the benign nature of the syncopal spells in terms of adverse events. Known trigger should be identified and strategies to potentially avoid them discussed. The patient should be taught to maintain hydration and take regular moderate physical exercise. In an observational study, a standardized educational protocol significantly reduced traumatic injuries and syncope recurrence in subjects with VVS [70].

For the VVS patients needing treatment, there are some evidence-based therapies. Therapeutic choice mainly depends on the presence and duration of prodromal symptoms [71]. In patients with recognizable prodromes and aged less than 70 years, the first-line treatment is CPM. In patients with no or minimal prodromes, disabling symptoms and asystole during monitoring, pacemaker implantation appears to be an effective treatment in most cases. However, an "area of uncertainty" remains and is represented by patients with VVS and no or minimal prodromes. For these patients, there is no clear evidence-based therapy and the treatment can be chosen by considering the clinical context, the risk of trauma, and possible comorbidities. The "area of uncertainty" is reported in Table 21.2.

Table 21.2 Current treatment of vasovagal syncope

First-line therapy	
Pts with well-recognizable prodromes	→ Counterpressure maneuvers
Pts with no or minimal prodromes, disabling symptoms, and ILR-documented asystole	→ Pacemaker
"Area of uncertainty": Patients with no or minimal prodromes	
Pts with VVS and hypotension	→ Midodrine
Pts with VVS and dehydration	→ e.v. saline, increase oral fluid and salt intake
Pts with VVS and anxiety, depression or phobias	→ Psychological therapy and/or paroxetine/reboxetine/venlafaxine
Pts with VVS treated with vasodilating drugs	→ Withdrawal of the drug or reduction of the dosage
Highly motivated young or middle-aged pts with VVS	→ Tilt training
Pts with VVS and chronic venous insufficiency	→ Lower limb compression
Pts with frequent episodes of VVS and severe cardioinhibitory response during tilt testing	→ Pacemaker

Abbreviations: *pts* patients, *VVS* vasovagal syncope

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Part VI

Special Issues

Sick Sinus Syndrome

22

Juan C. Guzman and Carlos A. Morillo

Key Points

- Syncope in the context of SSS is frequently abrupt and lacks typical prodromal symptoms.
- Syncope is frequently precipitated by sinus pauses following sinus node overdrive by atrial tachyarrhythmias such as atrial fibrillation.
- The diagnosis of SSS is usually obtained by combining clinical presentation and typical ECG findings that disclose evidence of sinus node dysfunction.
- Treatment is usually achieved by implanting a permanent pacemaker with complete resolution of syncope.

22.1 Introduction

The sinoatrail node (SAN), the dominant pacemaker in the heart, was originally described by Keith and Flack in 1907 [1]. The SAN is a subepicardial structure located at the junction of the right atrium and the superior vena cava [1]. The SAN spontaneous firing activity is not completely understood. Two predominant

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mechanisms are proposed to serve as the initiation of the sinus activity: The If channels (sodium and potassium ionic currents) and spontaneous intracellular calcium released by sarcoplasmic reticulum [2]. These two mechanisms are not mutually exclusive, and current evidence suggests that they may be complementary in their pacemaker actions. The SAN is richly innervated by the autonomic nervous system and the balance between the parasympathetic and sympathetic inputs modulate pacemaker rate. The vagal parasympathetic nerves slow the SAN rate and are dominant at rest, while increased sympathetic nerve traffic as well as adrenal medullary release of catecholamines increase sinus rate during exercise and stress.

Sick Sinus Syndrome (SSS) is characterized by dysfunction of the SAN secondary to gradual deterioration of the pacemaker cells and the surrounding atrial myocardium. The term was first coined by Ferrer et al. in 1968 [3] and is now commonly used to describe the inability of the SAN to generate a heart rate that meets the physiological needs of an individual [4]. Moreover, SAN remodeling in atrial tachyarrhythmias can be triggered by persistent changes in atrial physiology that result in increased vulnerability to further arrhythmias, particularly atrial fibrillation [4]. These abnormalities can lead to profound sinus bradycardia, sinus pauses, cardiac sinus arrest, and sinoatrial exit blocks. SSS is frequently associated with paroxysmal atrial fibrillation and manifests clinically as the bradycardia–tachycardia syndrome.

The clinical presentation, etiology, natural history, diagnosis and evaluation, as well as treatment of SSS will be reviewed in this chapter.

22.2 Clinical Characteristics

The clinical manifestations of SND are diverse, reflecting the range of typical sinoatrial rhythm disturbances. The most dramatic presentation is syncope and is associated with an abrupt pause in sinus impulse formation or sinus exit block, either spontaneously or after the termination of an atrial tachyarrhythmia, that causes cerebral hypoperfusion. The pause in sinus node activity is frequently accompanied by an inadequate, delayed, or absent response of subsidiary escape pacemakers in the AV junction or ventricular myocardium, which aggravates the hemodynamic consequences. The initial diagnosis of SSS is often clinical and patients may present with symptoms of dizziness, lightheadedness, syncope, shortness of breath on exertion, angina, and/or palpitations. Patients with symptomatic SSS are frequently older, have multiple comorbidities and high mortality rate. Clinical trials comparing pacing modes in patients with sinus node dysfunction have shown a mean age of 73–76 years and both genders are equally affected [5, 6].

SSS is defined by electrocardiographic criteria since clinical signs and symptoms may vary significantly. It is important to highlight that sinus bradycardia does not always confirm the presence of SSS (i.e., increase vagal tone (athletes) and medications that slow sinus rate). The characteristics of SSS include:

- Frequent events of inappropriate and often severe bradycardia [3].
- Sinus pauses, arrest and sinoatrial exit block with and, often, without appropriate atrial or junctional escape rhythms. The failure of timely rate response leading to extreme bradycardia and asystole can lead to syncope [3].
- Alternating bradycardia and atrial tachyarrhythmias [7]. Most commonly, atrial fibrillation (AF) but atrial flutter and paroxysmal supraventricular tachycardias can also occur. These can be triggered by a prolonged sinus node recovery time after spontaneous conversion from the tachyarrhythmia.
- The electrocardiographic manifestation may occur with or without symptoms.

22.3 Etiology

SSS occurs as a result of disorders in automaticity, conduction, or both. Abnormal automaticity, or sinus arrest refers to a failure of sinus impulse generation while abnormal conduction, or sinoatrail delay or block, is a failure of impulse transmission. These disorders may be the result of several different mechanisms. The most common cause of SSS is the replacement of the sinus node tissue by fibrotic tissue, which may be accompanied by degeneration and fibrosis of the conduction system including AV node [8]. Moreover, atherosclerosis, inflammatory processes, or embolic diseases can compromise the blood supply through the SAN artery [9]. Finally, SSS is less often due to a variety of disorders:

- Infiltrative diseases such as amyloidosis, sarcoidosis, scleroderma, hemochromatosis, and sometimes tumors [9]
- Epicardial and pericardial disease [9]
- Infectious diseases with inflammatory features (Chagas's disease, Lyme disease, etc.)
- Drugs such as parasympathicomimetic agents, sympatholytics, digoxin, calcium channel blockers, and lithium
- Toxins such as grayanotoxin produced by some plants and found in certain variety of honey [10]
- Cardiac trauma during surgery may affect the SAN directly or its blood supply
- Congenital and acquire heart disease as well as rare familial cases of SSS associated with specific gene mutations [11]

22.4 Natural History

SSS evolves with time. There are variable, and often long, periods of normal sinus node function [12]. Nevertheless, once present, SSS eventually progresses and manifests in most patients. Lien et al. [12] reported that, in patients presenting with sinus bradycardia associated with SAN block and SAN arrest, an average of 13 years were needed for progression to complete SAN dysfunction. Overall intrinsic sinus node function tends to deteriorate with age [13]. Atrial arrhythmias and conduction

disturbances become more common over time increasing the likelihood of SSS. Overall, patients with SSS are at increased risk of cardiovascular events including syncope, heart failure, chronic AF, or poorly tolerated atrial arrhythmias [13]. Multivariate analysis of cohort studies has identified independent predictors of a cardiovascular event including age, left ventricular end-diastolic diameter, and left ventricular ejection fraction. Independent predictors of syncope were a history of syncope and corrected sinus node recovery time ≥800 ms.

Finally, the mortality of patients with SSS is significant and not always due to cardiac causes. In the MOST trial [14], 2,010 patients (median age 74 years) were studied; 404 (20 %) died at a median of 33 months of follow-up. The cause of death was cardiac in 35 %, noncardiac in 49 %, and unknown in 16 %. Independent predictors of death included age, male sex, weight, prior myocardial infarction, cardiomyopathy, and measures of functional status and other comorbidities.

22.5 Diagnosis and Evaluation

The diagnosis and evaluation of SSS include both physiologic and pharmacologic testing. A number of different modalities have been used in the evaluation of suspected SSS:

- ECG: The diagnosis of SSS in persons with suggestive symptoms is often made from the surface ECG. The typical ECG manifestations were discussed in the clinical characteristics section of this chapter.
- Ambulatory ECG monitoring (Holter) and event recording have the potential advantage of prolonged ECG monitoring for days and weeks, and allows the correlation of symptoms with cardiac arrhythmias [15]. In patients suspected of having SSS, ambulatory ECG monitoring may provide important clues in 50–70 % of cases [15, 16]. In some cases, when the symptoms are infrequent, implantable loop recorders have been used for monitoring periods greater than 1 year [17].
- Exercise testing: Inappropriate increase in heart rate after exercise may be useful in the diagnosis of SSS (chronotropic incompetence) [18]. Clinicians diagnose chronotropic incompetence as either a near-constant nontachycardic heart rate over a 24 h period or the inability of achieving at least 80 % of the maximum predicted heart rate with exercise testing according to age and gender [18].
- Intrinsic heart rate (IHR) is defined as the heart rate after complete pharmacological autonomic blockade of the sinus node. This is achieved with the simultaneous intravenous administration of propranolol (0.2 mg/kg) and atropine (0.04 mg/kg) [19]. The IHR helps discriminate patients with intrinsic SSS (reflecting primary SA node dysfunction) from those who have bradycardia from extrinsic causes such as increased parasympathetic tone or drugs [20]. Intrinsic SSS is presumed to be present if the sinus rate does not exceed the predicted IHR after atropine. A normal IHR suggests extrinsic causes.
- Invasive electrophysiological studies (EPS) are not commonly used for the evaluation of SSS because of their limited sensitivity in eliciting

bradyarrhythmic abnormalities [15]. The salient aspects of electrophysiology studies that aid in eliciting a bradyarrhythmic abnormality include assessment of the sinoatrial node recovery time (SNRT), sinoatrial conduction time and corrected SNRT, and the sinus node and atrial tissue refractory periods [21]. cSNRT is perhaps the most useful test of overall sinus node automaticity. The concept is simple. The atria are driven rapidly; a normal SA node will have a recovery time within certain limits, while recovery will be delayed in a depressed or sick sinus node [22].

22.6 Treatment

The only treatment option available for symptomatic SSS is permanent pacing. Mode and selection of type of pacing are out of the scope of this review and current guideline recommendations are summarized in Table 22.1 [23]. The goal of pacing is to reduce the recurrence of syncope and presyncope and to improve chronotropic incompetence.

Table 22.1 Recommendations for permanent pacing in sinus node dysfunction [23]

Class I
1. Permanent pacemaker implantation is indicated for SND with documented symptomatic bradycardia, including frequent sinus pauses that produce symptoms. (Level of Evidence: C)
2. Permanent pacemaker implantation is indicated for symptomatic chronotropic incompetence. (Level of Evidence: C)
3. Permanent pacemaker implantation is indicated for symptomatic sinus bradycardia that results from required drug therapy for medical conditions. (Level of Evidence: C)
Class IIa
1. Permanent pacemaker implantation is reasonable for SND with heart rate less than 40 bpm when a clear association between significant symptoms consistent with bradycardia and the actual presence of bradycardia has not been documented. (Level of Evidence: C)
2. Permanent pacemaker implantation is reasonable for syncope of unexplained origin when clinically significant abnormalities of sinus node function are discovered or provoked in electrophysiological studies. (Level of Evidence: C)
Class IIb
1. Permanent pacemaker implantation may be considered in minimally symptomatic patients with chronic heart rate less than 40 bpm while awake. (Level of Evidence: C)
Class III
1. Permanent pacemaker implantation is not indicated for SND in asymptomatic patients. (Level of Evidence: C)
2. Permanent pacemaker implantation is not indicated for SND in patients for whom the symptoms suggestive of bradycardia have been clearly documented to occur in the absence of bradycardia. (Level of Evidence: C)
3. Permanent pacemaker implantation is not indicated for SND with symptomatic bradycardia due to nonessential drug therapy. (Level of Evidence: C)

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Vasovagal Syncope in Children

23

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Key Points

- Syncope during exertion or supine position should arouse more suspicion.
- Tilt testing is rarely indicated as a diagnostic tool.
- Especially in syncope during exertion echocardiographic evaluation of coronary arteries is mandatory.
- Breath-holding spells are benign and self-limiting in most cases; the serum iron checking may be useful.
- The medical therapy is rarely indicated; a greater salt intake and midodrine may be helpful in some cases.

Syncope is common in pediatric population, carrying a significant health and psychological impact. The incidence of syncope in the pediatric age that requires medical intervention is estimated at 125 of 100,000 subjects (0.125 %). An incidence peak occurs around the age of 15 years, with females having more than twice the incidence of males. A lower peak occurs in older infants and toddlers, most commonly referred to as "breath-holding spells" [1]. In the pediatric age, the most common etiology is certainly neurally mediated syncope (61–80 %), followed by neurological–neuropsychiatric loss of consciousness (LOC) (11–19 %) and cardiac syncope (6–11.5 %). The etiology remains undetermined in 15–20 % of cases [2].

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Current classification of syncope provides three main groups [1]:

- Reflex syncope (neurally mediated): vasovagal, situational, carotid sinus syncope, and atypical forms. Breath-holding spells (BHS) and postural orthostatic tachycardia syndrome (POTS) may be included in this group.
- Syncope due to orthostatic hypotension (primary or secondary autonomic failure, drug-induced orthostatic hypotension, volume depletion).
- Cardiac syncope: arrhythmias, structural heart diseases (including repaired or palliated congenital heart defects) and other causes like pulmonary embolism/hypertension and aortic dissection.

Conversely, there are some pediatric conditions classified as pseudosyncope or nonsyncope (without global cerebral hypoperfusion):

- Neurological syncope (epilepsy, cerebrovascular accidents, headache)
- Metabolic disorders (hypoglycemia, hypoxia, hyperventilation with hypocapnia)
- Intoxication (medications, drugs abuse)
- Psychogenic pseudosyncope (somatization and/or conversion disorder, psychogenic hyperventilation, depression, Munchausen syndrome)
- Cataplexy
- Drop attacks
- Trauma

23.1 Definition and Etiopathogenesis

Reflex syncope includes a heterogeneous group of functional disturbances characterized by episodic vasodilation and/or bradycardia resulting in a fall in arterial blood pressure and global cerebral perfusion. Cerebral ischemia lasting 8–10 s results in a complete LOC and, if it continues for more than 15 s, generalized tonic–clonic contractions may occur. Current hypotheses suggest that an abrupt increase in peripheral vascular pooling results in a sudden reduction in venous return to the heart, producing an increased ventricular contractility; hence, an erroneous hypertensive signal from myocardial C-fibers to the central nervous system that increases the reflex vagal tone, then vasodilation and bradycardia. For this reason, patients present a fall in blood pressure resulting in cerebral hypoperfusion and LOC.

The circumstances surrounding reflex syncopal events often include a recent change in posture, but may be associated with a wide variety of common situations [2].

23.2 Clinical Presentation

In patients with reflex syncope, there are typically three distinct phases to an event: a short prodromal period characterized by autonomic activation (diaphoresis, nausea, abdominal discomfort, pallor, hyperventilation, blurred vision, dilated

pupils, tachycardia followed by bradycardia), LOC usually of 5–20 s, and the recovery period (5–30 min) characterized by fatigue, dizziness, weakness, headache, and nausea.

As opposed to adults, children often panic at the onset of prodromal signs beginning to hyperventilate and further reducing cerebral perfusion by producing systemic hypocapnia.

While reflex syncope causes are generally benign, a syndrome of "malignant" vasovagal syncope has been used to describe those patients with frequent and recurrent episodes, without clear prodrome, with prolonged asystole, with fall to the ground, or those who have spells without an apparent trigger. Currently, there are no clear implications regarding prognosis and treatment for this form of vasovagal syncope but these patients do not necessarily require more aggressive therapy [1–3].

23.3 Classification

Reflex syncopes in the pediatric age are classified into vasovagal and situational while "breath-holding spells" deserve special mention and a separate classification [1, 4–6].

Vasovagal syncope is a transient LOC triggered by emotional or orthostatic stress (fear, pain, standing quickly, and prolonged standing). It is usually preceded by prodromal symptoms of autonomic activation (sweating, pallor, nausea).

Situational syncope traditionally refers to reflex syncope associated with some specific circumstances/triggers (Table 23.1).

Carotid sinus syncope in its rare spontaneous form is triggered by mechanical manipulation of the carotid sinuses. In the more common form, no mechanical trigger is found and it is diagnosed by carotid sinus massage (asystole >3 s with or without at least 50 mmHg fall in systolic blood pressure). This kind of syncopal event is not common in pediatric age, predominantly affecting older males.

Atypical vasovagal syncope is defined as a transient LOC not preceded by an evident trigger, positive tilt test, and absence of any competing diagnosis.

Table 23.1 Possible reflex syncope triggers

Emotional stress (pain, sight of blood, venepunctures)
Immediately after exercise
Coughing, sneezing, swallowing, vomiting, defecation, urination, stretching
Fasting, lack of sleep, menstruation, rapid weight loss, headache, fever
Prolonged standing (in hot and crowded environments)
Standing up quickly, arising from squat
Carotid sinus pressure
Self-induced hyperventilation
Medications, illicit drugs and alcohol abuse
Supraventricular tachycardias

Breath-holding spells are a common source of considerable anxiety for parents even though they are mostly benign. They occur in approximately 5 % of the population with equal distribution between males and females, most commonly in children between 12 and 24 months (uncommon in the first week of life or after 2 years of age).

The diagnosis relies on the recognition of a specific and stereotyped sequence of clinical events. The spell is a reflex reaction to an unpleasant stimulus (fear, scolding from parents, quarrel with brother) followed by a silent and prolonged exhalation associated with variation in skin color and, in severe forms, LOC, and loss of postural tone. The etiology is still unclear, although the association between spasms and iron deficiency is known for a long time, probably for the role of iron in enzymes and neurotransmitters metabolism of the central nervous system. In this context, LOC is supposed to be caused by vagally mediated cardiac inhibition. BHS can be divided into two forms: cyanotic and pallid.

The cyanotic form is the more common; the clinical presentation begins with a loud cry followed by a forced expiration then apnea, cyanosis, and LOC (myoclonic jerks and rigidity may be associated). The pallid form usually begins after injury or pain followed by interruption of breathing and LOC [2, 7].

23.4 Diagnostic Workup

Even if clinical presentation of different types of syncope is quite similar, medical history, physical examination, blood pressure, and 12-lead ECG often allows obtaining of useful information to achieve an etiological diagnosis (96 % sensitivity for cardiac syncope as showed by Ritter et al.). The medical history conducted properly and in a systematic manner can be diagnostic in up to 45 % of cases. The family history is of paramount importance and should include questions about syncopes or sudden deaths in young kindreds, primarily or secondarily arrhythmic diseases (Long QT syndrome, cardiomyopathies, and neuromuscular diseases), sudden infant death syndrome (SIDS), congenital heart diseases, myocardial infarction at a young age, deafness, and seizures. Finally, do not forget to ask if the parents fainted during blood samplings [1, 2, 4]. Personal medical history should focus on previous structural or arrhythmic heart disease, metabolic and neurological disorders, and any taken medications (including drug and alcohol abuse in adolescents). Secondly, the circumstances of the syncopal event should be investigated: the surrounding environment, the position of the body, the relationship with food and circadian rhythms, any precipitating factors and prodrome, the characteristics of syncopal attack by the witnesses (mode of falling to the ground, skin color, duration of LOC, the characteristics of breath, eyes deviation, involuntary movements, tongue biting). Physical examination, as for adults, should investigate any neurological or cardiac causes of syncope, avoiding traumatizing the child. Heart rate, blood pressure, and respiratory rate should be noted. Blood pressure should be obtained in the supine, sitting, and standing positions in order to exclude orthostatic hypotension and other autonomic disorders such as type III Ehlers–Danlos syndrome and familial dysautonomia (Riley–Day syndrome). Remarkably, at least 60 % of children with familial

Table 23.2 Clinical features suggesting a cardiac etiology of syncope

Family history:
Early myocardial infarction
Unexplained sudden death in family members <40 years old
Known familial arrhythmia or heart disease (LQTS, SQTS, CMP)
Past medical history:
Symptoms suggesting heart disease
Known structural or arrhythmic heart disease
Event features:
No prodrome
Palpitations or chest pain before syncope
Exercise or stress
Supine position
Syncope in swimming pool
Triggered by a loud noise
Need for cardiopulmonary resuscitation
Neurological sequelae
Abnormal physical examination:
Irregular pulse, pathological tones and murmurs, pericardial rubs
Pathological ECG findings

LQTS long QT syndrome, *SQTS* short QT syndrome, *CMP* cardiomyopathies

dysautonomia have breath-holding spells during the first 5 years of life [2, 3]. To complete the initial assessment is mandatory to perform a 12-lead ECG paying particular attention to QT duration, the presence of ventricular preexcitation, bundle branch block pattern (Brugada syndrome and right ventricular cardiomyopathy), left ventricular hypertrophy, pathological T waves, atrioventricular block (congenital or acquired following acute rheumatic fever, Lyme disease, viral myocarditis), pacemaker, or implantable cardioverter defibrillator malfunction [1]. A special mention is required for the relief of right bundle branch block pattern and syncope during fever, which necessitates repeating the ECG during hyperpyrexia to unmask a possible Brugada syndrome.

Because of the significantly worse prognosis, cardiac causes (arrhythmic or structural) must be carefully excluded facing a syncopal event in the pediatric age (Table 23.2).

Here below we report the most common findings that lead one to suspect a non-syncopal LOC [1, 6, 7]:

- Hypoglycemia: transient LOC preceded by intense sweating and tremors. High suspicion in patients with known diabetes and on hypoglycemic therapy.
- Transient ischemic attack: focal neurological symptoms associated with transient LOC.
- Psychogenic pseudosyncope: very frequent transient LOCs, long-lasting, eyes closed during attack, many psychosomatic disorders.

Table 23.3 Differential diagnosis between epilepsy and syncope

	Seizure	Syncope
Trigger	Rare	Frequent
Prodrome	Aura	Diaphoresis, nausea, blurred vision, abdominal discomfort
Type of fall	Usually tonic	Usually flaccid
Skin color	Typically pale	May be cyanotic
Eyes deviation	Generally lateral	Generally upwardly
Muscle twitching	Tonic–clonic, rhythmic, prolonged (≈1 min), may precede LOC	Tonic–clonic, arrhythmic, short-term, appear late
LOC duration	Often >5 min	Usually <1–2 min
Automatisms	Quite frequent	Very rare
Tongue biting	25 % of cases	Very rare
Signs/symptoms at recovery	Prolonged confusion, muscle pain, headache, can often stand early in recovery	Confusional state generally absent or lasting <5 min, nausea, vomiting, sweating, pallor, difficult to stand before complete recovery

Modified from Alboni [3]

- Cataplexy: LOC preceded by an emotional trigger in patients with known narcolepsy.
- Epilepsy, as in adulthood, deserves a particular focus because of differences regarding specific triggers, prodromes, characteristics of syncopal attack, signs/symptoms during recovery period, obtainable by careful examination of history (Table 23.3).

  Electroencephalography (EEG) may be indicated for these patients even if many authors stressed the overutilization of the EEG and its low diagnostic value in syncope patients.

23.5 Diagnostic Tests

Second-level cardiological tests such as echocardiography, head-up tilt test, 24 h Holter ECG, 24 h blood pressure monitoring, loop recorder/event recorder, exercise stress test, and invasive electrophysiological study should be carried out on the basis of data obtained from medical history, clinical evaluation, and 12-lead ECG.

Echocardiography is useful to exclude structural and some arrhythmic heart diseases. It should be performed only in patients with positive family history for heart diseases, arrhythmias, and sudden death, abnormal cardiovascular examination or pathological ECG. In the context of exertional syncope, one should pay particular attention to congenital and acquired coronary artery diseases (Anomalous Left Coronary Artery From the Pulmonary Artery – ALCAPA, Anomalous Coronary Arteries Originating from the Opposite Sinus of Valsalva – ACAOS, coronary artery fistulas, Kawasaki disease), cardiac walls thickness (hypertrophic cardiomyopathy),

myocardial dysfunction (Emery–Dreifuss, Becker and Duchenne muscular dystrophies, myocarditis), right ventricular size and function (arrhythmogenic right ventricular cardiomyopathy, repaired tetralogy of Fallot), left ventricular outflow tract obstruction (obstructive hypertrophic cardiomyopathy, aortic stenosis), right ventricular outflow tract obstruction (tetralogy spells in unrepaired Fallot or transposition of the great arteries with pulmonary stenosis), and pulmonary hypertension (Eisenmenger patients). Obstructive lesions may require stress echocardiography (exercise or pharmacological stress) to unmask fake low pressure gradients at rest [1, 2].

Tilt table testing may be used to confirm the diagnosis of reflex syncope in children and adolescent. The tilt test consists of positioning the patient on a floating lounger which is progressively increased up to the vertical position during ECG and blood pressure (beat to beat) monitoring. The test is considered positive when the patient has symptoms of syncope or presyncope. There are two principal methods of tilt table testing. The first uses a passive tilt for a period of 45 min at an angle between 60° and 80°. The second method frequently uses a shorter period of upright tilt in association with a variety of provocative agents (isoproterenol or sublingual nitroglycerin) and it may be indicated in selected cases. From the limited data available in the literature, tilt testing in the pediatric age has a low diagnostic power, with many false positives (40 % after instrumentation with an intravenous line) and false negatives (up to 50 %) in adult series, so it should not be considered as the gold standard for the diagnosis of neurally mediated syncope. Despite this, postural orthostatic tachycardia syndrome (POTS) must be mentioned because of the specific pattern of response to tilt testing defined as tachycardia (increased heart rate >30 b/min or heart rate >120 b/min) and symptoms of cerebral hypoperfusion (palpitations, lightheadedness, fatigue, blurred vision, and possible syncope) that occur within 10 min after the upright position [2, 7].

ECG Holter monitoring is often limited by the poor diagnostic sensitivity since the majority of patients relapse monthly or annually. Modern endless *loop recorders–event recorders*, allowing the long-term recording up to 7–10 days, are increasingly prescribed and seem to have a better diagnostic power. Prolonged ECG monitoring plays a crucial role in the diagnosis of sick sinus syndrome; supraventricular and ventricular tachycardia, which characterize some congenital heart diseases after repair (Fallot patients); palliation (Mustard/Senning and Fontan patients), or during natural history (Ebstein's anomaly, congenitally corrected transposition of the great vessels). Finally, *implantable loop recorder* has indications restricted to exceptional cases for rarity and family history, in which the favorable benefit/risk ratio justifies the invasiveness of the procedure [1, 2, 5].

Blood pressure Holter monitoring allows the assessment of circadian blood pressure trend and may be a viable alternative to tilt testing for the diagnosis of neurally mediated syncope, particularly in patients too young for it.

Exercise stress test should be performed by those patients with exercise-related syncope, in order to clarify if the episode occurs during or after exercise, which traditionally means from cardiac causes or from dehydration, even if exceptions transform this classification in a minefield. A special mention should be made for cases of borderline length of corrected QT interval and catecholaminergic

polymorphic ventricular tachycardia (often with normal baseline ECG) in which the stress ECG may reveal an altered QT hysteresis in the first case or show the arrhythmia in the second.

Electrophysiological study (*EPS*), in skilled hands, is useful to diagnose and/or treat arrhythmias, particularly in case of previously operated congenital heart disease. Anyway, EPS has a very minor role in pediatric patients with syncope and its safety is strictly bound to the child's weight [1, 2, 5].

23.6 Treatment and Prognosis

The first approach to all forms of neurally mediated syncope is only education (and reassurance for parents!): to avoid hot and/or crowded environments, dehydration, to perform maneuvers capable of removing blood from the lower limbs (hand gripping, leg crossing, squatting, and caffeine for Fallot patients) or to quickly take the supine at the onset of prodrome. Sometimes even tilt testing may have simultaneously an educative and therapeutic role, teaching the child to recognize the warning symptoms. Some studies have suggested a true tilt training for highly motivated patients, that is, progressively prolonged periods of enforced upright posture, although results are controversial [2, 5, 7].

If the symptoms persist, it may be necessary to establish a pharmacological treatment, especially if syncopal episodes have generated physical trauma. Three pharmacological agents showed to be effective in the pediatric age in prospective, randomized, placebo-controlled studies: midodrine (starting with 5 mg twice or three times per day) or pseudoephedrine, selective alpha-agonists, are used to increase the peripheral vascular resistance and venous tone even if side effects are often intolerable; paroxetine, a selective inhibitor of serotonin reuptake (effective in the treatment of POTS); and fludrocortisone to support the maintenance of blood volume (most effective in combination with high salt and fluid intake) [1, 2].

Drug therapy may be interrupted after a symptom-free period of at least 12 months; approximately 80 % of adolescents will not require further therapy while the remaining group will return under treatment for at least 1–2 years. As a general rule pacemaker implantation should be avoided, exceptions can be made for documented prolonged asystole and/or repeated disabling physical trauma [7].

BHS deserve a special mention. Neither cyanotic nor pallid BHS require any specific therapy other than reassuring parents that the episodes are not dangerous. Iron supplementation showed in some cases a reduction in the frequency of spells. In severe cases it is mandatory to perform a 12-lead ECG and eventually monitor with loop recorder to exclude arrhythmic diseases. Numerous case reports suggested that pacemaker implantation could be reasonably considered in subjects with frequent and severe BHS, poor response to medications, and demonstration of cardioinhibition during spells [1, 7].

Despite pediatric reflex syncope being a common occurrence, a source of great anxiety for parents (and often physicians), and the prognosis is ultimately benign, it must be "won" through careful exclusion of more ominous etiologies.

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Vasovagal Syncope in the Elderly

24

Andrea Ungar and Martina Rafanelli

Key Points

- The incidence of syncope increases with age. Comparing the causes in the general population and in the elderly, vasovagal syncope is the most frequent in both populations.
- In the elderly, a vasovagal syncope could occur without predisposing conditions and could be heralded by typical nausea, blurred vision, and diaphoresis, but prodromal symptoms can also be short and the loss of consciousness can start abruptly, leading to falls and injuries.
- Considering the relevant presence of retrograde amnesia for the loss of consciousness in the elderly, it is important to collect the clinical history supported by a witness's account. However, the clinical history has a limited value in the differential diagnosis between cardiac and neurally mediated cause of syncope in older patients.
- The first-line evaluation should include cognitive status examination. The assessment of the neurological and locomotor system should supplement the physical examination, in order to identify coexistent diseases or disabilities. A very important part of the initial evaluation is the active standing test, as the rate of orthostatic hypotension increases with advancing age. The carotid sinus massage could also be performed during the first-line evaluation, because of the high prevalence of carotid sinus syndrome.

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- Tilt testing, well tolerated even in the elderly, is useful in the differential diagnosis between vasovagal syncope and other forms of hypotension or autonomic dysfunction and between syncope and unexplained falls. In older patients, it is advisable to run a complete neuroautonomic assessment, through tilt test, active standing test, and carotid sinus massage, because of the possible coexistence of different neurally mediated mechanisms in the genesis of syncope.

24.1 Epidemiology

Syncope is a relevant problem in the clinical practice, particularly in geriatric patients [1, 2], as its incidence increases with age [3].

In a study conducted in an Emergency Department (ED), the mean age of patients admitted for syncope was 71 years, and the proportion of patients older than 65 years was 60 % [4]. Similarly, in a cross-sectional study on patients with syncope identified from the USA National Inpatient Sample (NIS) database for the years 2000–2005, the mean age was 69 years and only 7.7 % of patients below the age of 40 suffered from syncope [5].

Comparing the causes of syncope in the general population (EGSYS 2, Evaluation of Guidelines in Syncope Study 2) [6] and in the elderly (GIS, Group for the Study of Syncope in the elderly) [7], vasovagal syncope (VVS) is the most frequent in both populations. The prevalence of orthostatic hypotension (OH) is about 30 % in older people living in the community and 33 % in inpatients [7] (Table 24.1). An observational study on community dwelling people older than 65 years showed a lower prevalence of OH of 12.5 % [8].

Mortality data about syncope in older patients differ among studies. Getchell et al. reported a mortality rate of ~50 % in subjects with syncope aged ≥70 years versus ~9 % in those aged <70 years [9]. In patients with a main diagnosis of syncope identified from the USA NIS data sets for the years 2000–2005, mortality rates progressively increased from the sixth to the tenth decade of life [5]. Roussanov et al. observed that the mortality rate in the three age groups (middle age, older, and elderly) was similar to that recorded in the general population after adjustment for age and comorbidities (~8 %) [10]. In a more recent study, the overall 2-year mortality was ~18 %, whereas it was ~35 % in the oldest subgroup of patients (i.e., those between 80 and 89 years old). Only cardiac syncope discriminated between deceased and survivors, whereas vasovagal and unexplained syncope were similar in the two groups. However, at multivariate analysis, the type of syncope was not predictive of mortality. Syncope recurrence was ~33 % of elderly patients and was unrelated to the underlying etiology [11].

Table 24.1 The comparison between the causes of syncope in general population (EGSYS 2, Evaluation of Guidelines in Syncope Study 2) [6] and in the elderly (GIS, Group for the Study of Syncope in the elderly) [7]

	EGSYS 2	GIS		
	All	65–75 years	>75 years	
	$n=465$	$n=71$	$n=160$	P
Cardiac (n, %)	74 (16)	8 (11.3)	26 (16.3)	Ns
Neuroreflex (n, %)	309 (66)	44 (62)	58 (36.3)	0.001
Orthostatic (n, %)	46 (10)	3 (4.2)	49 (30.5)	0.001
Cerebrovascular (n, %)	0 (0)	0	0	/
Iatrogenic (n, %)	2 (0)	3 (4.2)	8 (5)	Ns
Unexplained (n, %)	11 (2)	10 (14.1)	14 (8.8)	Ns

*<75 years vs >75 years GIS

24.2 Pathophysiology

Age-related changes should be considered in the pathophysiology of syncope in older adults, such as reduced left ventricular compliance (which increased susceptibility of the cardiac output to preload and atrial contraction), altered blood volume control, and decreased baroreceptor sensitivity. Many diseases, such as cardiac failure, diabetes, and chronic obstructive lung disease increase the risk of cerebral hypoperfusion.

While the blood pressure adjustment on standing in the young patient relies essentially on an increase of the heart rate and myocardial contractility, in the older one it depends more on an increase of peripheral resistance [12], justifying the role of vasoactive drugs as precipitating factor of syncope [1]. In older patients with syncope, it was evidenced that cerebral blood flow velocity was lower than in younger subjects. However, autoregulatory indexes reflecting dynamic cerebral autoregulatory function were similar either at supine rest or during tilt testing (TT) [13]. In generally healthy individuals, age and baseline blood pressure (BP) has only a minor effect on the lower limit of BP necessary for maintenance of consciousness. On the other hand, higher baseline BP provides older individuals a greater blood pressure "reserve" for maintenance of consciousness compared with younger subjects [14, 15].

24.3 Diagnosis

First-Line Evaluation

Vasovagal syncope is commonly induced by triggers such as fear, pain, and instrumentation, or precipitated by orthostatic stress and exposition to high environmental temperature. In the elderly, it is frequently an atypical presentation; syncope can indeed occur with uncertain or even apparently absent triggers.

More than 70 % of older patients with syncope have one symptom before the episode, with the highest prevalence of nausea, blurred vision, and diaphoresis in VVS, whereas dyspnea is more predictive of cardiac syncope [16]. Nevertheless, prodrome could be short and the loss of consciousness could start abruptly, leading to falls and injuries [17].

The clinical history regarding the episodes should be pursued by a witness's account for the relevant presence of retrograde amnesia in this group of age. Particular attention should be paid to the time of the day, season, meals, nocturnal micturition, drugs, duration of treatment, and time-relationship between drugs and adverse effects such as syncope. The clinical history should include systemic diseases, physical frailty, and locomotor disabilities. However, considering the limited value of the medical history in the differential diagnosis between cardiac and neurally mediated cause of syncope in older patients [17], the neuroautonomic evaluation becomes an essential step in the diagnostic pathway.

The cognitive status should be evaluated and the mini-mental state examination, a 30-item internationally validated tool, is adequate for this purpose. Syncope is indeed one of the most frequent reasons for hospitalization in patients with Alzheimer's disease; nevertheless, a complete and guideline-based assessment is not often perfomed in these patients because of logistic difficulties and ageism. Details of social circumstances, injuries, impact of events on confidence, and ability to carry out activities of daily living independently should be recorded [18].

As part of the first-line evaluation, the physical examination in the older patient has to include the neurological system assessment, searching for signs of Parkinson's disease or other neurodegenerative conditions which can be associated with autonomic dysfunction. A careful observation of gait and standing balance both with eyes open and closed is useful in the evaluation of the locomotor system and consequently the risk of falling. Syncope is indeed one of the major causes of falls; 26 % of older patients referred to the ED had a syncope-related fall [19]. Even presyncope, which occurs in cases of transient arrhythmias or orthostatic hypotension, in a physically frail body could be a cause of fall and predicts the occurrence of a future syncopal episode.

A very important part of the initial evaluation is the active standing test. The rate of orthostatic hypotension increases with advancing age, reaching 24.3 % in the eighth decade and 30.9 % in the ninth decade as showed recently [20]. Two clinical syndromes of OH are described in the older patient: (1) the first is the classic OH diagnosed with the active standing and defined as a systolic blood pressure decrease at least by 20 mmHg within 3 min of orthostatic position or a decrease to less than 90 mmHg with or without symptoms; (2) the second is the delayed (progressive) OH characterized by a slow progressive decrease of systolic blood pressure on assuming the standing position. In this syndrome, hypotension can manifest clinically up to 30 min after the achievement of upright position and passive TT is necessary for the diagnosis [18].

OH is not always reproducible in older adults, especially when it is related to medications or predisposing conditions; therefore, active standing test should be repeated, preferably in the morning and/or "promptly" after the syncope [18]. Unfortunately, active standing test is not performed enough in the clinical practice, particularly in the ED. In a study conducted on patients older than 65 years consecutively referred to the ED for a transient loss of consciousness, the prevalence of OH syncope was 12.4 %. Patients with OH syncope were more likely to be affected by Parkinson's disease and by other neurological diseases. Nitrates and diuretics were independently related to OH syncope, identifying the majority of the cases of syncope as adverse drugs reaction, a preventable risk factor for syncope and falls in the older population [21]. Moreover, a recent study showed that predictors of orthostatic hypotension were varicose veins and treatment with alpha-receptor blockers, nitrates, or benzodiazepines, frequently used in older people and to which more attention should be paid, in order to reduce the recurrence of syncope [20].

The European Society of Cardiology (ESC) guidelines on management of syncope [18] propose the execution of the carotid sinus massage (CSM) during the first-line evaluation, because of the high prevalence of carotid sinus syndrome (CSS) as a cause of syncope and unexplained falls in the elderly. In patients ≥80 years old, carotid sinus massage is positive in 41 % of the cases, maintaining a high efficacy and safety. The Insertable Loop Recorder (ILR) in patients with recurrent syncope and cardioinhibitory carotid sinus hypersensitivity predicts asystole during a spontaneous syncope and suggests that a pacemaker would be useful to prevent syncope recurrence [22].

Second-Line Evaluation

The diagnostic protocol proposed by the ESC guidelines on management of syncope is well enforceable also in older patients and the rate of unexplained syncope decreases to 10.4 % [7, 18].

Tilt testing has been validated using the Italian Protocol (400 mcg of sublingual nitroglycerine), it is well tolerated even in the elderly and maintains a positivity rate and specificity similar to that observed in younger patients [23]. To our knowledge, in the literature there are no data regarding the safety of TT in patients older than 75 years. Data not already published, from a sample of 285 patients with a mean age of 84 years, evaluated in the Syncope Unit of the Department of Geriatric Cardiology and Medicine of Florence, showed adverse reactions after TT in 3.1 % of the cases. One patient experienced typical chest pain, without electrocardiogram abnormalities and myocardial enzymes increase; another patient experienced persistent bradycardia with spontaneous recovery.

A recent multicenter observational study conducted in patients older than 40 years with VVS showed that TT was unable to discriminate between presumed VVS and not, with the exception of an asystolic response which was highly specific [24]. However, in older patients the test still represents a key point in the diagnostic pathway, especially for what concerns the differential diagnosis between vasovagal syncope and other forms of hypotension or autonomic dysfunction, which can be involved in the transient loss of consciousness.

A recent study demonstrated that the neuroautonomic evaluation (TT, CSM, and active standing test) was diagnostic in a similar percentage both in young and older patients, also in those older than 80 years. TT positivity was the same across the age groups, except in the second decade, where the rate of TT positivity was 90 %. Positivity of CSM increased with advancing age, reaching a rate of 20 % in the tenth decade, as OH (Fig. 24.1). Interestingly, patients ≥65 years old had a higher rate of "complex diagnosis," namely the positivity in two of the three tests performed. The most frequent association was the presence of OH and VVS on TT in 89 patients (15.8 % of the diagnoses). The double diagnosis rate grew with the age, 6.7 % in the seventh decade and 20 % in the tenth decade (Fig. 24.2) [20]. It is indeed frequent in the clinical practice to casually find OH in patients candidate to pacemaker implantation for a CSS. A syncope relapse after a pacemaker implantation, if not explained or expected by the physician, could have an emotionally negative impact on the patient and relatives; therefore, it is particularly important to search for the coexistence of different neurally mediated mechanisms in the genesis of syncope, especially in older patients.

Frequent falling, which may be multifactorial in origin, is typically included among the major geriatric syndromes. Unexplained falls are frequent (37 %) in patients with fall-related injuries admitted to orthopedic wards [25]. In some of the cases, a misdiagnosed syncope may underlie an unexplained fall. This is particularly likely in older fallers, in whom the circumstances often cannot be clearly established and amnesia for the loss of consciousness is common [25, 26]. In this clinical context, once again TT can be useful in guiding the diagnosis, as recently confirmed in a study comparing patients with unexplained syncope to those with unexplained falls, in which the positivity prevalence of TT and of CSM were similar, suggesting that neuroautonomic evaluation should be routinely performed in older patients with unexplained falls [27] (Table 24.2).

Older subjects are more likely to have an indication for an ILR implantation than younger ones. It has been demonstrated in a population of highly selected patients, with a mean age of 71 years and an initial diagnosis of either likely epilepsy or unexplained fall that ILR gave a documentation of a relapse of their index attack and that, in about a quarter of patients, the final diagnosis was of arrhythmic syncope. Moreover, in the other patients, in whom no arrhythmia was documented at the time of a spontaneous attack, ILR monitoring definitely excluded an arrhythmic cause [28]. ILR has a high diagnostic value when a comprehensive evaluation did not demonstrate a cause of syncope but also in those conditions in which an initial diagnosis is only suspected and the demonstration of an arrhythmic mechanism could definitively guide the therapy.

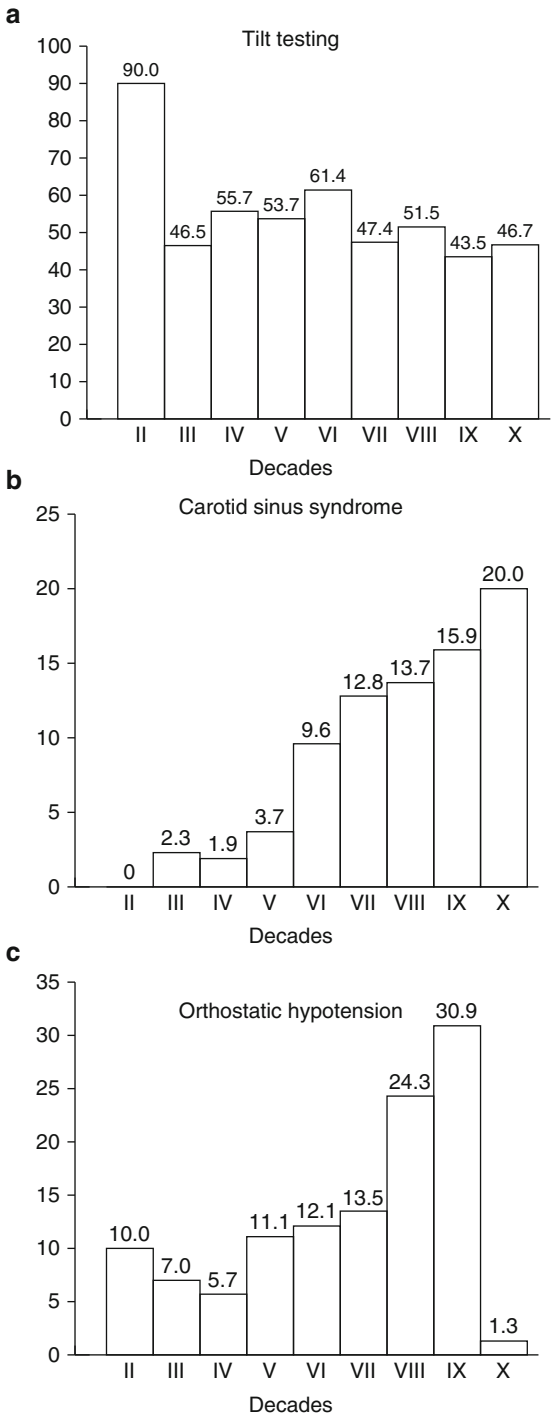

Fig. 24.1 (**a**) Tilt testing positivity; (**b**) Carotid Sinus Syndrome; (**c**) Orthostatic Hypotension in different age classes [20]

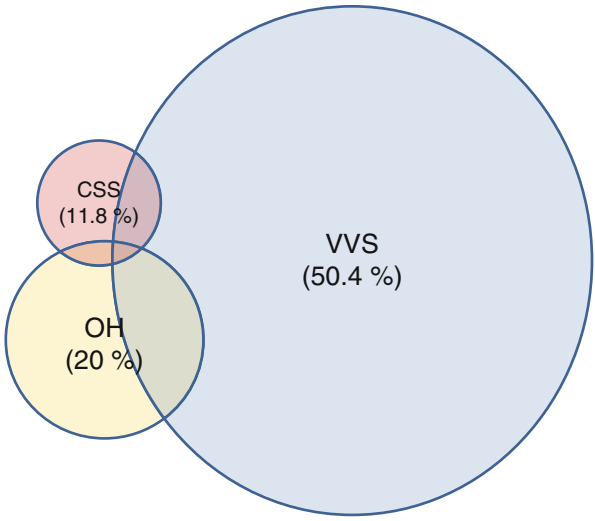

Fig. 24.2 Prevalence of different forms of neurally mediated neuromediated syncope and complex diagnosis in patients older than 65 years [20]. *CSS* Carotid Sinus Syndrome, *OH* Orthostatic Hypotension, *VVS* Vasovagal Syncope

Table 24.2 Tilt testing in patients with unexplained fall and syncope [27]

	Unexplained falls	Unexplained syncope	
	$n=298$	$n=989$	p
Performed (n, %)	275 (92.2)	944 (99.4)	0.001
Diagnostic (n, %)	99 (36.0)	485 (51.3)	0.001
VASIS I (n, %)	25 (25.2)	115 (23.7)	0.743
VASIS 2A (n, %)	1 (1.0)	17 (3.5)	0.190
VASIS 2B (n, %)	7 (7.0)	72 (14.8)	0.039
VASIS 3 (n, %)	60 (60.6)	261 (53.6)	0.202
Dysautonomic (n,%)	6 (6.0)	20 (4.1)	0.394

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Vasovagal Syncope During Driving, Working, and Exercise

25

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Key Points

- Vasovagal syncope affects aspects of daily life, including driving and working.
- Driving requires an adequate management of the vasovagal syncope patient.
- Specific working activities may facilitate vasovagal syncope.
- Risky jobs require a proper management of the patient with vasovagal syncope.
- Post-exercise recovery phase is associated with an increased risk of syncope.
- Regular physical activity may exert beneficial effects in patients suffering from vasovagal syncope by reducing its recurrence rate.

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25.1 Introduction

Vasovagal syncope may deeply affect patients' daily lives, in particular during *working* and *driving*. Data on the latter, however, are still controversial. Authors claimed that vasovagal syncope is quite uncommon while driving and did not result in major injuries [1, 2]. Conversely, others [3, 4] stated that syncope is not rare and driving itself might promote vasovagal syncope because of the long-lasting sitting position, the potential warm environment in the vehicle, and, possibly, the emotional stress related to driving. In addition, a working warm/hot environment, a prolonged standing position, a physically demanding job, or a working task requiring repetitive standing-up maneuvers [5] are all recognized triggers for syncope [6].

A benign event such as vasovagal syncope may turn into a life-threatening condition for the fainter and for the third party when occurring during driving or hazardous jobs. Therefore, a patient suffering from vasovagal syncope, particularly if syncope relapse is present, should receive personal and suitable doctor advice before returning to driving or resuming a risky job. It is important to point out that the prompt recognition of presyncope symptoms, such as blurred vision, dizziness, nausea, abdominal discomfort, sweating, might be crucial to identify an impending syncope, thus potentially preventing harm. However, to be actually useful, these symptoms should be consistent, recognizable, and last for a sufficient time.

In this chapter, we briefly report a conceptual model to help physicians to stratify the *working risk*, including the professional driving, in patients who had previously suffered from a spell of syncope.

Since physical exercise characterizes several job types, particularly hard labor, in this chapter we will also address the problem of vasovagal syncope in relation to acute and chronic exercise based on pathophysiological findings. Finally, we will briefly mention the European Society of Cardiology recommendations [7, 8] about restrictions to physical activity in patients who suffer from vasovagal syncope.

25.2 Vasovagal Syncope and Driving

Typical vasovagal syncope occurs most of the times in the upright position and when the loss of consciousness takes place while lying down or sitting it is thought to be related to a cardiac cause. Surprisingly, vasovagal syncope turned out to be the most frequent cause of loss of consciousness during driving as reported by Soraija et al. [4].

Out of 3,877 patients who presented with syncope during the period of the study, 9.8 % had syncope during driving. The most frequent cause of syncope during driving was the neurally mediated one (37.3 %), while the cardiac arrhythmic types were only 11.8 %. Different potentially underlying mechanisms were hypothesized including an abnormal venous pooling in the legs due to the sitting position, excessively high temperatures inside the vehicle and strong emotional stimulation while driving [4, 9, 10]. Notably, the aforementioned findings do not support the concept that driving itself predisposes to syncope.

In order to establish fitness to drive for a patient with syncope, a formula (*Harm Formula*, HF) was developed by the Cardiovascular Canadian Society [11]. This

formula takes into account the driving time over the day, the type of vehicle, the risk of Sudden Cardiac Incapacitation, that is, and the probability that such an event will result in a fatal or harmful accident. Given a risk of harm accepted by CCS of 0.005 % per driver per year, the yearly acceptable risk of syncope recurrence is 22 % for private cars and 1 % for professional driving [11]. Consequently, the HF can easily be applied in establishing fitness to drive for a patient with syncope based on the estimation of *syncope recurrence risk*. However, it must be emphasized that this latter might largely vary in the different population considered [4, 12–14].

More recently, Sakaguchi and Li [15] compared different recommendations for resuming *private driving* [11, 16, 17] in patients with vasovagal syncope. In agreement on the data already reported, the authors concluded that patients with a low risk of syncope relapse, may soon return to private driving with minimal or no restrictions.

25.3 Vasovagal Syncope and Working

There are few data concerning syncope and its relation to different work activities. This unknown scenario involves a large sector of the population who work in activities that may promote vasovagal syncope or are employed in *risky jobs*. This is of paramount importance in developing countries where the safety procedures and devices to prevent falls or other accidents potentially related to a loss of consciousness during work, are still inappropriate. The most dangerous jobs and relative cause of death, classified on the basis of the number of associated fatalities by the U.S. Bureau of Labor Statistics, are summarized in Table 25.1. Considering these risky jobs, a simple and benign vasovagal syncope may turn out to be the cause of a

Table 25.1 The most dangerous jobs by the U.S. Bureau of Labor Statistics (www.bls.gov) in 2012

Job tasks	More frequent cause of death or fatalities
Timber and logging workers	Contact with objects and equipment
Fishermen and related fish industry workers	Transportation incidents
Aircraft pilot and flight engineers	Transportation incidents
Structural iron and steel workers	Contact with objects and equipment
Farmers and ranchers	Transportation incidents
Roofers and linemen	Falls
Electrical power-line installers and repairers	Harmful substances exposure/environment
Drivers and truck drivers	Transportation incidents
Refuse and recyclable material collectors	Transportation incidents
Military and police personnel	Transportation incidents
Construction laborers	Falls
Firefighters	Fires and explosions
Helpers, construction trades	Falls
Grounds maintenance workers	Falls

The classification is done considering the number of fatalities and the main cause of deaths registered for the different type of jobs

Table 25.2 Working features promoting neurally mediated syncope

Work features
Prolonged standing position
Warm work environment
Environmental temperature changes
Frequent change of posture during work
High-level job demand with emotional and stressful stimulus
Heavy protective clothing and equipment
Physical stress

dramatic and life-threatening event. In addition, features triggering neurally mediated syncope [6] may be present in some working activities as reported in Table 25.2.

Working in Warm Environment

High environmental *temperatures and humidity* as well as rapid temperature changes, particularly if the worker has to wear heavy protective clothes, or perform an intensive physical exercise, may promote a transient orthostatic intolerance or presyncope, eventually leading to syncope [18–20]. This might be the case of blue collars such as construction workers, firefighters, bakers, farmers, and miners. Changes in the work organization and environment in order to reduce temperature and humidity, and recovery time in a cool place might represent effective intervention potentially preventing syncope relapse. Moreover, fluid and salt intake might be considered as an additional therapeutic suggestion particularly in elderly, overweight or obese subjects and in patients suffering from cardiovascular disease or diabetes. As recently reported [20], daily aerobic exercise training may favor *heat acclimation* since thermoregulatory capacity and blood volume increase with physical fitness.

Working with Body Harness System

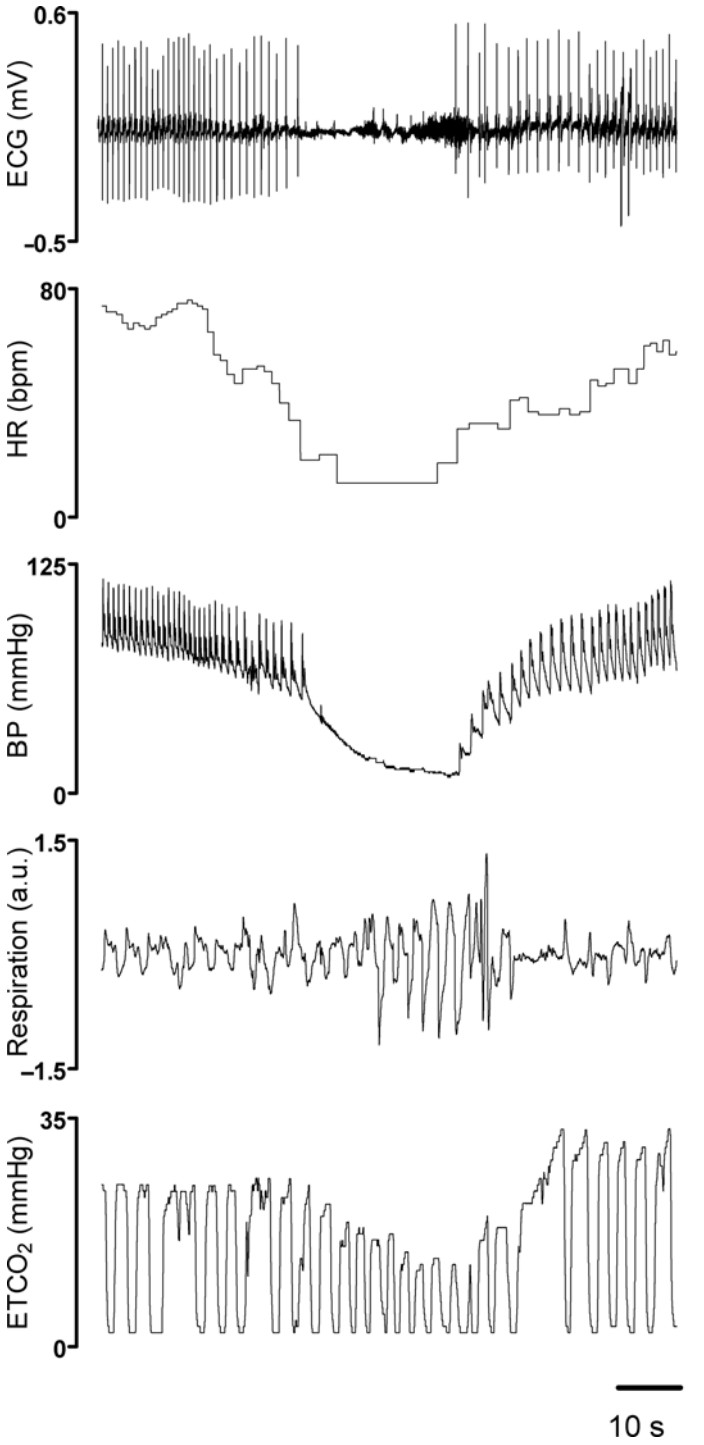
In working activities such as construction and maintenance of buildings, in timber and logging workers, in those abseiling walls in roofers and linemen, the *risk of falling* is present. To prevent falls, personal protection devices consisting of at least a body-holding device (i.e., a harness of some type), a lanyard and a reliable anchor are mandatory and their use is increasing. An example of this safety device used by timber and logging workers is shown in Fig. 25.1. Also, the rescue operations in hostile environments (mountainous or other difficult terrain, helicopter winching in sea rescues) need *body harness systems*. It has to be pointed out that such specific working conditions may promote syncope because of the prolonged orthostatic position with reduced or absent muscle movements, finally resulting in a "*suspension trauma*." In addition to the hypovolemia due to a reduced venous return, a vagal

Fig. 25.1 Timber logging workers using a protective body harness system. The prolonged posture maintained with such a device might promote syncope or suspension trauma

phenomenon (either reflex or from nociceptive stimulus) seems to be involved in the pathophysiology of suspension trauma [21]. Figure 25.2 depicts the hemodynamic changes occurring during a 75° head-up tilt in a healthy man working as mountain rock climbing guide who fainted. This subject was referred to our syncope laboratory because of a previous loss of consciousness during a provocative test reproducing his suspension job activity. Notice the abrupt sinus arrest lasting more than 20 s, without presyncope symptoms. Interestingly, the loss of consciousness was characterized by an increased rate and depth of breathing, producing a decrease in end-tidal CO_2 values (bottom panel). A following complete cardiac workup was normal. The patient resumed his work after an appropriate medical counseling to prevent syncope relapse by changing his lifestyle and by recognizing the prodromes.

Pseudosyncope and Work

The high prevalence of psychiatric disease, particularly depression and anxiety, in patients with recurrent syncope is well-known [22, 23]. The risk of syncope recurrence in the year following the syncope event is more than threefold higher in patients with psychiatric disease compared to healthy subjects [22]. *Panic attacks*, particularly if situational [24, 25], represent a condition that might be facilitated by specific working organizations in predisposed patients and may mimic simple vasovagal syncope. The pressing working rhythms, the high level of perceived responsibility, and *conflicts and stress during work* might facilitate syncope related to panic disorders. This condition needs to be ruled out and treated. To prevent syncope recurrence in patients with panic disorders, it is important to identify the trigger often represented by hyperventilation. This latter, by reducing circulatory CO_2 might induce a cerebral vasoconstriction, thus promoting the loss of consciousness.


0.6
ECG (mV)
-0.5
80
HR (bpm)
0
125
BP (mmHg)
0
1.5
Respiration (a.u.)
-1.5
35
ETCO2 (mmHg)
0
10 s

Cardiac Devices, Work, and Syncope

Patients with syncope, including those with the vasovagal one, should be adequately advised concerning the risk of potential Electromagnetic Interference (EMI) in the workplace, if they are carrying a pacemaker (PM). Indeed, workers can be exposed to *electromagnetic fields* (EMFs) not only more frequently but also by a larger magnitude than in daily life [26] because of the presence of electrically driven machines. For example, it has been calculated that close-to-metal, inert-gas-welding machine activities, EMF are high enough to potentially generate EMI resulting in PM malfunctioning. A recent study by Tikkaja et al. [27] concluded that patients after PM implantation can return to work only after an appropriate risk assessment aimed at quantifying the magnetic fields intensity in the workplace [26]. In syncope patients with cardiac devices, the role of the occupational physicians in the decision making about fitness to work is crucial.

25.4 How to Manage Patients Who Are About to Resume Work

To promote a safe return to specific risky job, patients with vasovagal syncope, should be referred to an outpatient multidisciplinary syncope clinic (*Syncope Unit*). The aspects to be considered are as follows:

- The syncope recurrence risk: For the vasovagal syncope, the recurrence risk is well-predicted by the number of spells in the year preceding the syncope reference event, as reported by Sumner et al. [14].
- The characteristics of the job task and the environmental working conditions potentially promoting syncope [28].
- The capability of the worker of recognizing symptoms preceding syncope. A specific training, including the *physical countermaneuvers* [29] that workers may perform in their work settings, may promote safety.
- The possibility of modifying potentially unfavorable environmental features or of suggesting additional *safety devices*.

If necessary, a temporary removal from high-risk jobs might be considered by an expert occupational physician.

Fig. 25.2 Hemodynamic changes during an atypical orthostatic syncope induced by a 75° head-up tilt in a healthy mountain rock climber guide. The loss of consciousness occurred abruptly and without prodromes. Notice that the sinus arrest lasts more than 20 s. Interestingly, the last period of loss of consciousness was characterized by an increase of rate and depth of breath, thus producing a decrease in the values of the end-tidal CO_2 (*bottom panel*). *HR* indicates heart rate; *BP* blood pressure, $ETCO_2$ end-tidal CO_2

25.5 Vasovagal Syncope and Exercise

Restrictions to physical activity in patients with vasovagal syncope have been addressed in both athletes and in participants to leisure-time noncompetitive sports [7, 8]. Similarly to work and driving safety restrictions, in patients with vasovagal syncope only physical activities characterized by an intrinsic high risk such as cycling, diving, equestrian, rock-climbing, and others [7] should be avoided if the vasovagal syncope recurrence risk is high.

Since physical exercise characterizes several job types, particularly hard labor, the problem of vasovagal syncope in relation to acute and chronic exercise can be addressed also from a pathophysiological standpoint. This may provide practical therapeutic suggestions, although nonevidence based.

It has been reported that *prolonged endurance exercise* decreases orthostatic tolerance in the period just following the end of the physical activity and promotes syncope [30–33]. The likely reason is the concomitant presence of both a remarkable peripheral vasodilation and complex autonomic changes characterized by a cardiac sympathetic overactivity [34]. In keeping with these concepts, Fig. 25.3 shows that after exercise (b, bottom panels), there was an increase of cardiac sympathetic activity at rest, suggested by the reduced RR and increased LF_{RR}

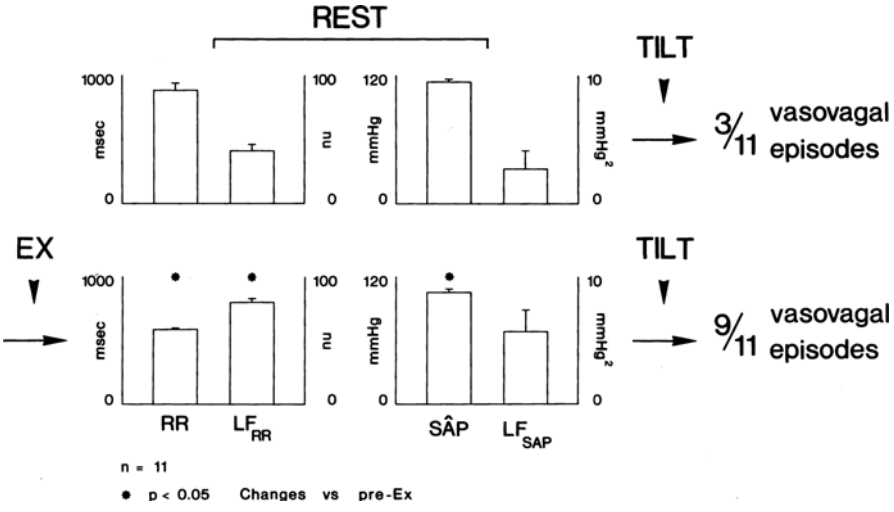


Fig. 25.3 Short-term effects of a single bout of heavy dynamic exercise on orthostatic tolerance. After a 15 min 75° head-up tilt test, 11 healthy subjects performed a treadmill stress test up to exhaustion followed by 4–6 200-m repetitive runs in the field in order to achieve an average exercise time of about 30 min. Thereafter, they repeated the tilt procedure. Compared to the preexercise condition (**a**, *upper panels*), a higher cardiac sympathetic modulation was present, as indicated by reduced values of RR interval, and greater values of LF_{RR} were observed concomitantly with reduced values of systolic arterial pressure (*SAP*) (**b**, *botton panels*). After the maximal exercise, the number of subjects who fainted during the tilt maneuver was higher (9 out of 11) compared to that observed before exercise (3 out of 11)

(see Chap. 8) and signs of peripheral vasodilation, indicated by reduced systolic pressure values. Accordingly, there were an increased number of subjects (9 out of 11) who suffered from vasovagal syncope compared to preexercise condition. Without more striking, evidence-based data, it is reasonable to suggest that an appropriate *warm-down exercise* should be followed after intense physical activity to reduce the risk of a post-exercise typical vasovagal orthostatic syncope [35].

Notably, whenever syncope occurs during or immediately after the end of exercise, a cardiac cause should be ruled out [36]. The exercise testing with prolonged observation in the recovery phase may be useful to establish the diagnosis [37]. On the other hand, a mixed *aerobic and isometric physical training* has been proposed as a nonpharmacologic treatment of vasovagal syncope because of its capability to improve orthostatic tolerance by increasing arterial baroreflex sensitivity [38, 39]. This effect was observed either in healthy subjects [40, 41] and aged individuals [38]. In keeping with these results, Gardenghi et al. [39] found, in patients with NMS who underwent a *specific physical training program*, a lower syncope recurrence together with an increase of vagal and sympathetic arterial baroreflex gain. The 4-month training program consisted of three 60-min exercise sessions per week, each session consisted of 5 min stretching exercise, 40 min of cycling, 10 min of local strengthening exercise, 5 min of cooldown with stretching exercise [39].

Finally, patients with vasovagal syncope seem to benefit from physical exercise [38] when it is integrated by tilt training and physical maneuvers such as leg crossing or isometric arm tension [17, 29].

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Orthostatic Intolerance and Vasovagal Syncope After Spaceflight

26

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Key Points

- Postflight orthostatic intolerance is commonly observed in astronauts after their return to Earth.
- It is defined as the development of symptomatic intolerance to upright posture after flight, with concomitant tachycardia and progressive hypotension.
- With sustained upright posture, progression to frank vasovagal syncope is possible, though rare.
- This phenomenon is a consequence of several physiologic and autonomic adaptations that occur during spaceflight, including loss of plasma volume, muscle mass, cardiac atrophy, loss of vasoconstrictor function, vestibular dysfunction, and alterations in autonomic function.
- A variety of in-flight and postflight countermeasures have been developed to counteract these neurophysiologic consequences of spaceflight.

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26.1 Definition

Postflight orthostatic intolerance is a clinical syndrome commonly encountered by space travelers upon their return to Earth. Upright symptoms of dizziness, lightheadedness, nausea, palpitation, diaphoresis, and blurred and tunnel vision are associated with exaggerated orthostatic tachycardia, normal, low, or rarely high blood pressure. With sustained upright posture, progression to presyncopal events or vasovagal syncope can occur.

26.2 Incidence

Reported incidence varies and depends on length of spaceflight, applied countermeasures, and characteristics and interpretation of postflight testing. Early reported incidence was between 17–20 % [1] and 64 % [2] in shuttle astronauts returning from short-duration flights (<2 weeks). The incidence is proportional to mission length and approaches 83 % following long-duration flights [1]. Interestingly, more recent study has showed a marked reduction in the incidence of orthostatic intolerance after prolonged spaceflight, which may reflect better selection of cosmonauts and/or optimized countermeasures [3].

26.3 Clinical Characteristics

Post-space-flight orthostatic intolerance shares many clinical features of young female patients with postural orthostatic tachycardia syndrome (POTS), and patients after prolonged immobilization.

Symptoms

Dizziness, lightheadedness, nausea, palpitation, diaphoresis, blurred and tunnel vision, and fatigue are commonly described.

Orthostatic Tachycardia

An increase in heart rate greater than or equal to 30 beats per minute during standing for at least 3 min.

Orthostatic Hypotension

A decrease in systolic blood pressure of more than 20 mmHg or diastolic pressure reduction of more than 10 mmHg upon standing. In returning astronauts, this typically occurs during the late phases of upright position, between 3 and 10 min.

PreSyncope/Syncope

Presyncopal events after spaceflight are common. Neural-mediated syncope, defined as orthostatic intolerance with sudden loss of consciousness, is rare. Most presyncopal incidents in astronauts occur during careful observation and testing and are preceded by a steady decline in blood pressure. Testing is aborted prior to frank syncope, which likely explains its rarity.

26.4 Pathophysiological Mechanism

There are multiple contributing etiologies of postflight orthostatic intolerance (Fig. 26.1). Dehydration in returning astronauts plays a significant role. Decreased plasma volume is a well-established physiologic adaptation to spaceflight, and is the result of decreased fluid intake, fluid shifts from the intravascular to interstitial space, and reductions in red cell mass [4]. Hypovolemia in returning astronauts contributes to significant reductions in cardiac preload and stroke volume upon standing [5], provoking a responsive tachycardia, symptoms of orthostatic intolerance, decreased mean arterial pressure, and potentially syncope.

The effects of hypovolemia, namely decreased stroke volume, are perpetuated by the physical deconditioning which occurs during spaceflight. In the absence of gravity, both skeletal and cardiac muscle begin to atrophy [6, 7]. Abnormal contractile mechanics in the setting of cardiac atrophy alters the Starling relationship, accentuating the decrease in stroke volume with upright positioning. Skeletal muscle atrophy, particularly of the lower extremities, also impairs central venous return. Skeletal muscle decreases the compliance of the large veins of the lower legs and facilitates cephalad venous flow while standing. Impairment of this "muscle pump" after flight promotes venous pooling and leads to further orthostatic decreases in stroke volume.

In addition to these nonneural mechanisms, alterations in autonomic nervous system function during spaceflight also contribute to the development of postflight orthostatic intolerance.

Short-duration spaceflight increases sympathetic nervous system activity [8] and impairs vagal baroreflex function [9, 10]. These changes in autonomic function have also been demonstrated in postflight testing, both in observations of increased postflight plasma norepinephrine levels [11, 12], as well as decreased vagal baroreflex responses [13, 14]. While plasma norepinephrine levels are increased during postflight, increases in serum norepinephrine levels were diminished in subjects who experienced more severe postflight orthostatic intolerance [15]. This suggests that subnormal sympathetic output may prevent an appropriate vasoconstrictor response, leading to orthostatic intolerance. These findings were supported by Buckey et al. (1996), who found that presyncopal subjects showed smaller increases in peripheral vascular resistance (PVR) with standing, as compared to those without presyncope [2]. Decreased vagal baroreflex sensitivity in postflight testing has also been associated with orthostatic intolerance [13].

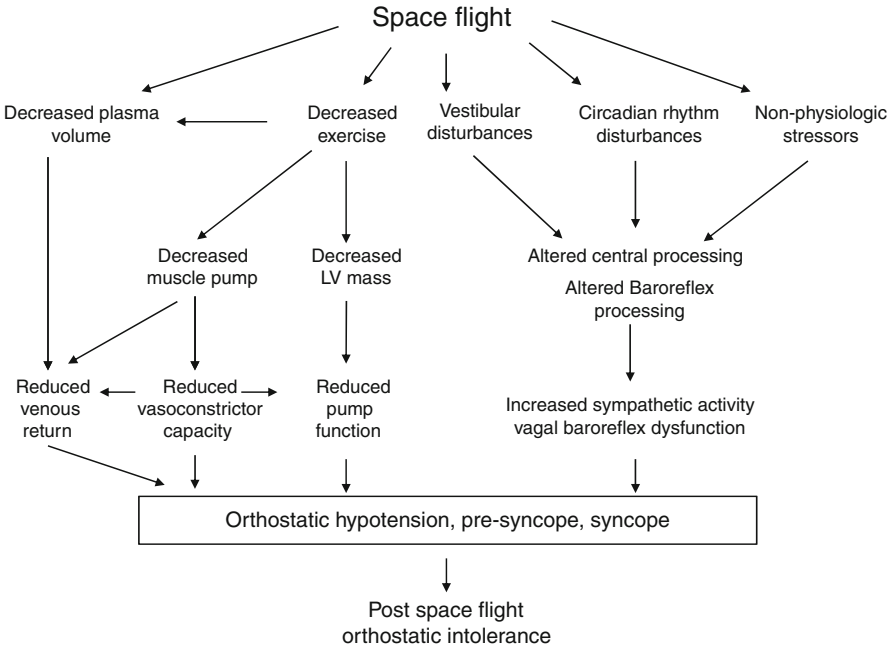

Fig. 26.1 Mechanism of orthostatic intolerance after space flight. The human cardiovascular system adapts to microgravity with normal function in space but dysfunction after return to Earth

Through more focused evaluation of pre- and postflight sympathetic responses, Meck et al. (*2004*) have shown that subnormal α_1-receptor responsiveness before flight, and altered central autonomic processing during flight, may contribute to postflight orthostatic intolerance [16]. Microgravity may affect central autonomic processing, leading to impaired efferent baroreflex function and an inability to appropriately increase peripheral vascular resistance after landing.

The disruption of vestibuloautonomic reflexes may, in part, underlie these changes in central autonomic processing in space. Spaceflight alters the gravity-dependent sensory function of the vestibular organs of the inner ear [17]. Recent work has demonstrated a vestibuloautonomic reflex, which provides a physiologic primer in advance of the baroreflex, to support and maintain blood pressure during an orthostatic challenge [18, 19]. Vestibuloautonomic reflexes have not been directly studied in space, though there is evidence from terrestrial studies that impairment of the vestibulosympathetic reflex may contribute to orthostatic hypotension [20]. Alterations and impairment of vestibular function with exposure to microgravity may similarly disrupt vestibuloautonomic reflexes and contribute to postflight orthostatic intolerance [21].

26.5 Countermeasures

Countermeasures during space flight target prominent features of microgravity exposure: loss of gravitational forces, relatively low venous pressures, cephalad-fluid shifts, hypovolemia, cardiovascular deconditioning, vestibular dysfunction, and muscle atrophy.

Anti-G Suits and Compression Garments

Thigh occlusion cuffs ("Braselyets" or "Bracelet") were introduced in cosmonauts in an effort to prevent fluid loss during space flight [22–25]. Thigh cuffs inhibit the fluid shifts in central and peripheral circulation that occur during weightlessness and decrease venous stasis in the cervical-cephalic region [26]. They have been shown to reduce the increase in heart rate during orthostatic stress after landing, but have no effect on duration of orthostatic stress tests [27]. No effect on orthostatic tolerance has been found in other studies [23, 25, 26, 28]. After landing, the use of inflatable antigravity suits ("Anti-G") or noninflatable compression garment called "Kentavr," prevent pooling in the lower extremities and enhance central venous return. Astronauts also wear cooling garments to prevent peripheral vasodilatation. Anti-G suits and cooling garments have both been shown to improve orthostatic hemodynamics after flight [29, 30].

Lower Body Negative Pressure Suction

Lower body negative pressure suction (LBNP) is routinely used in the Soviet space program as a countermeasure against postflight orthostatic intolerance [31]. Cosmonauts wear flexible vacuum trousers ("Chibis suit"), which applies external negative pressure to the lower body. LBNP promotes redistribution of blood and fluid to the lower extremities, counteracting the cephalad shift of fluid in microgravity. Leg movements during operation permit negative pressure exposures without causing hypotension. In-flight LBNP may prevent postflight orthostatic intolerance by increasing plasma volume, promoting fluid retention in extravascular tissue, improving cardiopulmonary and carotid sinus baroreceptor function, and decreasing blood pooling after landing by restoring lower extremity vascular compliance and responsiveness. [31–33].

Artificial Gravity

Artificial gravity produced by short-arm centrifugation utilizes centripetal force to provide continuous linear acceleration to simulate the downward force of gravity.

Centrifugation provides orthostatic stress similar to LBNP, while additionally engaging postural muscles and vestibular sensory organs [34, 35]. Use of intermittent centrifugation during flight may prevent plasma volume loss, maintain baroreflex function, and preserve vestibular autonomic reflexes.

Exercise

Exercise is an effective countermeasure. It improves muscle pump function, prevents muscle atrophy, preserves venous return and cardiac stroke volume, and maintains general cardiovascular fitness [36, 37]. Additionally, it increases plasma volume and restores vagal baroreflex function [38]. Structured in-flight exercise has become an important component of both short- and long-duration missions, and includes cycle ergometry, treadmill exercise, and resistance training.

Fluid Load

Astronauts consume approximately 1 L of water and 8 g of sodium, the equivalent of 1 L of normal saline, 1.5–2 h prior to deorbit maneuvers. Fluid loading decreases postflight tachycardia and preserves postflight mean arterial blood pressure, and has become standard procedure on both American and Russian spaceflights [36].

26.6 Pharmacological Treatment

Mineralocorticoid and antidiuretic hormone administration can be applied to enhance the plasma volume expansion of fluid loading. Sympathomimetic and anticholinergic agents have also been used to increase the peripheral vasoconstrictor response, or increase cardiac output [39–41].

Fludricortisone is a synthetic corticosteroid with mineralocorticoid activity, which stimulates renal sodium reabsorption and fluid retention. It causes plasma volume expansion and is a common agent used in the treatment of orthostatic hypotension on Earth. Experimental use of a single dose of fludricortisone improved plasma volume in astronauts after landing, but did not decrease the incidence of orthostatic intolerance [42].

Midodrine is a peripherally acting α_1-adrenergic agonist and may reduce postflight orthostatic hypotension by increasing peripheral vascular resistance. It has been shown to improve orthostatic tolerance following bed rest [43]. Midodrine is well tolerated when used postflight [44], and has been used successfully in an astronaut with prior postflight orthostatic intolerance [45]. Its use as an effective countermeasure in a larger cohort of astronauts has not yet been tested.

Conclusion

Postflight orthostatic intolerance or syncope is, in and of itself, quite benign. The inability to assume and maintain an upright posture immediately after landing, and the potential for vasovagal syncope, however, does pose a unique, and serious, safety concern for returning astronauts.

Conflicts of Interest None

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Vasovagal Syncope and Sudden Death: Is There a Liaison?

27

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Key Points

- Vasovagal syncope does not significantly increase the incidence of sudden death.
- Results of animal experiments suggest that hopelessness could be responsible for sudden death due to vagal overactivity. However, it is unknown whether these results can be generalized to humans.
- Vasovagal syncope could be responsible for sudden death when the subject remains upright because of peculiar situations. Notably, this event appears to be extremely infrequent.
- Results of animal experiments and studies based on autopsy in humans suggest that the emotional vasovagal reflex could be responsible for sudden death when it occurs simultaneously with the diving reflex.

Vasovagal syncope (VVS) is considered to be a benign condition, not associated with increased mortality. The main source of prognostic information on VVS comes from the Framingham study, where this type of syncope was not associated with an increased risk of any of the major outcomes during a mean follow-up of about 9 years [1]. Even subjects with prolonged asystole during tilt testing seem to have a

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good prognosis and an increased risk of sudden death has not been observed [2, 3]. However, these studies were not powered to detect such increase. Since long, a possible role of paroxysmal vagal overactivity in the genesis of sudden death has been discussed. Many data suggest that a parasympathetic overactivity may be the pathophysiological underlying mechanism promoting sudden death in infants. A vagal origin of sudden death has also been hypothesized in individuals who are no longer infants. Indeed, it has been suggested that the sudden death of ostracized persons in primitive societies, voodoo death, may be attributable to vagal overactivity secondary to feeling of hopelessness [4]. The perceived lack of control over a powerful external force, such as a wizard that causes demise, makes the victims hopeless, without power to alter their life course, that is, in a condition against which they have no defense. The results obtained in animal experiments by Richter [4] (see in the following text) suggest that hopelessness could be responsible for sudden death due to vagal overactivity. However, we do not know whether these results can be generalized to sudden death in humans in a context of hopeless situations.

Even if VVS does not increase significantly the incidence of sudden death, it is possible that in peculiar situations, VVS can result in sudden death. Some years ago, we treated a middle-aged woman with recurrent VVS (tilt positive) without heart disease or any competing diagnosis. During a syncopal episode, her husband took her upright, thinking to help her, and she died. It is possible that the death was due to the forced erect position during VVS. However, this event appears to be extremely infrequent. We believe, on the basis of data obtained both in animals and humans, that the emotional vasovagal reflex, responsible for alarm bradycardia (see Chap. 1), can also be responsible for sudden death when it occurs simultaneously with the diving reflex, which is in turn responsible for the diving bradycardia [5].

27.1 Vasovagal Reflex Associated to Diving Reflex

Diving Bradycardia

A feature of all air-breathing vertebrates, diving bradycardia is triggered by apnea and accentuated by immersion of the face or whole body in cold water. While little is known about the afferent pathways of the diving reflex, the efferent part of the reflex circuit is known to be constituted by the cardiac vagal fibers. Diving bradycardia is associated to vasoconstriction of selected vascular beds and a reduction in cardiac output. The bradycardic response to diving varies greatly from species to species and, in humans, from subject to subject, the reduction in heart rate ranging from 10 to 60 % [6]. Diving bradycardia is eliminated by pretreatment with atropine, as an expression of a vagal response. Although swimming increases heart rate, it has been demonstrated in ducks that, at the same level of O_2 uptake, heart rate during underwater swimming is significantly lower than during swimming on the surface [7]. Vasoconstriction is associated to a redistribution of the blood flow, which saves oxygen (O_2) for the O_2-sensitive organs, such as the heart and the brain.

The results of several investigations carried out in both animals and humans have shown that the diving reflex has an O_2-conserving effect, both during rest and exercise, thus lengthening the time to the onset of serious hypoxic damage.

Alarm Bradycardia

The most common animal response to fear/threat is actively the so-called "fight-or-flight" response, which is characterized by activation of the sympathetic system (increased physical activity, rise in systolic blood pressure and heart rate). In contrast to this active response, many animals display a passive response to fear/threat by remaining motionless (tonic immobility), especially when attacked by predators from which there is no possibility of escape. During tonic immobility, which is a reflex response, the animal typically assumes a recumbent posture to achieve the lowest body profile, in order to simulate death, while nevertheless remaining alert. Alarm bradycardia appears frequently during tonic immobility, though its prevalence in unknown. It is eliminated by pretreatment with atropine, which demonstrates that the fear-induced central reaction induces bradycardia through activation of the efferent vagal system. Alarm bradycardia has been documented in all classes of vertebrates and is more frequent in young animals than in old ones. The reduction in heart rate varies greatly from species to species; a 60–70 % fall in heart rate has been reported. Typical tonic immobility is not observed in humans and a slowing of heart rate during fear/threat is mainly observed in the context of emotional syncope. Alarm bradycardia appears to be a defense mechanism to reduce myocardial O_2 consumption when cardiac strain is excessive (see Chap. 1).

27.2 Influence of the Cerebral Cortex on Diving Bradycardia

Many data obtained in animals and in humans suggest that diving bradycardia is an autonomic reflex that is subject to many modulation forces acting through cortical connections. Heart rate has been measured during voluntary and forced diving in birds and mammals. In these experiments, the bradycardic response was always much more accentuated when the animals were forcibly immersed than when they were diving voluntarily [8, 9]. In contrast with intact animals, the fall in heart rate in decerebrated muskrats was approximately the same during voluntary and forced dives [9]. These data demonstrate a role of psychogenic factors on the intensity of the bradycardic response. Wolf [10] reported that in humans the bradycardic response on facial immersion was less pronounced when the subjects were distracted or harassed and more pronounced during intense anxiety. Ross and Steptoe [11] found that the bradycardic response after facial immersion was significantly attenuated when the subject performed mental arithmetic, even after pretreatment with beta blockers, thus demonstrating that the diving reflex can be modified by stimulation from the cerebral cortex.

27.3 Effects of the Two Vagal Reflexes on Heart Rate

Some cases of animals threatened while diving have been published. The results are summarized in Table 27.1. The effects of the two simultaneous and independent vagal reflexes on heart rate have been observed in mammals such as muskrats, seals,

Table 27.1 Heart rate response during prediving, diving, and when the animal is threatened underwater

Reference	Animal (no. of animals)	Predive HR (beats/min)	HR during diving (beats/min)	HR during threatening stimulus (beats/min)	Type of threat
Mammals					
[12]	Muskrats (5)	~300	~280	~30	Sudden hand movements
	Ondatra zibethicus				
[13]	Seal (9)	~80	~30	~4–5	Trap dive
	Halichoerus grypus				Inflated balloon
[15]	Mink (5)	208 ± 5	210 ± 7	56 ± 6	Trap dive
	Mustela vision				
Birds					
[16]	Platypus (NR)	~180	~70	~2	Trap dive
	Ornithorynchus anatinus				
[7]	Duck (8)	121 ± 14	96 ± 5	46 ± 4	Trap dive
	Aythya fuligula				
Reptiles					
[18]	Snake (1)	29	11	6	Trap dive
	Farancia abacura				
[19]	Alligator (1)	NR	25–35	3–5	Sudden appearance of a man
	Alligator mississipiensis				
[20]	Caiman (1)	~20	~15	~5	Sudden appearance of a man
	Caiman crocodilus				
[21]	Turtle (6)	NR	38 ± 4	12 ± 3	Touch stimulus
	Terepene ornata				
Amphibians					
[22]	Salamander (NR)	NR	NR	Slowing of HR with sinus pauses up to 4 s. second-degree AV block	Moving shadow
	Necturus maculosus				

Abbreviations: *AV* atrioventricular block, *HR* heart rate, *NR* not reported

and mink [12–15] and in other species of air-breathing vertebrates [7, 16–22]. After submersion, heart rate almost always decreased. The animal was then threatened in some way, for example, by a sliding door or other barrier, which prevented it from surfacing (trap diving) or by a person (sudden approach, sudden hand movements, movement of objects). Fear/threat always induced a very profound decrease in heart rate, sometimes as low as 2–6 beats/min. Heart rate was measured when the animal apparently became aware of the threat. In the studies [13, 17, 19, 21] in which the animals' behavior was described, the slowing of heart rate was associated to a sudden cessation of muscular movements for a variable period, suggesting underwater tonic immobility. MacArthur et al. [12] documented fear-induced slowing of heart rate associated to tonic immobility in muskrats, both on land and during diving, and noted that the slowing of heart rate was more marked underwater. In other studies, a profound slowing of heart rate in response to a threatening stimulus has been described in muskrats, ducks, and snakes while diving, but precise HR values have not been reported [23–26].

Diving bradycardia and fear-induced bradycardia are separate physiological responses and have different afferent pathways; however, the efferent pathway appears to be the same: cardiac vagal fibers. Therefore, when the two reflexes occur together, the slowing of heart rate can be very severe.

27.4 Sudden Death Due to Emotional Vasovagal Reflex Associated to Diving Reflex

In an experiment carried out several years ago, Richter [4] placed wild rats, which are able to swim for many hours, in a water-filled cylinder fitted with a collar that prevented escape. The rats showed progressive slowing of heart rate, with sinus pauses occurring until ultimate cardiac arrest. Pretreatment with atropine prolonged survival. On autopsy, there were no signs of drowning ("dry lungs"). Richter attributed these sudden deaths to vagal overactivity triggered by psychological factors, in particular hopelessness, when the animals became aware that they could not escape. In support of this assumption, Richter reported that when the feeling of hopelessness had been eliminated, the rats did not die. This was achieved by repeatedly immersing the rats in the cylinder for a short time and then freeing them. In this way, the rats quickly learned that the situation was not actually hopeless; thereafter, they became aggressive, did not seem resigned to their fate and showed no signs of giving up. Therefore, as previously reported, hopelessness appears to be a predisposing factor for vagal sudden death.

In a later experiment, Binik et al. [27] investigated domestic rats. One group of rats was stressed by being caged singly and handled five times a week (gently stroked for 10–15 s). Another group of rats was not stressed; they were housed four to a cage and not handled. The rats were subsequently placed in a tank full of water for 20 min; 27 % of the "stressed" animals died soon after immersion (mean time to death: 4 min), while none of the "unstressed" animals died. The heart rate patterns over time differed strikingly between surviving and dying animals. In the surviving

animals, heart rate generally decreased after immersion and maintained a relatively stable pattern over the 20-min immersion period. This was in sharp contrast to the dying animals, which always showed an immediate drop in heart rate upon immersion and a gradual slowing over time until cessation of electrical activity. The slowing of heart rate seen in the dying animals was similar to that reported by Richter [4]. Autopsy of the rats that had died in the tank revealed no evidence of drowning. Binik et al. [27] hypothesized that the diving reflex may play a major role in the genesis of vagal sudden death, though they also considered psychological factors. In this regard, the dying rats spent progressively more time underwater. Those that survived spent less time underwater; the diving reflex was thus elicited to a lesser degree. In our opinion, the results of these experiments clearly show the possibility of sudden death due to vagal overactivity; it is very likely that the synergic stimulation of the vagal cardiac fibers by the two independent vagal reflexes, one dive-mediated and the other originating in the brain, causes vagal sudden death.

27.5 Clinical Implications

The cerebral cortex modulates the bradycardic response during the diving reflex. When an animal is threatened while diving, very low heart rates can be observed. In very stressful conditions, the animal can suffer from sudden death due to vagal overactivity after immersion. In humans, there are no clear data on vagal sudden death; however, some deaths could be attributed to vagal overstimulation. It has been reported that in 10–15 % of the people who die after falling into water (sea, swimming pool), little or no water is found in the lungs on autopsy (no signs of drowning) [28, 29]; this observation is more frequent in women than in men [29]. In such situations, both vagal reflexes probably could play a role in causing sudden death. As a general rule, the vagal system protects the heart; however, as other defense mechanisms (e.g., antibody production), it can be sometimes a potential source of negative effects, in particular when two independent vagal reflexes occur simultaneously.

Conclusions

Large studies have shown that VVS is benign and does not increase significantly the incidence of sudden death. However, during peculiar (and very infrequent) situations, as a protracted upright position during loss of consciousness, VVS could be responsible for sudden death. One might hypothesize that sudden death results from a vagal overactivity leading to a prolonged cardiac standstill, which, in association to very depressed cardiac output and coronary perfusion, could result in malignant ventricular arrhythmias. Conversely, a lack of ventricular filling because of the prolonged upright position in the setting of VVS could be responsible per se for sudden death. The results of animal experiments suggest that the feeling of hopelessness could be responsible for vagal sudden death, but that remains to be demonstrated in humans. In our opinion, the results of animal experiments and of autopsy studies in humans suggest that a vagal sudden death

can occur when the emotional vasovagal reflex is associated to the diving reflex. Nowadays, a sudden vagal death can be highly suspected after exclusion on autopsy of structural or coronary heart disease, of other acute disorders and, through a molecular autopsy, of channelopathies, in particular long QT syndrome and catecholamine-induced ventricular tachycardia/fibrillation; in this regard, diving and swimming are established triggers for malignant ventricular arrhythmias in these primary electrical diseases [30, 31].

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