



New classification of haemodynamics of vasovagal syncope: beyond the VASIS classification

Analysis of the pre-syncopal phase of the tilt test without and with nitroglycerin challenge

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We believe that the pattern of blood pressure response to tilt during the time preceding the development of the vasovagal reaction may provide adjunctive diagnostic information. A group of 101 consecutive patients affected by syncope of uncertain origin underwent passive tilt testing for 45 min at 60° followed, if negative, by oral (sublingual) trinitroglycerin (TNG) 0.4 µg with continuation of the test for 20 min. Three main patterns were observed: the classic (vasovagal) syncope pattern was observed in 36 patients who, during the preparatory phase, had a rapid and full compensatory reflex adaptation to upright position, resulting in stabilization of their blood pressure values until abrupt onset of the vasovagal reaction; the dysautonomic (vasovagal) syncope pattern was observed in 47 patients in whom steady-state adaptation to upright position was not possible. There was thus a progressive fall in their blood pressure until the occurrence of a typical vasovagal reaction; the orthostatic intolerance pattern was observed in 18 patients in whom there was a progressive fall in blood pressure, similar to that of the dysautonomic group, but this was not followed by a clear vasovagal reaction.

Compared with the classic, the dysautonomic patients were older, had a higher prevalence of co-morbidities, a very much shorter history of syncopal episodes, and a prevalence of mixed and vasodepressor forms of the VASIS classification. The patients with orthostatic intolerance had clinical characteristics similar to the dysautonomic group but they could not be classified according to the VASIS classification. In conclusion, in patients with syncope, a variety of abnormal responses is observed during tilt testing, suggesting that different syndromes can be diagnosed by the test. A more detailed, although still arbitrary, classification may form the basis of a number of future drug and pacemaker trials, as well as help towards a greater understanding of the different mechanisms of tilt-induced syncope.

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Key Words: Tilt testing, vasovagal syncope, autonomic nervous system, haemodynamics of vasovagal syncope.

Introduction

More than 10 years of worldwide tilt testing has shown that the number of patients whose syncope remains unexplained has dramatically reduced. However, the population of patients who show a positive response to the test is very heterogeneous, raising the possibility that

different syndromes can be diagnosed by tilt testing. Many drugs, as well as cardiac pacing, have been proposed for patients with tilt-induced syncope; however, a consensus on management has not been achieved due to the unsatisfactory results of therapy trials which have been undertaken. Classification by the Vasovagal Syncope International Study (VASIS) in 1992 facilitated the understanding of the different types of vasovagal reaction observed during tilt-induced syncope^[1]. This has recently been extended to tilt testing with pharmacological challenge^[2,3]. Like other current classifications of positive responses to tilt testing, the VASIS classification is based on the behaviour of blood pressure

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and heart rate observed when vasovagal reactions and symptoms occur. To date, the cardiovascular patterns preceding the development of the vasovagal reaction have received little study. We believe that the pattern of blood pressure response to tilt may provide more strict diagnostic information and that a more detailed, although still arbitrary, classification may form the basis of a number of future drug and pacemaker trials as well as help towards a better understanding of the different mechanisms of tilt-induced syncope. We therefore propose the following classification to be used as complementary and additive to the VASIS classification. We tried to correlate this classification with some simple clinical variables.

Methods

At the end of 1997, based on a retrospective review of our tilt test traces, we developed a new classification of the positive responses to tilt testing based on the behaviour of blood pressure during the pre-syncope phase of the test. In 1998 we started a prospective validation of this classification in all consecutive patients referred to us for the execution of tilt testing. We planned to stop the study when the data of the first 100 patients suitable for evaluation had been collected.

Patient population

The study population comprised patients in whom the cause of syncope had remained uncertain despite a standardized basic evaluation that consisted of careful history, full physical examination, baseline laboratory testing, neurological evaluation, 12-lead electrocardiogram, 24-h ambulatory monitoring, chest X-ray, echocardiography and any other test necessary for a definitive diagnosis of the cause of the syncope. The patients with histories suggestive of vasovagal syncope (considered if a precipitating event such as fear, severe pain, or instrumentation could be identified), or situational syncope (considered if syncope was clearly correlated with coughing, micturition, defecation or swallowing) combined with negative above-mentioned investigations were included. Patients with associated carotid sinus hypersensitivity were also included. Carotid sinus hypersensitivity was defined as the reproduction of syncope in the presence of abnormal cardio-inhibition (asystole >3 s), vasodepression (fall in systolic blood pressure >50 mmHg) or both. Carotid sinus massage was performed according to the Method of Symptoms, which has been described in previously published reports^[4,5]. In accordance with the literature^[6], patients with the following characteristics were considered to have a definite or potential cause of syncope and were therefore excluded from the study: postural hypotension (defined as a decline of at least 20 mmHg in systolic blood pressure, or of at least 10 mmHg in

diastolic blood pressure, within 3 min of standing or using a tilt table in the head-upright position, at an angle of at least 60°^[7]); conversion reaction; seizure disorders; transient ischaemic attack; subclavian steal syndrome; drug-induced syncope; aortic stenosis; pulmonary hypertension; hypertrophic cardiomyopathy; arrhythmias (sick sinus syndrome, symptomatic supraventricular tachycardia, second or third-degree atrioventricular block, ventricular tachycardia of more than five beats); generally accepted abnormalities found at electrophysiological study^[5,8]. Patients with a permanent pacemaker were also excluded.

Tilt test protocol

Patients underwent the standardized protocol of upright tilt testing with trinitroglycerin (TNG) challenge, currently used in our department for the diagnosis of unexplained syncope^[3,4,9]. This consisted of 60° tilt for 45 min or until syncope occurred. If the test did not induce syncope, 0.4 µg (sublingual) oral spray TNG was administered while the patient remained in the same tilt position, and the test was continued for a further 20 min^[2]. During the test, the beat-to-beat finger arterial pressure was monitored continuously by the Finapres method^[10,11].

Suggested new classification of abnormal responses

In most patients with an abnormal response during tilt testing, the 'syncope phase' can easily be differentiated from the preceding 'pre-syncope phase' by a clear change in the behaviour of blood pressure and heart rate, which correlates with the time of onset of the vasovagal reaction. The time of onset of the syncope phase varies greatly from patient to patient; it depends also on the passive or TNG phases of occurrence of syncope. The period of time elapsing between the assumption of the upright position and the onset of the syncope phase constitutes the pre-syncope phase. We have observed three main patterns:

Classic (vasovagal) syncope pattern (Figs 1 and 2). In this form, the behaviour of blood pressure during the pre-syncope phase is indistinguishable from that observed in patients with a negative response and, therefore, it reflects a rapid and full compensatory reflex adaptation to the upright position. This results in rapid stabilization of blood pressure values shortly after the assumption of the upright position or TNG administration with no change or a slight increase of about 10 mmHg in the diastolic blood pressure (which reflects activation of sympathetic-mediated vasoconstriction) for all the duration of the pre-syncope phase. Systolic blood pressure does not change or decreases slightly, although it may show some fluctuation. As a consequence, pulse pressure also remains approximately of

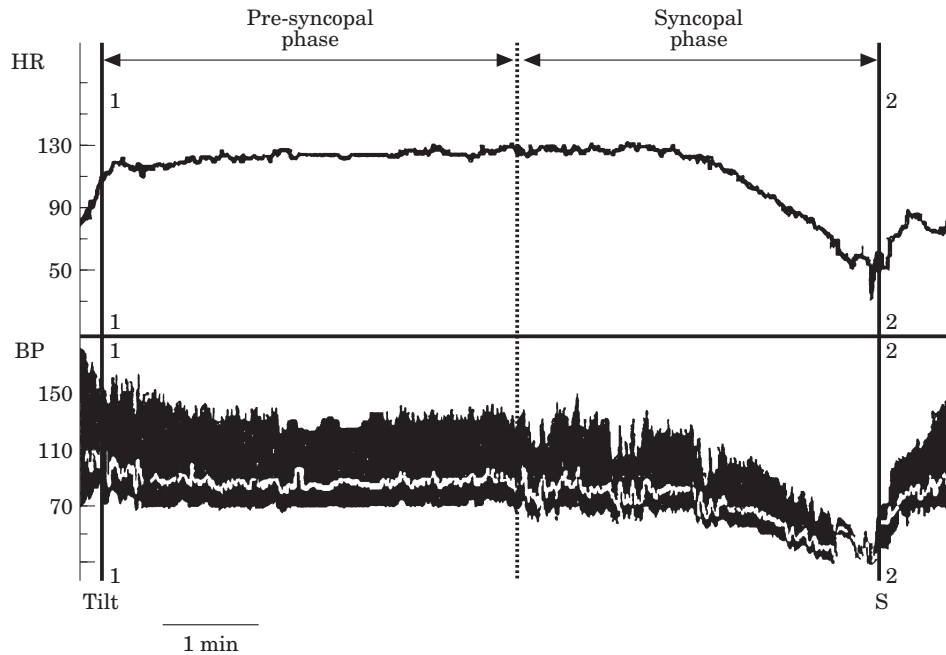


Figure 1 A case of classic (vasovagal) syncope occurring during the passive phase of tilt testing. Top trace shows the heart rate curve; bottom trace shows systolic, diastolic and mean blood pressure curves. Blood pressure stabilizes shortly after the assumption of the upright position with no changes in diastolic blood pressure for the duration of the preparatory phase (about 4 min); the heart rate immediately rises, then stabilizes. The vertical dashed line indicates the time of onset of the vasovagal reaction which is characterized, at first, by fluctuations and a mild decrease in diastolic blood pressure without changes in heart rate; later, both blood pressure and heart rate rapidly fall and syncope occurs. The total duration of the vasovagal reaction is about 4 min. HR=heart rate; BP=blood pressure; S=syncope.

the same magnitude or slightly decreases. Compared with the supine position, the heart rate increases during this phase. Patients are asymptomatic. The onset of the syncopal vasovagal phase can easily be determined at the time of an abrupt fall in diastolic blood pressure suggesting sympathetic withdrawal. This is accompanied by a decrease in systolic and pulse pressure. The decrease in heart rate, coincides with, or follows shortly after, the decrease of blood pressure. Vasovagal symptoms coincide with this phase.

Dysautonomic (vasovagal) syncope pattern (Figs 3 and 4). In this form, no steady-state adaptation to upright position is present. There is a slow but progressive fall in the diastolic blood pressure, which begins immediately after the assumption of the upright position or after TNG administration and continues until the onset of the vasovagal reaction. Systolic blood pressure falls with an even greater magnitude so that pulse pressure also decreases. Compared with the supine position, the heart rate increases during this phase by a variable amount. Patients are asymptomatic or develop mild symptoms of hypotension. The vasovagal reaction occurs when a critical value of blood pressure is reached (usually a value of systolic blood pressure of 70–

80 mmHg). The onset of the syncopal phase can be appreciated by a change in the slope of decline of blood pressure, as well as by a change in heart rate behaviour which usually starts decreasing or, more rarely, stops increasing. Once the vasovagal reaction starts, it is indistinguishable from that observed in the classic syncope pattern.

Orthostatic intolerance pattern (Fig. 5). In this form there is also a slow but progressive fall in diastolic blood pressure which begins immediately after the assumption of the upright position or after TNG administration, which is indistinguishable from that observed in the dysautonomic syncope pattern. The difference is that there is no clear vasovagal reaction to be discerned and, therefore, the test is characterized only by a long preliminary phase which lasts until the end of the test. No decrease in heart rate occurs throughout the test. Systolic pressure decreases to values below 80 mmHg and, therefore, symptoms of hypotension such as dizziness, blurring of vision, lightheadedness, sweating occur which persist for several minutes until the end of the test, but complete loss of consciousness does not occur for at least 5 min from the onset of the symptoms, at which time the test is interrupted.

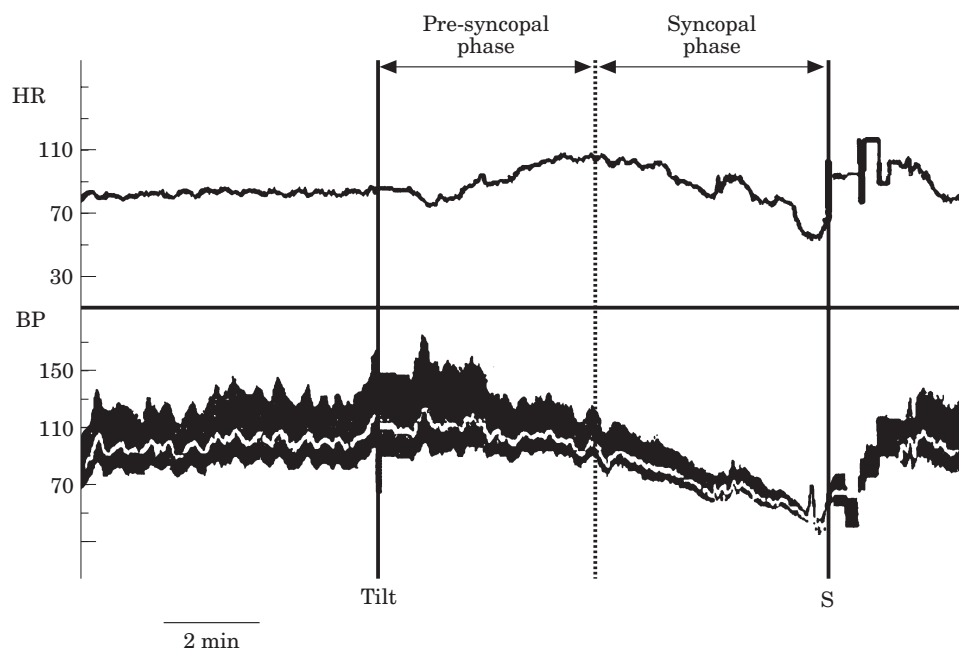


Figure 3 A case of dysautonomic (vasovagal) syncope occurring during the passive phase of tilt testing. Top trace shows the heart rate curve; bottom trace shows the systolic, diastolic and mean blood pressure curves. There is an absence of adaptation of blood pressure to the upright position; during the pre-syncope phase (of about 5 min) blood pressure declines slightly; since systolic pressure decreases more than diastolic, pulse pressure also decreases. The heart rate rises less than in the classic pattern. The vertical dashed line indicates the time of onset of the vasovagal reaction, which is characterized by a change in the slope of blood pressure decrease as well as a decrease in heart rate. HR=heart rate; BP=blood pressure; S=syncope.

Results

Among 189 patients who underwent tilt testing during the study period, abnormal responses were observed in 115 (Fig. 6). We were able to attribute to one of the three classes of the new classification 101 of these patients (88%): classic (vasovagal) syncope in 36, dysautonomic (vasovagal) syncope in 47 and orthostatic intolerance in 18. Fourteen patients (12%) proved impossible to evaluate because of atypical patterns or very short duration of the pre-syncope phase.

Some details regarding the results of tilt testing are shown in Table 1. Passive tilt testing was more often positive in patients with the classic pattern than in those of the other two groups, although the difference was not significant. In the patients with the classic and dysautonomic patterns the mean length of the pre-syncope phase was 19 ± 15 min for the 17 patients with a positive response during the passive phase and 3.1 ± 1.3 min for the 64 patients with a positive response during the TNG phase. No difference was observed between classic and dysautonomic groups (Table 1). Conversely, the duration of the pre-syncope phase (during TNG challenge) was longer for the 17 patients with the orthostatic intolerance pattern (8.5 ± 4.3 min; $P=0.000$). The mean duration of the vasovagal syncope phase was slightly longer when it

occurred during passive than during TNG (2.7 ± 1.5 min and 1.8 ± 0.9 respectively, $P=0.02$). No difference was observed between classic and dysautonomic groups (Table 1). During the pre-syncope phase, heart rate increased more in the classic group than in the other two groups.

The VASIS classification could be attributed to all patients in the classic and dysautonomic groups, but not to the patients with orthostatic intolerance, as they did not develop vasovagal syncope (Tables 2 (a) & (b)). Cardio-inhibitory forms were more frequently observed in the classic group, whereas mixed and vasodepressor forms were more common in those with the dysautonomic pattern. The median duration of asystolic pauses was 8.5 s and 8.0 s, respectively, in the two groups; pauses ranged from 3 s to 41 s.

Several different clinical features were present in the three groups of patients (Table 2). The patients with dysautonomic syncope differed from those with classic syncope in terms of age, prevalence of structural heart disease and duration of syncopal episodes, but had a similar prevalence of history of vasovagal or situational events. The patients with orthostatic intolerance were those who differed from those with classic syncope. Carotid sinus hypersensitivity was more frequent in the dysautonomic group than in the other two groups.

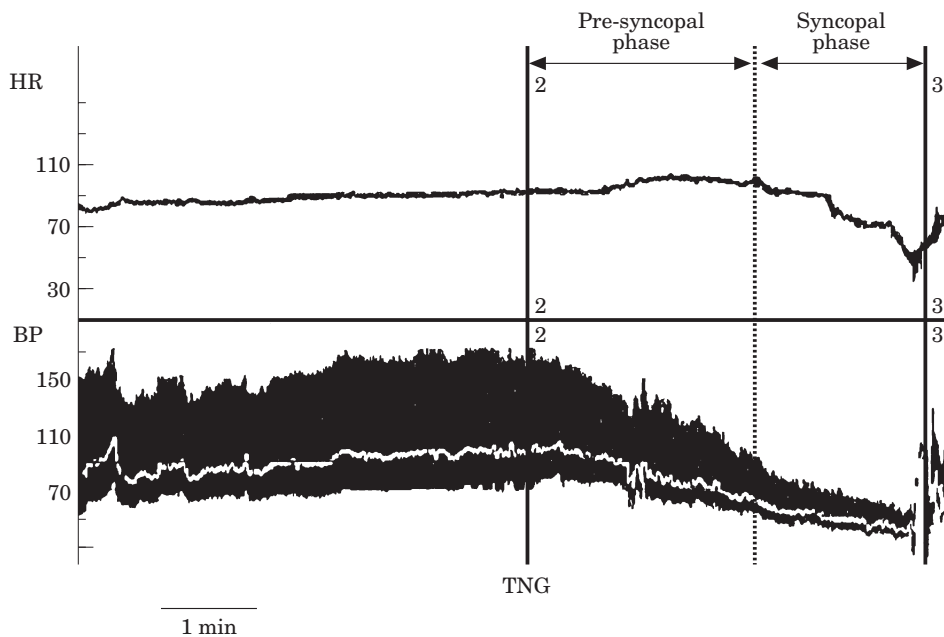


Figure 4 A case of dysautonomic (vasovagal) syncope occurring during TNG challenge. The figure is expanded and the first part of the passive phase of tilt testing is not shown. The top trace shows the heart rate curve; the bottom trace shows systolic, diastolic and mean blood pressure curves. There is an absence of adaptation of blood pressure to the upright position; blood pressure declines slightly and progressively throughout the pre-syncopal and syncopal phases without a change in slope; since systolic pressure decreases more than diastolic, pulse pressure also decreases. During the pre-syncopal phase, while the heart rate rises the increase is less than in the classic pattern. The vertical dashed line indicates the time of onset of the vasovagal reaction which, in this case, can be identified only by the decrease in heart rate. HR=heart rate; BP=blood pressure; TNG=trinitroglycerin; S=syncope.

Discussion

This classification is based on some previous observations. For example, the terms 'classic' and 'dysautonomic' have already been used by Grubb *et al.*^[12] to describe anecdotally various phenomena occurring during tilt testing which are similar to those described by us. Patterns that seem similar to our orthostatic intolerance pattern, although not completely overlapping, have been previously described as 'exaggerated response'^[4,9] and 'progressive orthostatic hypotension'^[13,14]. However, our study is the first to evaluate systematically and prospectively a population of consecutive patients, to classify them according to pre-defined categories and to correlate the classes of patients so obtained with clinical variables.

It is important to note that the age range of our population is wide, from teenage to very old patients, but the mean age was 60 years, namely about 10–20 years older than that reported in most other studies. This explains the high percentage of cases with baroreflex failure.

The patients with the classic pattern show a full compensatory reflex adaptation to the upright position, which suggests normal baroreflex function. The onset of the vasovagal reaction cannot be predicted by changes in

blood pressure or heart rate and the time of onset is very variable. Once the vasovagal reaction starts, it leads to syncope within a few minutes. The patients with the classic form are largely those who are young and healthy. They have a long history of syncope with long periods of time free of recurrences. Indeed, in our population these patients had a median of three syncopal episodes during a median 9 year period. In many cases the first syncopal episodes had occurred in the teenage years. Secondary trauma is infrequent and, if it occurs, is mild. We know from studies which recorded neural activity^[15], performed in patients presumably affected by classic vasovagal syncope, that the vasovagal reaction is not preceded by changes of low-frequency sympathetic or vagal rhythms^[16] or spontaneous vagal baroreflex gain^[17] and that it is ushered in by an abrupt cessation of sympathetic nerve traffic to the skeletal muscle vascular bed. The mechanism responsible for switching from haemodynamic compensation to vasovagal physiology remains largely to be determined^[15]. Classic syncope is felt to represent a 'hypersensitive' autonomic system that over-responds to various stimuli^[12]. For all these reasons we are reluctant to consider this phenomenon as a disease.

The patients with the dysautonomic pattern are unable to achieve a steady-state reflex adaptation to the

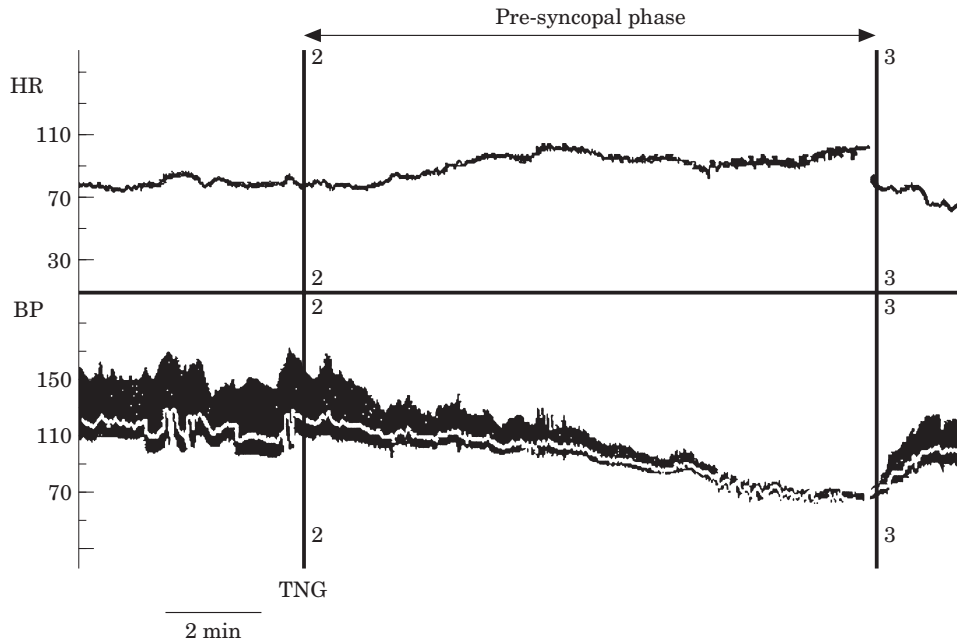


Figure 5 A case of orthostatic intolerance pattern occurring during TNG challenge. The figure is expanded and the first part of the passive phase of the tilt testing is not shown. The top trace shows the heart rate curve; the bottom trace shows systolic, diastolic and mean blood pressure curves. There is an absence of adaptation of blood pressure to the upright position; blood pressure declines slightly and progressively throughout the test, as in the dysautonomic pattern, but differs by showing no clear vasovagal reaction. The heart rate continuously rises until the end of the test. Thus, the test is characterized only by a prolonged pre-syncopal phase (13 min) which lasts more than in the other two patterns. Systolic blood pressure declines below 80 mmHg for more than 5 min and the patient has symptoms of hypotension but not syncope, then the test is interrupted. HR=heart rate; BP=blood pressure; TNG=trinitroglycerin; S=syncope.

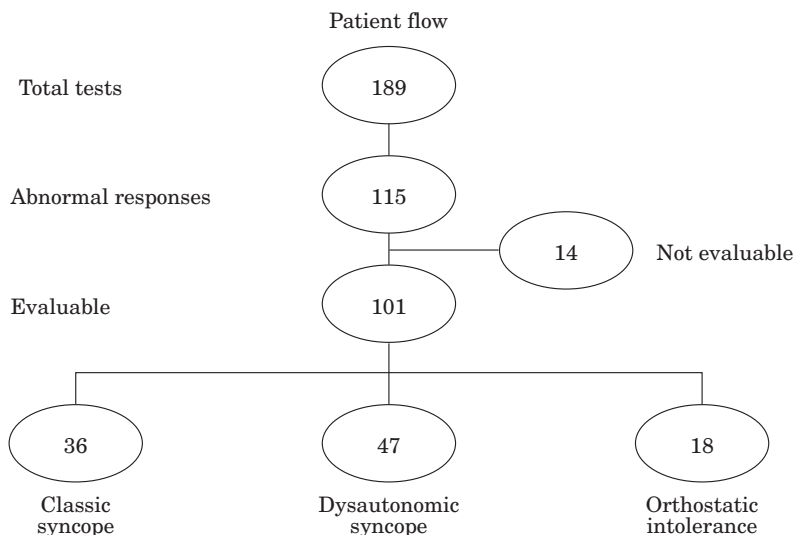


Figure 6 Patient flow. See text for explanation.

upright position, suggesting an impaired baroreflex response or an impaired function of the target organs, the heart and the peripheral vasculature. Accordingly, the value of the maximum heart rate reached by this

group is lower than that of the classic group. Typically, the vasovagal reaction begins when systolic blood pressure decreases to a critical value of about 70–80 mmHg. Therefore, it seems that prolonged orthostatic hypo-

Table 1 Tilt test results: details observed in the 3 groups of patients

	Classic syncope n=36	Dysautonomic syncope n=47	Orthostatic intolerance n=18	P value
Phase of the positive response				
Passive phase	12 (33%)	7 (15%)	1 (6%)	ns
TNG phase	24 (67%)	40 (85%)	17 (94%)	(1 vs 3: p=0.07)
Pre-syncope phase duration (min)				
Passive phase (when positive)	17 ± 16	22 ± 10	–	ns
TNG phase	3.5 ± 1.4	2.9 ± 1.2	8.5 ± 4.3	0.000 (1&2 vs 3)
Syncope phase duration (min)				
Passive phase (when positive)	2.5 ± 1.4	3.0 ± 1.7	–	ns
TNG phase	2.0 ± 0.8	1.6 ± 0.9	–	ns
Heart rate behaviour				
Maximum heart rate rise (beats . min ⁻¹)	105 ± 18	96 ± 20*	93 ± 20**	0.04 (1 vs 2&3)
Difference from baseline (beats . min ⁻¹)	37 ± 16	31 ± 15*	30 ± 15**	ns
Maximum heart rate <90	7 (19%)	14 (32%)*	8 (47%)**	0.04 (1 vs 3)

* evaluated in 44 patients (excluded 3 patients in atrial fibrillation).

** evaluated in 17 patients (excluded 1 patient in atrial fibrillation).

Table 2(a) Tilt test results according to the VASIS classification

	Classic syncope n=36	Dysautonomic syncope n=47	P value
Type 1 mixed	15 (42%)	28 (60%)	ns (0.08)
Type 2A cardio-inhibitory	15 (42%)	6 (13%)	0.003
Type 2B cardio-inhibitory	3 (8%)	2 (4%)	ns
Type 3 pure vasodepressor	0 (0%)	9 (19%)	0.004
Chronotropic incompetence (exception 1)	1 (2%)	2 (4%)	ns
Excessive heart rate rise (exception 2)	2 (6%)	0 (0%)	ns

Table 2(b) Tilt test results according to the modified VASIS classification

	Classic syncope n=36	Dysautonomic syncope n=47	P value
Type 1 mixed	15 (42%)	28 (60%)	ns (0.08)
Type 2A cardio-inhibition without asystole	6 (17%)	3 (6%)	ns
Type 2B cardio-inhibition with asystole	12 (33%)	5 (11%)	0.01
Type 3 pure vasodepressor	0 (0%)	9 (19%)	0.004
Chronotropic incompetence (exception 1)	1 (2%)	2 (4%)	ns
Excessive heart rate rise (exception 2)	2 (6%)	0 (0%)	ns

tension may play a role as a trigger for the vasovagal reaction. This issue has been recently addressed by Gaggioli *et al.*^[18] who demonstrated that treatment with vasodilator drugs, effectively reducing systemic pressure both at rest and upright, was able to increase the positivity rate of tilt testing in predisposed patients. The patients with the dysautonomic pattern are predominantly old, but it may also occur in some younger subjects; many have associated diseases. The patients have a short history of syncope (median duration of 1 year) with a median of two episodes per patient; therefore, syncopal episodes begin late in life, suggesting they are due to the occurrence of some underlying neural dysfunction. Carotid sinus hypersensitivity is frequently present in these patients, but not in those of the other two groups, suggesting that an impairment at some level of the carotid sinus baroreflex arc is also associated and,

therefore, a more complex autonomic dysfunction is present. For all these reasons we suppose that dysautonomic syncope is due to disease of autonomic function, which begins frequently late in the patient's life and is characterized by a compromised capability to adapt promptly to some external influences ('hyposensitive' autonomic function).

Patients with the orthostatic intolerance pattern are a group with syncope in whom tilt testing is unable to elicit a typical vasovagal reaction. The result of the test suggests that the cause of the syncope is an atypical form of orthostatic hypotension. Among the three groups, this form is the most similar to the syndromes of autonomic dysfunction, such as pure autonomic failure, the postural orthostatic tachycardia syndrome and the chronic fatigue syndrome^[19-21]. However, it differs from these with its blunted tachycardia reflex to upright

Table 3 Clinical characteristics of the three groups of patients

	Classic syncope n=36	Dysautonomic syncope n=47	P value (vs classic)	Orthostatic intolerance n=18	P value (vs classic)
Age (years)	50 ± 20	65 ± 17	0.000	72 ± 15	0.000
Males	18 (50%)	23 (49%)	ns	10 (50%)	ns
Co-morbidities:					
systemic hypertension	10 (28%)	21 (45%)	ns (0.09)	11 (61%)	0.02
structural heart diseases	5 (14%)	17 (36%)	0.02	7 (39%)	0.04
ECG abnormalities	7 (19%)	15 (32%)	ns	9 (50%)	0.02
diabetes	1 (3%)	2 (4%)	ns	1 (6%)	ns
History of syncopal episodes:					
total number (median)	4.9 ± 6.4 (3)	3.1 ± 4.5 (2)	ns	2.6 ± 3.4 (1)	ns
duration, years (median)	13 ± 14 (9)	7 ± 15 (1)	0.003	1 ± 1.5 (0.5)	0.000
situational symptoms	13 (36%)	12 (26%)	ns	2 (11%)	0.05
vasovagal symptoms	13 (36%)	9 (19%)	ns (0.06)	0 (0%)	0.002
situational or vasovagal	18 (50%)	18 (38%)	ns	2 (11%)	0.05
pre-syncopal episodes	20 (56%)	21 (45%)	ns	5 (28%)	0.01
secondary trauma	11 (31%)	22 (47%)	ns	10 (56%)	ns (0.07)
vasoactive therapy	9 (25%)	18 (38%)	ns	11 (61%)	0.02
Carotid sinus hypersensitivity	4 (11%)	20 (43%)	0.001	3 (17%)*	ns
cardioinhibitory form	2	13		1	
vasodepressor form	2	6		2	

* $P=0.04$ vs dysautonomic group.

posture and different clinical manifestations. In these patients, both the clinical characteristics and the behaviour during the pre-syncopal phase were similar to the patients with dysautonomic syncope, except for the lack of history suggestive of vasovagal or situational episodes and the lack of a tilt-induced vasovagal reaction. Thus, it seems that the patients with orthostatic intolerance may suffer from some form of autonomic failure and not vasovagal syncope. Patterns similar to that of orthostatic intolerance are those previously defined as exaggerated responses. They were described during pharmacological tilt testing both with isoproterenol^[4] and TNG^[9], whereas they have been rarely found during passive tilt testing^[4]. Since exaggerated responses were also observed in many control subjects without syncope, their diagnostic value has remained uncertain. The present study is helpful in clarifying their implication in impaired baroreflex function, which can be observed both in patients with and without syncope. The term orthostatic intolerance seems preferable to that of exaggerated response.

Carotid sinus hypersensitivity and tilt-induced syncope

Carotid sinus hypersensitivity is well known to be frequently associated with a positive response to tilt testing although the reason for this association remains unclear^[4,5]. In this study, carotid sinus hypersensitivity was associated with the dysautonomic pattern, but not with the classic or the orthostatic intolerance patterns. The cause of this association is not advanced age per se, since carotid sinus hypersensitivity was not associated with the orthostatic intolerance group. This study

suggests that carotid sinus hypersensitivity and the dysautonomic pattern are probably manifestations of the same disease of autonomic failure or they share common pathways. In contrast classic vasovagal syncope and carotid sinus syndrome are two distinct syndromes.

The 'new VASIS classification' and practical implications

Both the original and the modified VASIS classifications of the vasovagal phase are applicable to both the classic and dysautonomic groups and can be used in conjunction with the haemodynamic classification. The resulting new VASIS classification may have practical implications. The classic group showed a prevalence of cardioinhibitory forms, whereas the dysautonomic group showed a prevalence of mixed and vasodepressor forms. It seems unlikely that the three groups would benefit from the same treatment. Future therapy trials should enrol patients taking account of their tilt test patterns. We can anticipate that dysautonomic patients might benefit from the therapy usually used for the syndromes of autonomic dysfunction with orthostatic intolerance, namely increasing blood volume (fludrocortisone), reducing blood volume in the lower limb of the body (compression stockings, sleeping with the head of the bed upright) or using alpha stimulating agents, such as midodrine and etilefrine. Recent controlled studies have shown that midodrine is superior to placebo in the syndrome of orthostatic hypotension^[22] and in severely symptomatic old patients affected by 'hypotensive' syncope^[23]. If preventive therapy fails, pacemakers may be useful in the cardio-inhibitory forms, especially in those with asystole, and when carotid sinus hypersensitivity

may be associated. In the latter case, cardiac pacing is definitively of proven efficacy^[24,25]. Most patients with classic syncope probably do not need any treatment owing to its benign course with long periods of absence of recurrences. However, we can expect that the results of pharmacological treatments will be disappointing and similar to those in some placebo-controlled prospective trials that have been unable to show a benefit of the active drug over placebo^[26–29]. The role of pacing in severe cardio-inhibitory forms remains to be defined; due to the benign course; its role, however, has to be limited to very rare selected cases. Tilt training is a new therapeutic strategy which seems to be especially suited to patients with classic vasovagal syncope^[30].

Conclusion

Any descriptive classification of pathophysiology at an early stage in its understanding must be expected to receive criticism and undergo modification. It should be remembered that, when we observe nature, we see what we want to see according to our understanding at that time. In order to make some sense of the apparent chaos of nature, we try to classify it into a coherent system that conforms to our expectations. Thus, any system of classification is in some way arbitrary and open to debate^[31]. It seems that rather than having a clear differentiation, there is a wide spectrum of disorders of orthostatic cardiovascular homeostasis including, on the one side, vasovagal syncope and, on the other, the syndromes of autonomic dysfunction such as in the postural orthostatic tachycardia syndrome, chronic fatigue syndrome, pure autonomic failure, etc. In this respect patients with the dysautonomic pattern and those with the orthostatic intolerance pattern during tilt testing may represent a link. Future studies should evaluate whether there are different neural and endocrine mechanisms responsible for the different syndromes of tilt-induced orthostatic intolerance.

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