Nitrate stimulated tilt testing for the diagnosis of vasovagal syncope

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NITRATE STIMULATED TILT TESTING FOR
THE DIAGNOSIS OF VASOVAGAL SYNCOPE

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NITRATE STIMULATED TILT TESTING FOR THE DIAGNOSIS OF VASOVAGAL SYNCOPE

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit Maastricht,
op gezag van de Rector Magnificus,
Prof.mr. G.P.M.F. Mols,
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen
op donderdag 20 januari 2005 om 16.00 uur

door

Arnaud Johannes Jacobus Aerts
geboren op 7 december 1958 te Meerssen

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Denk breed
maar vergeet niet
de precisie.
Wees plichtsgetrouw
maar vergeet niet
de toegeeflijkheid.
(Confucius)

Aan mijn ouders

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CHAPTER 1

Introduction to the thesis

HISTORICAL BACKGROUND

For centuries, the phenomenon of fainting or loss of consciousness has been an intriguing entity in medicine. In the past this phenomenon was referred to as *syncope*, derived from the Greek term “syncopein”, or as *collaps*, derived from the Latin word “collapsus”. In Anglo-Saxon literature, however, the term *common faint* prevailed.

The term *vasovagal* was initially coined by W. Gowers in 1907, but he applied it to a vague psychogenic description soon to be abandoned. It was Sir Thomas Lewis who, in 1918, initially applied the term vasovagal to the condition previously known as “common” faint in shell shock world war I soldiers.¹

Sir William Richard Gowers.

Sir Thomas Lewis.

As progress was made in the analysis of heart rhythm and blood pressure, he was the first to report on the clinical and hemodynamic characteristics of vasovagal syncope in 1932. An association was made between a spectrum of typical premonitory symptoms generally occurring whilst in an upright position, and bradycardia, hypotension and syncope.² Schematically presented in Figure 1, predisposing conditions identified were fatigue, recovery after illness, a period of fasting, confinement to an over-heated and/or overcrowded room, nervous agitation and emotional stress and pain. In addition, a triggering in sensory nerve endings of various organs may result in neurally reflex mediated loss of consciousness.

Figure 1 A schematic illustration of different causes of vasovagal syncope.

Though generally benign, especially in those without warning symptoms, a fall may be accompanied by injury.³ Patients experiencing recurrent falls may also suffer an accompanying decrease in their quality of life, seriously affecting their social and working lives.

PATHOPHYSIOLOGICAL CONCEPT OF VASOVAGAL SYNCOPÉ

It is currently generally accepted that syncope is defined as loss of consciousness due to a reduction in cerebral blood flow in response to a systemic hemodynamic collapse.^{4,5} A sudden critical reduction in cerebral flow for 6–10 seconds results in a complete loss of consciousness. Since cerebral flow is predominantly dependent on systemic arterial pressure, any factor that could influence circulatory hemodynamics may result in syncope. Consequently, a drop in systolic pressure to below 70 mm Hg or in mean pressure below 30–40 mm Hg is associated with syncope. As vasovagal syncope has been fundamentally linked to an inability to maintain an upright position, a disturbance in the regulation of afferent and efferent pathways of the auto-

onomic system which control postural hemodynamic changes has been presumed to cause this abnormality.

In 1867, Von Bezold and Hirt suggested the presence of mechano-receptors in the heart capable of affecting the circulatory system.⁶ This was specified further by Jarish and Zotterman in 1949, who concluded that the reflexogenic zone of this vasoactive reflex was to be found in the left ventricle of the heart. The Bezold-Jarish reflex is considered to be an inhibitory reflex originating in cardiac sensory receptors with vagal afferents, which may respond to either chemical or mechanical stimuli. Stimulation of the reflex results in an increase in parasympathetic activity and sympathetic withdrawal, resulting in bradycardia and hypotension.^{5,6}

In vasovagal syncope, activation of the reflex is attained when blood is pooled in the lower extremities whilst in an upright position. This may also be artificially provoked by upright tilting or by inducing lower body negative pressure. Normally a decrease of venous return results in reduced filling pressure, stroke volume and arterial pressure. This, in turn, elicits reflex tachycardia and vasoconstriction.

Together with the increase in heart rate and cardiac output, an impressive increase of the vasoconstrictor hormones adrenaline and vasopressin occurs, while renin decreases and levels of noradrenaline remain unchanged or increase modestly.^{7,8}

In patients with vasovagal syncope cardiac mechanoreceptor stimulation results in paradoxical withdrawal of sympathetic activity and an increase in parasympathetic activity, leading to a decrease of cardiac filling pressure, vasodilatation and bradycardia.⁷⁻⁹

EPIDEMIOLOGY OF VASOVAGAL SYNCOPE

Syncope is a frequently encountered problem in daily clinical practice and emergency departments, and accounts for approximately 1-5% of medical admissions and 3% of emergency room visits.¹⁰

These figures probably underestimate the real burden on the community, however, as in various population groups such as military recruits and students, up to 48% may have been experienced one or more syncopal episodes, with the majority not seeking medical attention.¹¹ Data derived from the Framingham Study undertaken in the period 1971 to 1998 with an average follow-up of 17 years showed that syncope had

occurred in 822 out of 7814 subjects included in the study.¹⁰ When broken down by etiology, the most frequently identified cause appeared to be vasovagal in origin (21.2%) and to a lesser extent cardiac syncope (9.5%) and orthostatic hypotension (9.4%). Although in the absence of any causal organic disease, syncope is generally attributed to younger persons, the Framingham data show that the prevalence of isolated syncope increases with age from 0.7% in men aged 35–44 years to 5.6% in those 75 years or older.

However, based on the results of several epidemiological studies, the prevalence of syncope is probably evenly distributed in each decade of life.¹⁵

The fact that in 36% of cases the cause of syncope remained unknown may be due to the unavailability of the tilt table test in the period in which the data were collected.

This could have led to an underdiagnosing of vasovagal syncope. Others have encountered a vasovagal origin of syncope in up to 50% of cases.^{12,13} Only the advent of the tilt test has introduced a new and feasible method of decreasing the number of undiagnosed, and therefore untreated, patients. In addition, correct and early diagnosis may prevent the use of low yielding and often expensive investigations.¹²

ECONOMICAL BURDEN OF INVESTIGATING SYNCOPE

Vasovagal syncope has a benign prognosis and the diagnosis is made by a combination of a careful examination of a patient's medical history and the tilt table test, thereby obviating the need for extensive investigations.¹⁴ Prior to the availability of the tilt test to stimulate syncope, expensive investigations were often carried out, which unnecessarily increased the cost of medical care. This is underscored by the findings of Calkins et al. who reported on the economic burden of unrecognised vasodepressor syncope.¹⁰ They examined the costs of diagnostic investigations performed before a vasovagal origin could be established by the tilt test. Although 6 of 30 patients (20%) underwent no major tests prior to referral, in the remainder, an average of \$ 4,704,- (range 1,025–16,606 US\$), was spent on diagnostic testing.

In a recent metropolitan area registry analysis of the year 2000, it turned out that of 38,330 emergency room presentations 1,290 (3.36%) were diagnosed as having either vasovagal or disease-related syncope. 54% of all patients with syncope were directly discharged and 34% were hospitalised (1.14% of all presentations).

In 115 of the hospitalised patients (23%), the cause of syncope was of vasovagal origin. Aside from the inconvenience for the patient of an unnecessary hospitalisation, cost-benefit analysis revealed an economic loss to the hospital.¹⁵

A comparable number of admissions for syncope was observed in our institute, in the eastern part of Limburg. A locally conducted survey revealed that 354 out of 20,294 (1.7%) emergency room attendees were hospitalised for syncope investigation.

The importance of accurate analysis of patients presenting with syncope was recently addressed by Brignole et al.¹⁶ They established that in hospitals with a syncope unit (including a tilt table test), the use of expensive examinations such as computed tomography of the brain and echocardiography was significantly reduced. Although the number of hospitalisations was comparable in hospitals with or without a syncope unit, the number of diagnoses (neurally mediated vasovagal syncope), was significantly increased in those with a syncope unit. The authors concluded that the presence of a specialised syncope unit in a hospital substantially enhances the efficient overall in-hospital management (including cost management) of patients with syncope.

Figure 2 Tilt table.

TILT TABLE TESTING FOR THE DIAGNOSIS OF VASOVAGAL SYNCOPE

Tilt table testing was used by Weiss et al. as early as 1936 to investigate the hemodynamics of vasovagal syncope.¹⁷ Using a tilt table and drug stimulation with amyl nitrite, they induced vagal reactions, at that time called vasodepressor syncope, in healthy subjects. From that time on, the tilt table test was increasingly used to study the effects of positional and gravitational forces on humans. This is especially evident from the large number of publications on the use of tilt tables (Figure 2) in aviation studies.^{8,17} Among these experiments was the landmark study by Kenny and Sutton in 1986 that described for the first time the use of tilt table testing for the diagnosis of vasovagal syncope.¹⁸ In that study, 15 patients with unexplained syncope and a control group of 10 normal individuals were studied. By using a tilt test at an angle of 40° for 60 minutes, the investigators induced syncope in 10 patients (67%) but in only one member of the control group. From that time on, numerous reports focused on the ideal tilt protocol. Various tilt angles from 40–90° and differing durations of between 10–60 minutes have been studied.¹⁹

Given the fact that no gold standard exists for the diagnosis of vasovagal syncope, but the clinical diagnosis of this disorder, a positive tilt test was based on the observations of similar prodromal signs and symptoms, hemodynamic and neurohormonal alterations of both spontaneous occurring and tilt induced syncopal episodes.²⁰ When analyzing the diagnostic value of the tilt test, it thus appeared to be reasonable to express this as the sensitivity of the test. The specificity of the test was defined as the proportion of subjects, without prior experience of syncope or presyncope, who have a negative tilt test.

In 1991, Fitzpatrick introduced the Westminster protocol: using a tilt table with footboard support at an angle of 60° for 45 minutes, without intravenous cannulation or drug challenge.²¹ In that study 71 patients with unexplained syncope and 27 normal controls were tested. They reported a sensitivity of 75% and a specificity of 93%.

However, several investigators reported later on the lack of sensitivity of the passive tilt test, and pharmacological stimulation was introduced in order to increase the yield of the test for the diagnosis of vasovagal syncope. In 1984, Yao and Waxman reported on the use of intravenous isoproterenol in patients with a history of syncope. They found a sensitivity of 66%.²² Later, in 1989, both Almquist et al. and Waxman et al. investigated the use of incremental dosages of isoproterenol infusion during tilt

table testing. The former study reported a sensitivity and specificity of 87% and 85% and the latter of 73% and 85% respectively.^{22,23}

Authors criticised the use of isoproterenol during tilt testing, however, because of a lack of specificity, especially with high dosages, and because of the occurrence of significant catecholaminergic related side effects such as angina pectoris, and even life-threatening ventricular arrhythmias.^{24,27} Also, aside from the cumbersome nature of intravenous testing, cannulation itself is reported to decrease the specificity of the test.²⁶

Known for its ability to induce vasovagal reactions, the use of intravenous nitrates as a drug challenge during tilt testing was introduced by Raviele et al. in 1994.²⁸ They reported a sensitivity and specificity of 53% and 92% respectively. In 1995, the same group²⁹ as well as Aerts et al.³⁰ reported on the use of sublingual nitrates during tilt testing to establish a diagnosis of vasovagal syncope. Both studies used different protocols, but the former reported a sensitivity and specificity of 51% and 94% and the latter of 87% and 70% respectively.

Although other provocative drugs (edrophonium, clomipramine and adenosine) were also investigated during tilt table testing, the use of nitrates during tilt testing has become a widely-used and well-accepted tool for facilitating a diagnosis of vasovagal syncope.^{27,32}

AIMS OF THE THESIS

As no golden standard for the diagnosis of vasovagal syncope exists, the true merit of the tilt test may be more appropriately determined in conjunction with a clinical diagnosis of the disorder. In this thesis, the value of the nitrate stimulated tilt test was evaluated in patients with a typical history of vasovagal syncope. We describe the diagnostic value of orally and intravenously administered nitrates during tilt testing for the diagnosis of vasovagal syncope. Moreover we analysed the reproducibility and predictive value of the test and focused on the mechanism of nitrate induced vasovagal syncope.

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CHAPTER 2

Intravenous nitrates for pharmacological stimulation during head-up tilt testing in patients with suspected vasovagal syncope and healthy controls

Arnaud J. J. Aerts, Paul A. Dendale, Cathy Daniels, Paul Meyvisch, Leonard Kaufman, Gunnar Strobel, Pierre Block

ABSTRACT

Objective: Nitrates may be used for pharmacological stimulation during tilt testing for the diagnosis of vasovagal syncope. In this study we assessed the diagnostic value of intravenous nitrates during tilt testing in patients with a typical history of vasovagal syncope.

Methods and results: Twenty patients and 23 controls were tilted at 70° for a maximum duration of 30 minutes. After a 10 minutes baseline supine phase, the test started with a continuous nitrate infusion at 1 µg/kg/min and increased every 5 minutes by 1 µg/kg/min, to a maximum of 6 µg/kg/min at the end of the test. The test was ended if the subjects developed a positive response (syncope or presyncope). Nineteen patients (95%) had a positive response and 17 (74%) of the controls. At test end sensitivity was 95%, but specificity 26% and accuracy 58%. Receiver operator characteristics (ROC) analysis revealed a maximum accuracy of 79% at 18 minutes, with a sensitivity of 80% and a specificity of 78%.

Conclusion: Intravenous nitrates during tilt testing in patients with typical clinical criteria of vasovagal syncope is highly effective in provoking vasovagal syncope. Based on the ROC analysis, a maximum accuracy of 79% was attained at 18 minutes (at a dose of 4 µg/kg/min), suggesting a good diagnostic performance when tilt duration is limited to this point. A positive result requiring more than 18 minutes of stimulated tilting should be interpreted with caution, due to the accompanying considerable decrease of specificity.

INTRODUCTION

Neurally mediated or vasovagal syncope is generally a benign event with a good prognosis but which can nevertheless handicap the patient.^{1,2,3,4} Moreover it is sometimes difficult to distinguish from other causes of syncope. The tilt test has become a useful tool to assess the diagnosis of vasovagal syncope.⁵⁻¹⁰ In patients with suspected vasovagal syncope, without a history or overt sign of organic heart disease, the utilization of often extensive screening medical examinations can be low yielding and not very cost effective.^{1,10-13} Unfortunately, passive tilt is not thought to be a very sensitive test in patients with a typical history of vasovagal syncope and may be very time consuming which limits the application of the test in clinical use.^{8,14} Therefor pharmacological stimulation is not only used to increase the diagnostic value of the tilt but also to shorten the total duration of the test.^{4,9,10,11,16,17}

Also the diagnostic yield of a stimulated tilt test is often determined in a population with syncope of unknown origin. However due to the lack of a gold standard, assessing the merits of a form of tilt test for the diagnosis of vasovagal syncope might be more appropriately done in a population with a typical history of vasovagal syncope.⁴ Nitrates are known to induce syncope with vasovagal characteristics and therefore can be used for pharmacological stimulation during tilt testing.^{5,8,18-21} The aim of this study was to assess the diagnostic value of intravenous nitrates, during head up tilt testing in patients with a typical history of vasovagal syncope. Our secondary goal was to develop a short and practical test which can easily be used in daily clinical practise.

METHODS

Patient selection

We studied 20 consecutive patients with a history of typical vasovagal syncope (mean number 4, range 1-20), one (5%) had one syncope and 19 (95%) had two or more, and 23 normal controls. A clinical suspicion of vasovagal syncope was diagnosed if the patient had at least one of the characteristics of each of the following groups: 1) Awareness of imminent syncope, loss of postural control. 2) Occurring in erect or sitting position. 3) Premonitory symptoms of warmth, nausea, sweating, visual dimming, precipitating anxiety or pain, mental stress, lightheadedness. 4) Rapid recovery with recumbency. The test were performed on an average of 14 days (median), range 1-110 days, after the last syncopal episode. Demographic characteristics are shown in Table 1. To exclude other causes of syncope, all patients had a full history and clinical (including neurological) examination, carotid sinus massage and orthostatic blood pressure testing (defined as blood pressure measurements supine and standing for 5 minutes), 12-lead electrocardiogram and routine laboratory tests. Patients taking cardiovascular or vasodilating drugs were excluded. Supplementary examinations as Holter 24 hour recording, echocardiogram, computed tomography of the brain and electroencephalogram were done when clinically indicated. Controls were mostly medical students who had never experienced a syncope before.

Tilt test protocol

The tests were done between 9.00 and 12.00 am and the subjects had to be in an overnight fasting state. The protocol was approved by the hospital ethics committee and informed consent was obtained from all subjects. We used a motorized table with footboard support located in a quiet room with a constant temperature of 21° Celsius. A 12-lead electrocardiogram (Marquette) was displayed continuously and blood

Table 1 Demographic characteristics (mean value) of patients and controls.

	Patients	Controls	P value
Heart rate	72±12	78±13	P=0.178
Systolic BP	134±20	123±10	P=0.0056
Diastolic BP	79±9	73±5	P<0.05
Age	41±15	25±5	P<0.001
Gender	10F/10M	8F/15M	P=0.23

BP = blood pressure.

pressure was measured every minute by an automatic sphygmomanometer (Dinamap). An intravenous catheter was inserted in a superficial vein in the forearm. After the cannulation the subject remained in a supine position for ten minutes to obtain baseline values of heart rate and blood pressure. Then the subject was tilted to 70° and nitrate infusion (isosorbide dinitrate) was started by 1 µg/kg/min which was increased every 5 minutes by 1 µg/kg/min to a maximum of 6 µg/kg/min at the end of the test. The tilt table was lowered when the subject developed a positive response (syncope or presyncope). A preceding passive tilt phase was not undertaken because in a previous study we reported the diagnostic value of 30 minutes of passive tilting, in patients with suspected vasovagal syncope, to be low (sensitivity 14%) and time-consuming.⁸

Definitions

Syncope was defined as a transient loss of consciousness with spontaneous recovery. Presyncope was defined as a state of light-headedness accompanied by signs and symptoms such as nausea, sweating, vomiting, pallor or weakness suggesting an imminent syncope. According to the hemodynamic response a positive response was classified as a mixed, vasodepressor or a cardioinhibitory reaction.

A *mixed response* was defined as a decrease in heart rate of ≥ 20 bpm and a decrease in systolic blood pressure of ≥ 20 mm Hg. A *vasodepressor response* was defined as a decrease in blood pressure of ≥ 20 mm Hg but no significant reduction in heart rate. A *cardioinhibitory response* was defined as a sudden decrease in heart rate of ≥ 20 bpm without a preceding decrease of blood pressure.

Statistical analysis

Demographic characteristics of both study groups were evaluated using a two-sample t-test for continuous variables and a chi-square test for categorical variables.

A log rank test, adjusting for the effect of group (patient/controls), is applied for each demographic characteristic (age, gender, blood pressure and heart rate) separately, to test whether there is an association with time to syncope. These log rank tests are based on Kaplan-Meier estimation. The relationship of the demographic characteristics which showed an effect on time to syncope, was investigated by Cox regression. The proportional hazards assumption was assessed.

A P value of less than 5% was considered statistically significant. All statistical analysis were done using SAS 6.11. Log rank tests were performed by Proc Lifetest, Cox regression was done by Proc Phreg.

RESULTS

Of the 20 patients, 19 (95%) had a positive response during nitrate stimulation, 18 (90%) developed syncope and one presyncope. In the control group of 23 normal subjects, 17 (74%) were positive; 9 (53%) had syncope and 8 presyncope.

Sensitivity, specificity and accuracy at the end of the test were 95%, 26% and 58% respectively, with thus an unacceptable low specificity. Therefore a receiver operator characteristic (ROC) analysis was done to investigate the influence of tilt duration on the sensitivity, specificity and accuracy of the test. A maximum accuracy was attained at 18 minutes (at a dose of 4 µg/kg/min) giving a sensitivity of 80%, a specificity of 78% and accuracy of 79% (Figure 1). Specificity decreased considerably after 18 minutes of tilting.

Mean time to a positive result in the patient group was 13 ± 6 minutes (range 1-23 minutes) and 19 ± 5 minutes (range 8-28 minutes) in the controls ($P=0.001$).

A log rank test, adjusted for the effect of group (patients/controls) showed that out of 4 demographic characteristics (age, gender, blood pressure and heart rate) only age was significantly ($P=0.027$) associated with time to syncope. A Cox regression analysis was done to investigate the influence of age on the test result. The result was that for each one-year increase in age the instantaneous risk (or hazard) of syncope during the test decreased by 5% ($P=0.009$). This decrease was the same for both groups.

Cox regression also showed that the instantaneous risk of syncope during the test was 6 times higher for patients as for controls ($P=0.001$).

Figure 1 Results of sensitivity, specificity and accuracy are shown during nitrate stimulation. Maximum accuracy is obtained at a cut off point of 18 minutes with a sensitivity of 80%, specificity of 78% and a accuracy of 79 %. At test end sensitivity is 95%, specificity 26% and accuracy 58%.

Hemodynamic response

A mixed response was found in 11 (58%) patients, a vasodepressor in 4 (21%) and a cardioinhibitory in 4 (21%). In the latter group all patients had an asystole with a mean duration of 28 ± 15 seconds (range 8–41 seconds). In the control group 13 (77%) had a mixed and 4 (24%) a vasodepressor response. No serious side effects occurred.

DISCUSSION

This study shows that, in patients with a typical history of vasovagal syncope, prolonged administration with intravenous nitrates during tilt testing, is highly effective to provoke a vasovagal syncope. On the other hand the high number of positive results in the control group, also shows the ability of nitrates to induce vasovagal syncope in normal persons.

ROC analysis revealed a maximum accuracy of 79% at 18 minutes (at a dose of $4 \mu\text{g/kg/min}$), indicating, when the test is limited to this point, a good diagnostic performance with a sensitivity of 80% and an still acceptable specificity of 78%. Prolongation of the test up to 30 minutes (at a dose of $6 \mu\text{g/kg/min}$) results in a modest

increase in the sensitivity but at the costs of a substantial decrease of the specificity making the clinical relevance of a positive test obtained after 18 minutes questionable.

Diagnostic yield of other stimulated tilt test protocols

Until now, no other data are available on the use of intravenous nitrates for stimulation in a population selected on the basis of a typical history of vasovagal syncope. Raviele et al.²¹ tested intravenous nitrates in patients, without premonitory symptoms defined as unexplained syncope, in a different protocol with supine rest periods between dose increments. They found a sensitivity of 53%, a specificity of 92% and an accuracy of 67%. This protocol had a total duration of 70 minutes. In our study comparable results were attained after 15 minutes of continuous tilting with a sensitivity of 45%, a specificity of 91% and a accuracy of 67%.

Our higher sensitivity but lower specificity may have several explanations:

1. By continuous tilting, as done in our study, the orthostatic stress might be higher than a protocol that uses supine phases in-between dose increments. This observation is supported by the findings of Kapoor et al.¹⁷ who compared both test modalities in normal controls. They found in a continuous isoproterenol stimulated tilt protocol a specificity of 35% and in a other matched control group a specificity of 55% ($P=0.2$) when using a protocol with supine periods in-between dose increments.
2. The ability of oral nitrites to induce vasovagal syncope in normal volunteers during 30 minutes of continuous tilting is well described in reports from the nineteen fifties.^{18,19} But to our knowledge no reports exist investigating, in patients with syncope, the influence of both stimulated tilt modalities, (in-between supine periods between dose increments or continuous tilting) on the test result.
3. By selecting only patients with a typical history of vasovagal syncope, as done in our study, the sensitivity could be higher than in a population with unexplained syncope. However this is only hypothetical since also patients with less premonitory symptoms could have an high incidence of positive vasovagal reactions. The influence of the patient selection on the value of the test has been shown when isoproterenol is used for stimulation. Waxman and co-workers found, using isoproterenol and supine phases between dose increments and a 60° tilt angle, a sensitivity of 50% in a group with unexplained syncope ($n=8$) and a sensitivity of 67% in a population selected by their typical history of vasovagal syncope ($n=12$).¹⁴ Only few other data are available on isoproterenol stimulated protocols in patients selected by

their history. Calkins and co-workers reported upon a group with a typical history of vasovagal syncope ($n=20$), using a tilt angle of 70° and supine phases in between dose increments. They found that isoproterenol induced in 15 out of 20 patients (60%) a positive response.¹⁵ In both studies mentioned before, a preceding short (10–15 minutes) unmedicated passive tilt phase, contributed little (0–10%) to the total responses.

4. Patients with suspected vasovagal syncope might be more susceptible to stimulation with nitrates. Raviele et al.²¹ who compared isoproterenol and intravenous nitrates for stimulation during tilt testing at a tilt angle of 80° reported that nitrates more frequently provoked a vasovagal response than isoproterenol (sensitivity 25% with isoproterenol vs. 53% with nitrates) in patients with unexplained syncope. That study also showed that nitrates were associated with considerably less side effects than isoproterenol.

The influence of instrumentation on the test result

During the first two minutes of tilting, 2 patients (10%) developed a vasovagal syncope. Orthostatic hypotension was excluded in all subjects before the test. The history revealed that both patients previously experienced syncope during blood sampling. Therefore we assume these responses were induced by the instrumentation. The negative influence of cannulation on the specificity in tilt testing is well described.^{22–24} In our study, instrumentation may have increased sensitivity by 10%, however the influence on the specificity could not be determined.

Influence of age

In our study, age was inversely related to the risk ($P=0.027$) of a positive response during the test. Each year of increase in age reduced the hazard of syncope during the test by 5%. Although it is generally assumed that the susceptibility to a vasovagal syncope is not age related,²⁵ clinical studies have shown a predominance of this syndrome in younger patients.^{26,27} Percentages of suspected vasovagal syncope in patients (age 35–39 years) admitted to the emergency department for syncope, vary from 28–38% compared to 0–2% in patients older than 70 years.²⁶ Also, several authors reported of a decreased susceptibility to vasovagal syncope during either passive or pharmacological stimulated tilt testing in elderly patients.^{4,21,26,28} As an explanation, it has been suggested that parasympathetic tone and mechanoreceptor sensitivity is reduced in elderly people.^{26,28} However an age related susceptibility, during isoproterenol stimulated tilting, is not a uniform finding.²¹

Limitations

The main limitation of any study assessing the value of a tilt test for the diagnosis of vasovagal syncope is the absence of a gold standard.⁴ However, in our view, selecting patients with a typical history of vasovagal syncope, rather than by negative examinations as done in syncope of unknown origin, seems to be a more appropriate way to assess the diagnostic value of a stimulated tilt test for the diagnosis of vasovagal syncope. Patients were significantly older than the controls. This may have influenced the accuracy of the test.

Clinical implications

Both passive and pharmacological stimulated tilt testing can be very time consuming which may limit their application in routine clinical use.¹⁶ In patients with suspected vasovagal syncope, a tilt test performed in an early phase, can be used to confirm the diagnosis and may preclude the utilization of other often low yielding examinations. We described a relatively short nitrate stimulated tilt test with a good diagnostic performance at a maximum of 18 minutes (a dose of 4 µg/kg/min). An almost optimal sensitivity of 95% can be reached by prolonging the test to 30 minutes but, due to the considerable decrease in specificity, a positive result appearing after 18 minutes should be interpreted with caution.

An option would be to perform an additional unmedicated passive tilt test (known for its excellent specificity), in patients with a positive test requiring more than 18 minutes of tilting. However as demonstrated in a previous report, this again would be very time consuming, and may be low yielding.⁸

CONCLUSION

The use of intravenous nitrates during tilt testing in patients with suspected vasovagal syncope is a promising tool for confirming the diagnosis of vasovagal syncope. A maximum accuracy of 79% was attained at 18 minutes (at a dose of 4 µg/kg/min). Prolongation of the tilt to 30 minutes enables to attain an almost optimal sensitivity of 95%, but due to the considerable decrease of the specificity after 18 minutes, a positive result obtained after this period, has to be interpret with caution. The value of a protocol with continuous stimulation with intravenous nitrates, in patients with unexplained syncope who have less or no clear premonitory conditions, needs to be determined in a future study.

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CHAPTER 3

Sublingual nitrates during head-up tilt testing for the diagnosis of vasovagal syncope

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ABSTRACT

Pharmacological stimulation during head-up tilt test (HUT) is used to increase the diagnostic yield of the test to detect vasovagal syncope. Reported lack of specificity of stimulation with intravenous isoproterenol has made a pharmacologic alternative desirable. Because nitrates are known to cause syncope of a vasovagal origin, we administered sublingual nitrates after passive tilt test in 32 patients with a history of typical vasovagal syncope and 20 healthy volunteers to assess the sensitivity, specificity, and accuracy of this new HUT technique. During the passive HUT four (13%) patients had syncope; after administration of sublingual nitrates, this number increased to 28 (87%). In the control group no subject had syncope during passive HUT, whereas during nitrate administration six (30%) had syncope. Sublingual nitrate stimulated HUT revealed a maximum accuracy of 83% at a cutoff point of 11 minutes, giving a sensitivity of 81% and specificity of 85%. Sublingual nitrate administration increased the accuracy of HUT in diagnosing vasovagal syncope in patients with a history of typical vasovagal syncope.

INTRODUCTION

The introduction of the head-up tilt test (HUT) has allowed many unexplained episodes of syncope to be classified as vasovagal.¹⁻³ A typical vasovagal response during orthostatic stress is preceded by a baroreceptor-mediated sympathetic stimulation (with a rise in heart rate and vasoconstriction) and prodromal symptoms such as nausea, sweating, pallor, giddiness, yawning, haziness, and tachycardia, followed by a sudden withdrawal of sympathetic tone with hypotension and bradycardia or asystole.⁴⁻⁶ Although the HUT is a generally accepted test for syncope of unknown origin, disparity of tilt protocols used is still apparent.⁷⁻⁹ Various protocols with different degrees and durations of tilt have been studied, resulting in varying results of accuracy.^{1,8-10} To increase the diagnostic yield of HUT, pharmacologic stimulation with intravenous isoproterenol has been used.^{8,11-14} Isoproterenol, however, is known to cause catecholamine-associated complications such as ventricular arrhythmias and angina pectoris (up to 18%)⁴ in patients with coronary artery disease, making it less desirable for an unselected population. Also, in some studies the percentage of false-positive results is reported to be as high as 73%,¹⁵ making an alternative to this pharmacological stimulation desirable.⁹ Intravenous nitroglycerin has been suggested as an alternative for pharmacologic stimulation during tilt testing.⁴ However, intravenous testing is rather cumbersome and time consuming, and venipunctures can also influence the specificity of the test.^{5,15,16} We therefore studied the

value of sublingual nitrates as an alternative method for pharmacologic stimulation in HUT in patients with a history of typical vasovagal syncope.

METHODS

Patient and control groups

HUT was performed in 32 patients (20 men and 12 women) aged 43 ± 21 years (range 16 to 87 years) with a history of typical vasovagal syncope. Patients included had at least one episode of syncope (mean three episodes, range one to 20 episodes). Nine (28%) patients had one episode of syncope and 23 (72%) had two or more. Typical vasovagal syncope was defined as a syncope preceded by provocative stimuli such as emotional stress, agitation, an overcrowded room, fatigue, illness, pain, blood or venipuncture, and prodromal symptoms of nausea, sweating, palpitations, and pallor, followed by complete and spontaneous recovery of consciousness and symptoms. Before performing a tilt test other causes of syncope were excluded by physical (including neurologic) evaluation, orthostatic blood pressure testing, carotid sinus massage, 12-lead electrocardiogram testing, and routine laboratory measurements. Supplementary examinations, such as computed tomography of the brain, electroencephalogram testing, and 24 hours of Holter monitoring, were performed when clinically indicated. Patients taking any cardiovascular or other drugs likely to produce hypotension were excluded from the study. In 20 healthy volunteers (16 men and 4 women, mostly medical students) who had never had syncope, a tilt test was performed to evaluate the specificity of the test. Mean age was 27 ± 4 years (range 22 to 38 years).

HUT

We used a motorized table with footboard support and a descent time of 20 seconds from 70 degrees to a supine position. A 12-lead electrocardiogram (Marquette) was continuously displayed, and blood pressure was monitored each minute by an automatic sphygmomanometer (Dinamap). The test started after the patients remained in the supine position for 10 minutes to obtain baseline values of blood pressure and heart rate. The table was then raised to a 70-degree upright position, and the subject remained immobile for a maximum of 45 minutes. In those subjects who did not have syncope after 45 minutes of passive tilt testing, isosorbide dinitrate 5 mg was given sublingually and the test was prolonged for a maximum of 15 minutes. The test was prematurely ended if (pre)syncope occurred. According to the hemodynamic response the outcome of presyncope was classified as (1) a mixed response, defined as

an increase in heart rate of $\geq 10\%$ compared with baseline followed by a rapid onset of bradycardia (defined as ≤ 60 /beats/min or a decrease in heart rate ≥ 20 beats/min compared with 1 minute before presyncope) or asystole and hypotension (defined as systolic blood pressure ≤ 90 mm Hg or decrease of ≥ 20 mm Hg compared with 1 minute before presyncope); or (2) a vasodepressor response with declining blood pressure (defined as ≥ 20 mm Hg compared to 1 minute before syncope) and no significant attenuation in heart rate.

Statistics

Statistical analysis was performed by a two-tailed Student *t*-test for unpaired observations, with a *P* value <0.05 considered statistically significant.

RESULTS

Table 1 shows the results of the passive (non-pharmacologic) and stimulated tilt test. Of 32 patients with a history of typical vasovagal syncope only four (13%) patients had a positive result within 45 minutes. Sublingual isosorbide dinitrate administration resulted in 28 (87%) positive results at test end in the patient group. Four (13%) patients remained negative after isosorbide dinitrate administration. In the control group no patient had a syncopal episode after 45 minutes, but after isosorbide dinitrate administration 6 (30%) had syncope.

When differentiating between patients with repetitive (more than two episodes) vs. first syncope, we found that the passive tilt test was not more sensitive in highly symptomatic subjects (Table 2). The percentage of positive results after sublingual nitrates administration tended to be higher in the group with repetitive syncope (83% vs. 71%, *P*=NS). The mean duration to syncope tended to be shorter in patients with repetitive syncope than in those with first syncope (6.8 vs. 9.4 minutes) (Table 3).

Of 28 patients with a positive result, 25 (64%) had a mixed hemodynamic response and 3 (11%) had a vasodepressor response. During nitrate stimulation, 7 (18%) subjects in the patient group had asystole (mean 10 seconds; range 4 to 15 seconds). In the control group one man had an asystolic episode of 6 seconds. None of the patients with syncope during nonstimulated HUT had an asystolic episode > 3 seconds. Results for sensitivity, specificity, and accuracy were calculated at the end of 45 minutes of nonstimulated HUT and during each minute of isosorbide dinitrate administration. The cumulative number of positive results (Table 4) shows that the passive

Table 1 Positive results after passive tilt test and isosorbide dinitrate administration.

Group	No.	Passive tilt test	ISDN
VVS	32	4 (13%)	28 (87%)
Control	20	0	6 (30%)

ISDN: isosorbide dinitrate; VVS: vasovagal syncope.

Table 2 Relation between the number of syncopal episodes and the result of the passive tilt test and after isosorbide dinitrate administration.

	1 Episode	≥ 2 Episodes
Total	9 (28%)	23 (72%)
45 min. passive tilt	2 (8%)	2 (8%)
15 min. ISDN tilt	5 (71%)	19 (83%)

ISDN: isosorbide dinitrate.

Table 3 Mean time to syncope during isosorbide dinitrate tilt in relation to symptoms.

	Baseline No. Syncopal episodes		P value
	1	>2	
No. subjects	5	19	
Mean duration (min.)	9.4	6.8	0.21
Range	6-13	4-13	

Table 4 Sensitivity, specificity and accuracy at different time intervals during tilt.

	15 Min. (%)	30 Min. (%)	45 Min. (%)	15 Min. (ISDN) (%)
Sensitivity	6	6	13	87
Specificity	100	100	100	70
Accuracy	42	42	46	81

ISDN: isosorbide dinitrate.

tilt test, in our population, had a sensitivity of 13% (n=4). After administering sublingual nitrates this figure increased to a maximum sensitivity of 87% (n=28) at the end of the test. Specificity of the nonstimulated HUT was 100%; during nitrate stimulation this percentage progressively decreased to 70% at the end of the test. Accuracy at test end was 81 %.

DISCUSSION

Organic nitrates, as potent venodilators, are known to cause syncope by enhancing venous pooling during upright posture.^{4,17} The predominant hemodynamic response of a spontaneously occurring vasovagal syncope with hypotension and bradycardia (i.e. mixed hemodynamic response) is well reproduced by nitrates, as we found in our study, when analyzing the hemodynamic responses of subjects with nitrate induced syncope. Only a minority of subjects (11%) with syncope in our study had a purely vasodepressor response. This finding suggests that nitrates cause vasodilation and, by decreasing the venous return, induce a cardiac emptying that triggers the ventricular mechanoreceptors, resulting in hypotension and bradycardia.^{15,18}

Although already described in 1937 and 1957,^{17,19} the idea of using organic nitrates for pharmacological stimulation in HUT was only rediscovered in 1993, when Raviele et al.⁴ reintroduced the idea of administering intravenous nitroglycerin during HUT. Comparing intravenous nitroglycerin with isoproterenol revealed a higher efficacy of nitroglycerin in provoking vasovagal syncope in the patient group (positive rate 53% vs. 25%) and a better predictive accuracy for the nitroglycerin test (67% vs. 50%). However, in their study the patients with presyncope necessitating to stop the test (exaggerated response) were not included in the final results. If syncope and exaggerated response were combined as a positive result, as done in our study, the sensitivity of the nitroglycerin and isoproterenol tests in their study would have increased to 83% and 50%, respectively, but their specificity would have decreased to 46% and 62%, respectively. In our study the number of positive responses (13%, $n=4$) after 45 minutes of nonstimulated HUT was considerably lower than in earlier studies (32% to 74%).^{9,20} However, most studies included patients with syncope of unknown origin determined by negative conventional investigations and not by clinical history. Patients with negative examination results and an atypical history were excluded from our study.

Sublingual nitrate administration resulted in an impressive increase of positive results in the patient group (87%) at the end of the test; at the same time, however, it reduced the specificity to 70% at the end of the test. The accuracy of the passive tilt test was 46%, which, during nitrate stimulation, increased to 81% at the end of the test (Table 4). Time to syncope after sublingual nitrate administration was shorter in patients with repeated syncope than in those with nonrepetitive syncope. Although this finding did not reach significance, it suggests a quantitative relation between the amount and duration of pharmacologic stimulation and the susceptibility of the subject.

The hypothesis is that vasovagal syncope can be had by anybody, but the intensity and duration of stimulation (orthostatic stress, emotions, etc.) to provoke the reaction might differ from one individual to another. In our study, as in others, the ability to induce vasovagal syncope with nitroglycerin in a normal population is a contribution to this hypothesis. The importance of a positive test result in a patient with syncope of unknown origin is therefore related to the occurrence of presyncope and the amount of stimulation, and perhaps duration, needed to provoke this reaction.

A highly symptomatic patient may have a syncopal episode after only 10 minutes of passive tilt testing, whereas a minimally symptomatic (solitary syncope) would probably need pharmacological stimulation to provoke vasovagal syncope. A difference in susceptibility expressed in occurrences of and time to develop syncope in a given patient belonging to either group (frequent or solitary syncope) might also become important when evaluating the effect of drug therapy. The high measure of similarity and recognition of symptoms of the nitrate induced vasovagal syncope is also important in the diagnosis.

Limitations

No gold standard exists for detecting vasovagal syncope. As has been stated in the review of Kapoor and Brant,²¹ the definitions of sensitivity and accuracy in syncope of unknown origin are artificial. They depend on the assumption that all the patients included did indeed have clinical vasovagal syncope. In our study we included only patients with typical vasovagal syncope noted in their clinical history. Therefore a calculation of sensitivity and specificity in this case seems more acceptable.

Also, the reproducibility of our test, an important consideration when testing for drug efficacy, is not known. Mean age of the control group was lower than that of the patient group, but the phenomenon of vasovagal syncope is known to not be age related,⁵ and the rate of positive results, especially by pharmacologic stimulation, is probably higher in younger people.⁴

Clinical implications

The two-phase sublingual nitrate stimulated tilt test can be used to assess the susceptibility for inducing vasovagal syncope in a patient. The passive (nonstimulated) test remains the first choice because it has a high specificity. If provocation and recognition of vasovagal syncope are needed and the passive tilt test result remains negative, the higher sensitivity of the stimulated tilt test is useful. Also, this new concept of pharmacologic stimulation in HUT can be a useful alternative to isoproterenol

testing because it is not accompanied by the rather high frequency (18%)⁴ of catecholamine-associated complications such as angina attacks or atrial or ventricular arrhythmias.

Moreover, sublingual nitrate testing avoids the limitations of venipuncture and intravenous testing and has shown to be a safe pharmacologic alternative of stimulation in tilt testing to increase the disappointing low sensitivity of the passive tilt test. Also, in nonstimulated tilt testing the result can be liable to a decrease in reproducibility, making obtaining two baseline tilt tests desirable before drug effectiveness can be evaluated.²² The feasibility of this new technique of sublingual nitrate stimulation in HUT to evaluate drug efficacy to prevent vasovagal syncope has to be further determined after the reproducibility is known.

CONCLUSION

Passive HUT is a not very sensitive test in patients with typical vasovagal syncope noted in their history. Pharmacologic stimulation with sublingual nitrates impressively increases the number of vasovagal syncopal episodes in this group with a moderate loss of specificity. This new method of HUT can be a useful and easily performed alternative to pharmacologic stimulation.

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CHAPTER 4

Reproducibility of nitrate stimulated tilt testing in patients with suspected vasovagal syncope and a healthy control group

Arnaud J. J. Aerts, Paul A. Dendale, Pierre Block, Willem R.M. Dassen

ABSTRACT

Objective: Nitrate stimulated tilt testing may be used to diagnose vasovagal syncope or to guide therapy. To date the reproducibility of the test, in patients with clinically suspected vasovagal syncope and healthy controls, is undetermined. A high reproducibility, is a prerequisite for correct interpretation of the test result. This study investigates the reproducibility of a nitrate stimulated tilt test, in patients with clinically suspected vasovagal syncope and a healthy control group.

Methods and results: We studied 43 patients (24 females, 19 males) with a typical history of vasovagal syncope and eighteen healthy controls (3 females, 15 males). We used a combined tilt protocol with a 30 minutes passive and 15 minutes nitrate stimulated phase. The second tilt test was performed 16 ± 12 days after the first. In both patients and controls, overall positive tilt responses were reproduced in the second test in 100%. In contrast to this, the reproducibility of a overall negative test was 50% in patients but 93% in controls. Overall hemodynamic responses to tilt were reproducible in 80%.

Conclusion: Nitrate stimulated tilt testing, in both patients with suspected vasovagal syncope and controls, has an excellent reproducibility of positive results but a moderate of negative ones. Importantly, these results are still valid at a repeat interval of two weeks and longer. This data suggests that in patients with suspected vasovagal syncope, a nitrate stimulated tilt test may provide a suitable tool to evaluate the efficacy of a therapeutic approach.

INTRODUCTION

Nowadays, head-up tilt testing is a widely used method of eliciting syncope of vagal origin in patients with unexplained syncope, or of confirming a clinically suspected or troublesome vasovagal syncope.^{1, 2} To overcome the low yield of the time consuming passive tilt test, stimulation with sublingual nitrates has become an established and practical mode of testing.³

Aside from the diagnosis, the test has also been used to guide therapy in selected population groups.³ A highly reproducible test in both patients and a healthy control group is a prerequisite for correct interpretation of test results or for situations in which the test is used to guide or evaluate the efficacy of therapy.⁴ Although many reports have assessed the reproducibility of passive⁴⁻⁸, and isoproterenol stimulated

tilt testing⁹⁻¹⁵, only one of them used a nitrate stimulated protocol in patients with unexplained syncope.¹⁶ Due to the absence of a gold standard for the diagnosis of vasovagal syncope, however, the diagnostic value of the test may be more appropriately determined when studying patients where a clinical suspicion of vagal syncope exists.

To date, no reports are available which set out to determine the reproducibility of the nitrate tilt test in patients with clinically suspected vasovagal syncope or in a healthy control group. The test result may be used to guide the choice of strategy or therapy in a given patient. However, the susceptibility to vasovagal syncope is variable over time, and the reproducibility of the tilt test seems to decrease if the test interval exceeds two weeks.¹⁵ In this study we assessed the reproducibility of two consecutive nitrate stimulated tilt tests, 1-3 weeks apart, in patients with suspected vasovagal syncope and a healthy control group.

METHODS

Patient selection

Forty-three patients with a suspected history of vasovagal syncope and eighteen healthy controls (mostly medical students) with no history of syncope were studied. The patient group consisted of 19 males (44%) and 24 females (56%) and there were 15 males (83%) and 3 females (17%) in the control group. The mean age of the patients was 46 ± 19 years (range 16-78) and that of the control group 26 ± 6 years (range 20-40).

Nine patients had suffered one syncopal episode (21%) and 34 two or more (79%). Vasovagal origin was suspected if the patient's history contained at least one of the following characteristics: 1) Syncope provoked by emotional and orthostatic stress. 2) Situational symptoms (micturation, defecation, swallowing). 3) Premonitory symptoms of warmth, nausea, sweating, visual dimming, light-headedness. 4) Symptom relief with recumbence. None of the patients had a history or overt signs of organic heart disease, and all had a normal physical and neurological examination. Carotid sinus hypersensitivity was excluded, as well as orthostatic hypotension (including orthostatic hypotension during the three minutes immediately after attaining an upright position).

All patients had a 12 lead ECG and underwent routine laboratory tests. Supplementary examinations such as a computerized tomography of the head, Doppler flow of neck vessels, 24-hour Holter recording, echocardiogram and electroencephalogram were done where clinically indicated. Patients taking cardio- and vasoactive medication were excluded. The study was approved by the institutional committee on human research.

Tilt test protocol

The protocol was approved by the hospital ethics committee and informed consent was obtained from all subjects. The tilt tests were performed between 9.00 and 12.00 am and the subjects had been fasting for at least 4 hours. We used a motorized table with footboard support situated in a quiet room and with a comfortable constant temperature.

A 12-lead electrocardiogram (Marquette) was displayed continuously and blood pressure (automatic sphygmomanometer Dinamap) and heart rate measurements were taken every 5 minutes. Supplementary measurements were taken when symptoms developed. A positive result was defined as syncope (loss of consciousness) or presyncope defined as symptoms of hypotension (systolic pressure < 90 mm Hg) and imminent syncope. Hemodynamic patterns of a positive response were classified as: mixed response, cardioinhibitory, and vasodepressor.

A mixed response was defined as a decrease in heart rate of ≥ 20 bpm and a decrease in systolic blood pressure of ≥ 20 mm Hg. A vasodepressor response was defined as a decrease in blood pressure of ≥ 20 mm Hg but with no significant reduction in heart rate. A cardioinhibitory response was defined as a sudden decrease in heart rate of ≥ 20 bpm without a preceding decrease of blood pressure.

The test started with a 10-minutes baseline supine phase. The subject was then tilted to 70° for a maximum period of 30 minutes. If no symptoms developed, 5 mg isosorbide dinitrate was administered sublingually and the test was prolonged if no symptoms occurred, for a maximum duration of 15 minutes.

Statistical analysis

A two tailed Student's t-test for unpaired observations, with a P value < 0.05 was considered significant.

RESULTS

37 out of 43 patients (sensitivity 86%) and three out of the control group of 18 (specificity 80%) had an initial overall positive tilt test (combined passive and nitrate test results). As shown in Figure 1, during the passive tilt 15 members of the patient group (sensitivity 35%) and none of the control group had a positive result (specificity 100%).

Figure 1 Reproducibility of passive tilting and after nitrate stimulation in patients and controls.

During the initial test the hemodynamic pattern in patients was predominately mixed ($n=26$, 70%), with 3 showing a cardioinhibitory response (8%) and 8 a vasodepressor response (22%). Asystole occurred in 2 (9%) during nitrate stimulation and in 1 (7%) during the passive tilt. Mean duration of the asystolic episodes was 14 ± 5 seconds (range 7–20). No serious side effects occurred during the tests. All three controls with a positive test had a mixed pattern.

Reproducibility

As shown in Table 1, all of the 37 patients with a positive initial nitrate tilt test had again a positive one 16 ± 12 days later. In all three subjects from the control group with a positive response, the second test was positive as well 9 ± 5 days later. The reproducibility of a positive nitrate tilt test result in both patients and controls was, therefore, 100%.

In 3 of the 6 patients and in 14 of the 15 controls with an initial negative nitrate tilt test, the second test was negative as well. Thus, the reproducibility of an initial negative nitrate tilt test in both groups was 50% and 93% respectively. The overall clinical

Table 1 Results of repetitive tilt testing in patients with vasovagal syncope and asymptomatic controls.

		Initial test			
		Patient n=43			
		PasPos	NitPos	NitNeg	Sum
Patient	PasPos	9	2	0	11
	NitPos	6	20	3	29
	NitNeg	0	0	3	3
	Sum	15	22	6	43
Repeat test		Control n=18			
		PasPos	NitPos	NitNeg	Sum
Control	PasPos	0	0	0	0
	NitPos	0	3	1	4
	NitNeg	0	0	14	14
	Sum	0	3	15	18

PasPos: Passive positive tilt test; NitPos: Nitrate positive tilt test; NitNeg: Nitrate negative tilt test.

reproducibility (concordance of positive and negative test results), of the nitrate stimulated tilt test in patients selected on the basis of a typical clinical history of vasovagal syncope was 93%.

When analyzing the results of the passive tilt phase only, 9 out of 15 patients with an initial positive passive test had a positive second test too. Thus, reproducibility of an initial positive passive test in patients was 60%. None of the control group had a positive passive test. 26 out of 28 patients and all members of the control group with an initial negative passive test also had a negative second test. On the basis of these data, the reproducibility of an initial negative passive test in patients and controls is 93% and 100% respectively. The overall clinical reproducibility of the passive test was 81%.

Clinical variables such as gender, age, symptomatology and the interval between the two tests were not predictive of reproducibility in patients or controls nor of positive and negative test results.

Reproducibility of hemodynamic patterns during consecutive tilt testing

In 32 out of 40 subjects (80%) with a positive nitrate tilt test, the initial hemodynamic pattern was reproduced during the second one. As shown in Table 2, combining both patients and the members of the control group with an positive nitrate tilt test, the reproducibility of an initial mixed, cardioinhibitory or vasodepressor response

Table 2 Reproducibility of hemodynamic patterns during consecutive tilt testing.

		Initial test			
		Mixed	Cardioinhibitory	Vasodepressor	Sum
Repeat test	Mixed	24	2	1	27
	Cardioinhibitory	2	1	0	3
	Vasodepressor	3	0	7	10
	Sum	29	3	8	40

Table 3 Influence of time interval on reproducibility of the tilt test in patients with suspected vasovagal syncope.

	1 week (n=15)	2 weeks (n=14)	≥ 3 weeks (n=14)
Passive tilt test			
Positive result (n)	5 → 3 (60%)	5 → 3 (60%)	5 → 3 (60%)
Negative result (n)	10 → 10 (100%)	8 → 8 (100%)	9 → 6 (67%)
Nitrate tilt test			
Positive result (n)	8 → 8 (100%)	5 → 5 (100%)	9 → 7 (78%)
Negative result (n)	2 → 1 (50%)	4 → 2 (50%)	0
Overall positive# (n)	13 → 13 (100%)	10 → 10 (100%)	14 → 14 (100%)

#: combined passive and nitrate results.

was 83%, 33% and 88% respectively. In positive passive tilting the (predominant) mixed response was reproducible in 10 out of 12 patients (83%).

Influence of the interval between tilt tests on reproducibility

A subanalysis was performed to investigate the influence of the time interval on the reproducibility of the test result. As shown in Table 3, the reproducibility of an overall positive nitrate tilt test was excellent (100%), even with an interval of three weeks or more between the tests. Reproducibility of a negative passive test was demonstrable within a two weeks interval, but decreased after 3 weeks or more. The poor reproducibility of a positive passive tilt test (60%), as is to be expected, remained unaltered even after two and three weeks.

DISCUSSION

The main findings of this study are that a positive nitrate stimulated tilt test result in patients with clinically suspected vasovagal syncope as well as in controls has an excel-

lent reproducibility of 100%. Importantly, the diagnostic performance of a positive test result was not influenced by a repeat test interval of one to three weeks. Moreover, within a 2 weeks interval, the reproducibility of a negative nitrate tilt test appeared to be poor in patients, but excellent in controls (50% vs. 93%). This finding indicates, in contrast to negative passive test results, that it is feasible to perform a second test 1–2 weeks later in patients with an initial negative nitrate tilt test.

In case of the tilt test, it is not possible to determine true sensitivity and specificity of the test in view of the absence of a gold standard. Nevertheless, our finding of a high reproducibility (93%) of a negative nitrate test in the control group underscores the good diagnostic performance of the test.

Comparison to other protocols

Nitroglycerin stimulated: Foglia-Manzillo et al. reported on the reproducibility of test results in 48 patients (aged 40 ± 22 years) with unexplained syncope. They used a nitrate stimulated tilt protocol consisting of a 45 minutes passive tilt at 60° and a further 20 minutes tilt after the administration of 400 mcg sublingual nitroglycerin spray.¹⁶ In their study employing two consecutive tests 1–28 days apart (median 2 days), they achieved a reproducibility of 79% for positive nitrate test results, 83% for negative test results, and 83% for a concordance of hemodynamic patterns.

In our study, with a longer interval between tests (median 14 days), we found a reproducibility of positive and negative test results and a concordance of hemodynamic patterns of 100%, 50% and 80% respectively. The higher reproducibility of positive test results in our study, may be explained by the difference in patient selection and also by the steeper tilt angle.

Passive tilt test: Blanc et al. investigated the reproducibility of a 60 minute 60° positive tilt test in 13 patients with syncope, aged 46 ± 22 years.⁴ They reported a positive passive tilt result, with an interval of seven days, to be reproducible in 62%. Using the same protocol and a median test interval of three days, Raviele et al. found a positive tilt result to be reproducible in 71% of cases and concordance of the hemodynamic response in 50%.⁵ Neither study addressed the reproducibility of a negative tilt result.

Brooks et al., however, did so and used a 25 minutes 70° tilt in 109 patients with unexplained syncope, aged 54 ± 21 years.⁷ Using a test interval of two days, they found the reproducibility of a positive test result to be 31%, and the reproducibility of a negative test to be 80%. The initial hemodynamic vasodepressor response (defined as bradycardia and hypotension) was reproduced in only 31% of cases. Ruiz et al.,

used a 60 minutes 75° tilt test, 10 ± 8 days apart, in 64 patients with syncope (age 35 ± 23 years), and reproduced a positive response in 55% and a negative one in 84%.⁶

In patients with a positive response, they found a higher reproducibility with a greater total number of syncopal episodes. Similar hemodynamic patterns were found in 67% of cases.

Isoproterenol tilting: Grubb et al. reported on the results of a study in 21 patients with unexplained syncope (aged 34 ± 19 years) using a 30 minutes 80° passive tilt, followed by gradual isoproterenol infusion.¹¹ They found an overall reproducibility of 90% (92% and 86% for a positive and negative test respectively), with a 3–7 day interval between the two tests. Fish et al. reported the immediate reproducibility of a 90° isoproterenol protocol in 21 young patients (median age 14 years) with suspected vasovagal syncope.¹² They found a reproducibility of a positive test of 67% and a concordance of the hemodynamic pattern of 48%. Negative test results were not included. They concluded that immediate repeat tilt responses were highly variable and therefore not suitable for the accurate assessment of therapeutic interventions.

Sheldon et al. determined the reproducibility of positive and negative tilt results using a 80°, passive (10 minutes)–isoproterenol protocol, in 46 patients with syncope.¹¹ The tests were done with a median interval of 15 days (range 1–6 weeks). Negative test results were reproduced in 85% of cases, and positive results, defined as frank syncope, in 60% of cases. When combining the results of syncope and presyncope (defined as bradycardia and hypotension), the reproducibility of a positive test result was 90%. Overall clinical reproducibility was 87%. These findings are in agreement with ours. With a comparable aged group and interval between tests, nitrate stimulated testing attained a similar overall clinical reproducibility of 93%. In the study of Sheldon et al., the influence of the test interval on the outcome of the reproducibility was not analyzed.

This was investigated in a very recent report by Sagrista-Sauleda and co-workers.¹⁵ They included 127 patients with syncope (aged 43 ± 19 years) after a positive or negative initial tilt test and randomly split them into four arms with second tests one and/or two weeks later. They used a 30-minutes 75° passive tilt followed by isoproterenol stimulation in incremental doses to a maximum of 20 minutes. They found a reproducibility of a positive test of 65% and 80% of a negative test. Analysis of the influence of the test interval on the reproducibility revealed that the rate of positive responses significantly decreased from 81% to 53% when performing the test at 1 or 2 weeks interval. This in contrast to the initial negative test results, which

remained unaltered during these test intervals (76% and 83% respectively). Reproducibility of separate positive passive and stimulated test phases was 74% and 87% respectively. Overall clinical reproducibility was 70%. Although reproducibility of the hemodynamic pattern was not specifically analyzed, reproducibility of the cardioinhibitory responses was attained in 5 out of 10 cases (50%).

This difference in reproducibility (70% vs. 93%), despite a comparable duration of the passive tilt phase, stimulation, tilt angle and age of the subjects, may have several explanations.

Firstly, the influence of patient selection on the yield of the tilt test for the diagnosis of vasovagal syncope has been frequently mentioned before.¹⁸ It may be more appropriate to evaluate test performance in a study group selected on the basis of a typical clinical history of vasovagal syncope rather than on the basis of negative examinations.³⁻¹⁷⁻¹⁸ Whereas in our study all of the patients were selected on this basis, only 70% of the subjects in the study of Sagrista et al. met this criterion. Separate results for this group were not mentioned in the article, and may differ from those attained in subjects with no prior history of syncope.

Secondly, the mode of pharmacological provocation employed differs in the two studies. Few reports exist comparing the value of nitrate stimulation and isoprenaline stimulation during tilt testing. Raviele reported that intravenous nitroglycerin was more sensitive than isoprenaline in patients with unexplained syncope.³

Thirdly, tolerance to tilting must be taken into account. As is known from placebo controlled tilt studies, repeat tilt testing showed a decrease in the number of positive responses in subjects receiving placebo treatment during follow-up examinations. Whereas in the study of Sagrista et al., reproducibility of a positive response decreased from 65% to 53%, this remained unaltered at an excellent level of 100% in our study throughout test intervals of 2 weeks and longer. This finding needs to be confirmed in a comparative study of the two modes of stimulation, however.

Limitations

Members of the control group were considerably younger than patients. Susceptibility to vasovagal syncope might decline with increasing age, and thus the reproducibility of the results obtained from tests carried out on elderly control subjects may differ from the ones we obtained in the present group. Although the results of reproducibility at given intervals indicated no differences, the influence of this

phenomenon during nitrate tilt testing needs to be addressed in a properly designed study.

Clinical implications

Nitrate stimulated tilt testing has an excellent reproducibility of positive results, but a moderate reproducibility of negative ones. This result is still valid at a repeat test interval of two weeks and longer. This data suggests that in selected patients with a clinical suspicion of vasovagal syncope, nitrate tilt testing might be suitable as a method of assessing the efficacy of drug therapy or other approaches. The clinical relevance of this needs to be addressed in a future study.

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CHAPTER 5

Diagnostic value of nitrate stimulated tilt testing without preceding passive tilt in patients with suspected vasovagal syncope and a healthy control group

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ABSTRACT

Background: The contribution of the passive tilt phase, in a combined nitrate stimulated tilt protocol may be low yielding. In order to develop an shortened, and thus easier to perform test, we investigated the optimal duration of a nitrate tilt protocol without an preceding passive phase.

Methods: 38 consecutive patients (18 females/20 males; mean age 46 ± 16 years) with clinically suspected vasovagal syncope and 31 control subjects (15 females/16 males; mean age 40 ± 18 years) were tested. The subjects were tilted to 70° for a maximum period of 30 minutes, and sublingual nitroglycerin 0.4 mg spray was administered directly after attaining erect posture. Receiver operator characteristics (ROC) analysis was done to determine the optimal test duration.

Results: In the patient group 31 (82%) and in controls 5 (16%) had a positive test. Sensitivity, specificity and accuracy at test end was 82%, 84% and 83% respectively. ROC analysis revealed that a maximum accuracy of 83% was attained at 14 minutes, with a sensitivity and specificity of 79% and 87% respectively.

Conclusion: Nitrate stimulated tilt testing, without a preceding passive tilt phase, and limited to a test duration of 15 minutes, provides an accurate, sensitive and specific method to provoke vasovagal reactions in subjects with clinically suspected vasovagal syncope.

INTRODUCTION

Vasovagal syncope is a frequently encountered problem in clinical practice. It is estimated that up to 50% of the population suffers at least one episode during their lifetime.¹ It is generally accepted that vasovagal syncope has a benign prognosis, but troublesome recurrent spells may require treatment. Diagnosis is made by a combination of careful examination of a patient's medical history and the tilt test.^{1, 2} If the diagnosis is certain in subjects without overt organic heart disease, then no further examinations are necessary, and reassurance and simple lifestyle advice are usually sufficient treatment.^{3, 4}

Utilization of the tilt table test has demonstrated not only an increase in the number of diagnoses in patients who present with syncope but it may also prevent the ordering of unnecessary and often expensive examinations.^{5, 6} Whether the tilt test may also be

used to guide or evaluate therapy, as is sometimes reported, remains undetermined.³ The role of the tilt test in a stimulation of syncope is underscored by its implementation in both North American and European guidelines on syncope.^{7,8}

However, despite its recommendation in the guidelines, its utilization in daily clinical practice may be tempered by laborious conceptual limitations.⁶ In addition, the tilt test in its initial form proved to be a low yielding test.¹¹ Although isoproterenol as a drug challenge during tilt, historically the first pharmacological stimulation to be used, successfully increased the yield of the test, the cumbersome nature of intravenous testing together with potential catecholaminergic side effects, and the questionable influence of cannulation on the specificity of the test, called for a alternative, simplified and practical tilt protocol.^{2,9,10}

As previously described and validated, the use of sublingual nitrates during tilt, after a passive tilt phase, offers an accurate alternative to intravenous testing but may still result in test durations of up to 35–60 minutes.¹¹ Current guidelines on stimulated protocols recommend a duration of the preceding passive tilt (angle 60° or 70°) of 20–45 minutes.^{7,8} In this study, we evaluated the diagnostic value of a nitrate stimulated tilt protocol without a preceding passive phase in patients with suspected vasovagal syncope and a healthy control group.

METHODS

Thirty-eight consecutive patients with clinically suspected vasovagal syncope and thirty-one subjects with no prior experience of syncope were tested. A clinical suspicion of vasovagal syncope was expressed when the patient had at least one of the typical premonitory signs or symptoms: 1) Awareness of imminent syncope, loss of postural control. 2) Occurrence in erect or sitting position. 3) Premonitory symptoms of warmth, nausea, sweating, visual dimming, precipitating anxiety or pain, mental stress, light-headedness. 4) Rapid recovery with recumbency.

To exclude other causes of syncope, all patients had a full clinical (including neurological) and full medical history examination, carotid sinus massage and orthostatic blood pressure testing (defined as blood pressure measurements supine and standing upright for five minutes), 12-lead electrocardiogram and routine laboratory tests. Patients taking cardiovascular or vasodilating drugs were excluded. Supplementary examinations such as 24-hour Holter recording, echocardiogram, computed tomography of the brain and electroencephalogram were done where clinically indi-

cated. The tests were done between 9.00 and 12.00 am and the subjects had been fasting overnight. The protocol was approved by the hospital ethics committee and informed consent was obtained from all subjects. We used a motorized table with footboard support located in a quiet room with a constant temperature of 21° Celsius. A 12-lead electrocardiogram (Marquette) was displayed continuously and blood pressure was measured every minute by an automatic sphygmomanometer (Dinamap). No preceding passive tilt phase was undertaken. Directly after attaining the upright position (tilt angle 70°), 0.4 mg nitroglycerin spray was given sublingually, and the test proceeded for a maximum period of 30 minutes.

The tilt table was lowered when the subject developed a positive response (syncope or presyncope), or when the test ended according to the protocol. Syncope was defined as a transient loss of consciousness with spontaneous recovery. Presyncope was defined as a state of light-headedness accompanied by signs and symptoms such as nausea, sweating, vomiting, pallor or weakness suggesting an imminent syncope. According to the hemodynamic response a positive response was classified as either a mixed, vasodepressor, or a cardioinhibitory reaction.

A *mixed response* was defined as a decrease in heart rate of ≥ 20 bpm and a decrease in systolic blood pressure of ≥ 20 mm Hg. A *vasodepressor response* was defined as a decrease in blood pressure of ≥ 20 mm Hg but with no significant reduction in heart rate. A *cardioinhibitory response* was defined as a sudden decrease in heart rate of ≥ 20 bpm without a preceding decrease of blood pressure.

Statistical analysis

Student's t-test and chi-square test were used for comparison between patient and control groups. A P value of 0.05 or less was considered significant. Sensitivity, specificity and accuracy was calculated for every time point to create an receiver operator curve.

RESULTS

We included 38 patients, 18 females and 20 males, with a mean age of 46 ± 16 years. The mean number of previously experienced syncopal spells (lifetime) was 3 ± 3 (range 1-10). In the patient group, 31 (82%) had a positive test response. In 28 (90%) of these syncope occurred and in 3 presyncope. Mean duration of a positive result was 7 ± 6 minutes, (range 5-25 minutes). According to the hemodynamic pattern, 26

Figure 1 Receiver operator characteristics analysis of sensitivity and specificity and accuracy during a 30 minutes nitrate tilt test. A maximum accuracy is obtained at a cut-off point of 14 minutes with a sensitivity of 79%, a specificity of 87% and an accuracy of 83%. At test end sensitivity is 82%, specificity 84% and accuracy 83%.

(84%) had a mixed response, 2 (6%) a vasodepressor and 3 (10%) a cardioinhibitory one, (asystole duration range 4–28 seconds). The control group ($n=31$) consisted of 15 females and 16 males, with a comparable mean age of 40 ± 18 years (ns). Five control subjects (16%) had a positive, mixed response. Mean duration of a positive response was 12 ± 5 minutes. Thus sensitivity, specificity and accuracy of a 30 minute nitrate stimulated tilt test, without a preceding passive phase, were 82%, 84% and 83% respectively.

As shown in Figure 1, receiver operator characteristics (ROC) analysis revealed that a maximum accuracy of 83% was already attained after 14 minutes of testing, with a sensitivity of 79% and a specificity of 87%. No serious side effects occurred during the tests.

DISCUSSION

The main finding of this study is that a nitrate stimulated tilt test, without a preceding passive phase, in patients with clinically suspected vasovagal syncope has a good diagnostic performance, offering good sensitivity and specificity. Moreover, based on the

ROC analysis, our results indicate that the test duration may be limited to 15 minutes, thus providing a short and practical test, suitable for use in a busy clinical practice.

Comparison to other nitrate stimulated protocols

Previous reports indicated that in nitrate tilt testing, the duration of the low-yielding and time-consuming preceding passive tilt phase (usually 30–60 minutes), could be reduced by approximately 50%, whilst at the same time preserving adequate sensitivity and specificity.¹¹ The possibility that the test could be even further shortened, was addressed in the study by Bartoletti et al.¹² They compared 84 patients (55 ± 22 years) with unexplained syncope against 25 controls (49 ± 17 years) using a nitrate protocol (tilt angle 60°) with a 45 minutes (conventional) or 5 minutes (accelerated) preceding passive tilt phase. They reported a significantly higher overall positive rate (51% vs. 35%) in the conventional protocol. They also reported that nitrates provoked an equal number of positive responses in both groups, and the authors therefore advocated the need of a preceding passive phase in order to maintain an accurate diagnostic performance of the test. On the other hand, as all positive nitrate responses occurred within 10 minutes, they proposed a decrease in the duration of stimulation from 20 to 10 minutes.

Our findings contradict this. Although our study was smaller, we found that, when analyzing the results using a cut-off point of 15 minutes, the positive rate in the patient group did not significantly decrease, and still attained a considerable higher sensitivity than the one reported in the study by Bartoletti et al. (79% vs. 51%).

This remarkable difference in sensitivity in the two studies may have several explanations: although of comparable age, the patients included in our study had been selected on the basis of a typical history of vasovagal syncope and, in contrast to patients selected with a negative history, may have had a higher likelihood of displaying a vasovagal reaction during tilt. This is supported by others who reported the yield of tilt test to be higher in patients with clinically suspected vasovagal syncope than in those with no indication at all.^{2,13,14} In addition, we used a slightly steeper tilt angle which may have contributed to a higher number of positive responses in our study. A higher positive rate due to a steeper tilt angle has been demonstrated in passive and isoproterenol protocols¹⁵, but to the best of our knowledge, the influence of this difference has not been analyzed in nitrate protocols.

As regards positive responses in controls, Bartoletti et al. reported one positive response in the accelerated nitroglycerin test, but five with a so-called exaggerated reaction. This was initially described by Raviele et al. as presyncope with

hemodynamic characteristics of a vasodepressor response. It was attributed to the pharmacological effects of nitroglycerin and was, therefore, not to be regarded as a vagal effect.¹⁶ In our study, a vasodepressor response with clinical presyncope (inability to maintain upright posture) was considered a positive vagal response as has also been done by others.¹¹

In the present study, all positive controls had a hemodynamically mixed response. Specificity in the study of Bartoletti was 96%, but when including those with an exaggerated response this dropped to 76%.

Several explanations could account for the higher specificity in Bartoletti's study as compared to ours (96% vs. 84%). Controls in our study were younger (40 ± 18 vs. 49 ± 17 years). As previously reported, the susceptibility to vagal provocation may decrease with inclining age, and this may have adversely influenced the specificity of our test.^{17,18} This possibility, however, is not supported by reports evaluating the specificity of nitrate tilting in children.¹⁹ On the other hand, similarly to patients, a steeper angle may have increased the number of false positive responses.¹⁵ In any case, the specificity we obtained in this study is in line with those reported in conventional nitrate tilting, and which vary from 63% to 100%.¹¹

LIMITATIONS

This study was performed to investigate the diagnostic yield of a nitrate tilt protocol, without a preceding passive phase, in order to develop a short and accurate test. Although our results suggest an at least equal diagnostic performance when compared to conventional tilting, with a combined passive and stimulated phase, a comparative study would be needed to confirm this.

CONCLUSIONS

Nitrate stimulated tilt testing, without a preceding passive tilt phase, and limited to a test duration of 15 minutes, provides an accurate, sensitive and specific method to provoke vasovagal reactions in subjects with clinically suspected vasovagal syncope. This new methodology of nitrate tilt testing provides a practical and easy-to-perform method of eliciting a diagnosis of vasovagal syncope. By reducing the cumbersome nature of the test, its availability and usage may be increased, thereby providing a positive contribution to the current management of patients with syncope.

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CHAPTER 5A

To the editor:
Nitrate stimulated tilt test

Arnaud J.J. Aerts, Paul A. Dendale

TO THE EDITOR

We read with interest the article by Del Rosso et al.¹ in the April 1998 issue and wish to make some comments.

The statement that cardioinhibition is specific for patients with vasovagal syncope is contradicted by our own experience and data from other researchers. Using a slightly different nitrate stimulated tilt test (HUT), we found an asystole of more than 6 seconds in a normal volunteer.² Dhala et al.³ provoked an asystole in 4% of controls with an unstimulated HUT, and Karp et al.⁴ induced bradycardia and asystole in 33% of normal volunteers. We therefore assume that the cardioinhibition is not specific for patients with vasovagal syncope and may be more related to the HUT protocol. We found a relatively high percentage of asystole with a motorized tilt table (in the patient group and the controls) with a descent time of approximately 20 seconds. Another group of investigators that used a manual table with a descent time of 1 or 2 seconds found no asystole at all. Therefore the assumption that HUT induced cardioinhibition might guide the initial therapeutic approach remains debatable, knowing that the presence of asystole during HUT does not predict the clinical outcome.⁵

The important shortening of the HUT with nitrates and the increase in sensitivity make it an interesting alternative to the passive test. Reproducibility of the test in our experience is excellent; with a sublingual stimulation of 5 mg isosorbide dinitrate after 30 minutes of passive tilt, a positive test was reproducible in 100% and a negative test in 94% of cases.⁶ We further examined the importance of the duration of the preceding unstimulated test when using nitrate stimulation: 45 minutes, 30 minutes, and no preceding passive tilt were compared. The accuracy of the 3 protocols was similar, with a slightly higher sensitivity for the longest test.^{7,8} We therefore believe that the HUT can be further shortened by dropping the unstimulated phase and directly proceed to the nitrate stimulation. In this way, a 15-minutes test duration would make HUT attractive even in a busy cardiology practice. This ultrashort nitrate stimulated HUT protocol should of course be tested in different populations to determine the reproducibility and the predictive accuracy.

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REPLY

TO THE EDITOR

In our study¹, as in the previous study from Raviele et al.,² no subject in the control group had a positive cardioinhibitory response to head-up tilt test (HUT). On the other hand, in both studies a positive response to HUT was observed in only 2 of the control subjects. The absence of a cardioinhibitory response in the control groups could be linked to the small number of positive responses. Therefore the observation that cardioinhibition is specific for patients with vasovagal syncope would need to be confirmed in larger samples.

Rather, the letter from Aerts and Dendale raises serious concerns about the classification of the positive HUT responses, in patients and control subjects, independently from the HUT protocol. Indeed, when we classify the positive responses to HUT as cardioinhibitory, we refer to bradycardia or asystolic pauses observed immediately before or at the moment of the loss of consciousness not to the response observed after the syncope occurrence while the patient is returning to the supine position.

In the latter phase a bradycardia is also frequently observed when the mechanism of syncope is dominant vasodepressor, particularly if the descent time of the tilt table is relatively long. Obviously the latter response is not considered significant for the mechanism of the loss of consciousness.

The clinical outcome of patients with asystole during HUT appears similar to that of patients who are syncopal but not asystolic.³

Nevertheless, in selected cases, the response to HUT may be used to guide the therapeutic approach. Indeed, the preliminary data of North American Vasovagal Pacemaker Study⁴ showed dual-chamber cardiac pacing with rate-drop sensing as able to reduce the syncope recurrence in selected highly symptomatic patients.

In our recent randomized study, we found the shortened HUT potentiated with oral nitroglycerin to have a positive rate similar to the conventional one.⁵ On the other hand, the further reduction of the basal phase to 5 minutes has been shown to reduce the positive rate of the test.⁶ Thus we do not agree with Aerts and Dendale when they propose the complete suppression of the basal phase of HUT.

Furthermore, the specificity of the Dendale's protocol was 88%⁷ in a population aged 26 ± 5 years, but data regarding older subjects are still lacking.

Finally, an observation of at least 3 minutes is mandatory to exclude orthostatic hypotension as a cause of syncope: ⁸ indeed, the immediate administration of nitroglycerin would not allow differentiation between vasovagal and orthostatic mechanism as a cause of syncope.

Therefore, at the present, when performing HUT potentiated with oral nitroglycerin, the shortened protocol with a basal phase of 20 minutes should be preferred.

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CHAPTER 5B

Editorial:

Nitrate stimulated tilt test: clinical considerations

Arnaud J.J. Aerts

Pharmacological stimulation with a nitrate during tilt testing, has become a well accepted tool to elicit syncope of vasovagal origin in patients with recurring syncopal attacks.¹⁻³ Nitrates, well known for their ability to induce vasovagal reactions, were introduced into tilt testing in 1993 by Raviele et al.¹ Nitrates lack the catecholaminergic effects of isoproterenol and are at least as effective as isoproterenol in a direct comparison.^{1,2} Moreover nitrates can be given orally. The precise mechanism of nitrates' contribution to vasovagal syncope is still not clarified, but as emphasized in a recent review, a complex interaction of hemodynamic (preload and afterload) effects, neurohormonal influences, due to alterations in baroreflex sensitivity, and even central activity of nitrate compounds appear to be involved.²

Though the diagnostic accuracy of the test has been well established in numerous reports, the matter of test-specificity has only occasionally been addressed. Due to the absence of a gold standard, the true sensitivity and specificity of the test cannot be appropriately determined. False positive responses in normal controls have been described during passive tilting alone (especially when using steep tilt angles), with higher incidence of syncope when nitrates or isoproterenol are administered intravenously.^{4,9}

Reports from the 1930's demonstrated that amyl nitrate, given to healthy controls, could induce vasovagal reactions.⁵ Other factors that may influence the test result are the intravenous cannulation procedure, environmental circumstances, a steep tilt angle (80°), duration of testing and age.⁶⁻⁸ Thus, one can expect that the incidence of positive responses in normal controls will vary with the circumstances of the test. The diversity of tilt test protocols is a recognized problem, making it difficult to compare tilt studies. Also in many tilt reports, the patient selection does show considerable differences, though this seems to be a less problem (negative history) in the control groups. Obviously it is essential to screen controls for known syncope-contributing factors (like cardiovascular disease and associated medications). In this issue of the journal, Athanasos et al. used a tilt protocol, with a preceding passive tilt phase, potentiated by sublingual nitrate in 13 patients with unexplained syncope and 13 controls of comparable age (32 ± 9 years) and gender distribution. In the control group, 6 out of 13 (46%), had a positive response, revealing a specificity of 54%. Controls with a positive response were predominately females (5 out of 6, 83%). The authors conclude that a nitrate stimulated tilt test is too lacking in specificity to provide a true diagnosis in patients with unexplained syncope. They support their finding with references to 2 other reports with specificities of 48-63%.

These findings contrast with numerous other reports. First some methodological remarks have to be made to interpret the results of Athananos et al. correctly. Aside from their small study size, the authors do not mention the precise details and circumstances of their protocol (was iv cannulation preceded? fasting state? nitrate dose?). Perhaps differences in these methodological details might explain why their specificity was so much lower than the 70–100% reported in previous studies.³ Looking across other published studies, one is struck by the lack of standardized protocol and a lack of clinical characterization of the general athletic fitness, work-experience and the presence of anxiety, of both patients and control subjects. In a study by Cohen et al. in patients with unexplained syncope, a high anxiety level before the test was associated with an positive tilt result while a negative one in those with a low level.⁸ Also on clinical grounds, one might expect that subjects who spend long periods of time on their feet vs. those who lead mostly sedentary lives would have differential sensitivity to tilting, with or without pharmacological challenge. Secondly, in a larger report (n=64), in older adults (>60 years), by Kumar et al., a 30–40 minutes passive tilt followed by 15 minutes of sublingual nitrate stimulation, was used. They did find a specificity of 48%. However in this study 27% of the controls, had a history of hypertension and were taking vasoactive medication at the time of the tilt test.

The ability of vasoactive therapy to enhance susceptibility to vasovagal syncope was previously demonstrated by Gaggioli et al.¹⁰ Their finding indicates that, in controls taking vasoactive therapy, not to be appropriate to determine the diagnostic value of the tilt test. Anyway Natale et al. found, in similar aged and healthy controls (n=16), not using vasoactive medications and using a less steep tilt angle (60° vs. 70°), a specificity of 88%.¹¹

So this report from Athanasos et al., though methodologically questionable, does remind that neurally mediated or vasovagal syncope is not a disease related entity but the syndrome may occur in anyone. The distinguishing capacity of the tilt test is not the identification of a fixed underlying pathology but merely the demonstration of differential responsiveness to baroreceptor and other reflexes, differential susceptibility to various stressors and circumstances encountered in daily life. Most importantly, we need to recognize the importance of basic clinical factors such as the athletic conditioning of patients or controls, and the extent to which prolonged standing plays a role in their daily life. Hypothetically it might even be so that a 'false positive' tilt responders represent those who will faint in the future.¹² It is important to note that the tilt test is not a gold standard for the diagnosis of vasovagal syncope but merely an attempt to create a standardized provocative test.

On the other hand, derived from recent tilt guided therapy studies, one should be cautious to translate a positive tilt test result into aggressive therapeutic approaches.¹³ Despite the impending importance of the utilization of implantable loop recorders we still have to await new devices capable of monitoring both the hemodynamic and heart rate characteristics of spontaneous vagal episode.

The diagnosis is, in tilt positive responders, substantially subscribed by the symptom recognition and maybe also from rare cases of reproduction of hemodynamic or heart rate characteristics registered from spontaneous syncopal attacks. This method of descriptive diagnosing is similar and generally accepted in electrophysiologic studies.¹² As Benditt and Brignole remarked, when is a diagnosis a diagnosis?¹⁴ This question is also applicable in tilt testing. The goal of the true merit of the tilt test must and will be further elaborated when do a better job at characterizing patients in respect to their athletic status and their prior experience with long periods in the upright posture. Perhaps we may do better when results of implantable loop recording, in patients with vasovagal syncope, will become available.

But until then the test remains the first choice and cost effective investigation, and in case nitrate stimulated, fast and accurate way of unmasking vagal origins in patients suspected by history or in those with no clue at all. This view is underscored by the implementation of the test in the guidelines of diagnosing and management of syncope in both European and North-American expert panels.^{15,16}

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CHAPTER 6

Nitrate stimulated tilt testing enhances the predictive value of the tilt test on the risk of recurrence in patients with suspected vasovagal syncope

Arnaud J.J. Aerts, Peter Vandergoten, Willem R.M. Dassen, Paul A. Dendale

ABSTRACT

Objective: Nitrate stimulated tilt testing may be used to diagnose vasovagal syncope and to guide therapy. However, to date the predictive value of the test is undetermined. This study analyses the risk of recurrence of syncope in vasovagal patients on the basis of a nitrate stimulated tilt result and other clinical factors.

Methods and results: We used a combined passive and nitrate stimulated tilt protocol. One year after the test a questionnaire, asking about recurrence of syncope and other demographic factors, was sent to 131 patients. Passive tilting was found not to be a useful predictor; recurrence rates after a positive and negative test were 26% and 30% respectively, ns. With the addition of sublingual nitrates the test became a significant predictor; recurrence rates of 34 (34%) with a positive tilt test and 4 (13%) with a negative ($P=0.031$). Univariate analysis of the clinical factors revealed that gender and pre-test symptomatology were significant predictors of recurrence. Multivariate analysis revealed no additional relationships.

Conclusion: In patients with suspected vasovagal syncope, a positive tilt test with sublingual nitrates together with the clinical factors gender and symptomatology, are predictors for recurrence of syncope during one year follow-up. Without specific therapy the prognosis of vasovagal syncope is good.

INTRODUCTION

Vasovagal syncope is a frequent cause for hospitalisation and expensive work-ups. In recent years, the development of tilt testing simplified the diagnostic approach. Due to the low sensitivity of unstimulated tilt testing, isoproterenol and nitrate stimulated tests have been introduced.^{1,2} The stimulation significantly increases the sensitivity and reproducibility of the test. On the other hand the prognostic value is less well studied; to be useful for therapeutic decision making, the test has to have a high predictive value for recurrence of syncope.³

This study was designed to analyse the predictive value of a nitrate stimulated tilt test result and demographic factors on the risk of recurrence during one year follow-up, in patients with suspected vasovagal syncope.

METHODS

All patients with a clinical history of vasovagal syncope, undergoing a routine diagnostic tilt test, during a period of two years were considered for inclusion in the study. We excluded all patients in whom a clear etiology of the syncope different from vasovagal syncope was shown by the work-up (electrocardiogram, full cardiac examination, Holter monitoring, electrophysiological study, neurological examination, etc. when indicated). Patients using vasoactive medication which could not be interrupted were excluded as well.

The tilt test protocol consisted of an unstimulated tilt test at 70° for 30 minutes followed by a stimulation phase of 15 minutes. We used 5 mg sublingual isosorbide dinitrate tablets. We used a motorized table with footboard support located in a quiet room with a constant temperature of 21° Celsius. A 12-lead electrocardiogram (Marquette) was displayed continuously and blood pressure was measured every minute by an automatic sphygmomanometer (Dinamap).

The test was stopped when syncope occurred and all patients with a positive test were given an explanation of the nature of their "disease" and of precautions to be taken, such as good hydration, avoidance of standing during prolonged periods, etc. No specific drug therapy or counter measures (squeezing of arms and legs, tilt training) were started for prevention of vasovagal syncope.

For the follow-up study, a questionnaire was sent, concerning the number of eventual recurrent syncopal attacks, the use of coffee, tobacco, cardioactive medication, the presence of varicose veins, family history of recurrent syncope, age and gender. Presyncope was not analysed, due to its difficulty in definition and quantification, even though it may significantly influence the quality of life in patients with vasovagal syncope.

Statistical analysis

Statistical analysis was performed by using the non-parametric Mann-Whitney U test for continuous and the Pearson chi-square test for categorical variables. A P value < 0.05 was considered to be statistically significant.

RESULTS

Demographic characteristics of the 131 patients studied are shown in Table 1. 38 (29%) subjects had a total of 106 recurrences of syncope with a median of 2 episodes (range 1–10). 15 (40%) subjects had 1 recurrence, 18 (47%) 2–5 and 5 (13%) 6–10. Vasovagal syncope had an excellent prognosis during one year follow-up. There were no deaths and only 5 out of these 38 subjects (13%) had recurrent syncope with moderate physical injuries, like scratches and hematomas, with none needing hospitalisation. Of the total population, 23 (18%) had a positive passive, unmedicated, tilt test and 108 (82%) a negative one. Subjects with a negative passive tilt continued the test with a nitrate stimulated phase. After administration of sublingual nitrates another 78 patients (72%) had a positive test and 30 (23%) remained finally negative. The test characteristics are shown in Table 2.

Using a combination of passive and stimulated tilting, the rates of recurrence were calculated of the passive test and combined with the results after nitrate stimulation (Figure 1). In patients with a positive passive tilt response, recurrence of syncope occurred in 6 out of 23 (26%) in contrast to 28 out of 78 (36%) with a positive nitrate stimulated test. In the tilt negative groups, there was recurrence in 32 out of 108 (30%) after the passive test and in 4 out of 30 (13%) after the nitrate stimulated one. The recurrence rate of a overall positive test was 34 (34%) and 4 (13%) for a negative one ($P=0.031$).

Gender

Further analysis demonstrated a significant influence of gender for recurrence of syncope. 27 out of 62 (44%) of the women had a total of 84 recurrent spells (median 2, range 1–10) vs. 11 out of 69 (16%) of the males with a total number 22 spells, (median 2, range 1–5). In females with recurrence, 5 (19%) had a positive passive tilt, 20 (74%) a positive and 2 (7%) a negative nitrate stimulated test. These results were comparable to recurrences among males, 1 (9%) had a positive passive test, 8 (73%) a positive and 2 (18%) a negative nitrate stimulated tilt test. The recurrence rate in females with a negative passive test ($n=49$), was higher than in those with a negative nitrate test ($n=2$), 45% vs. 18% respectively ($P=0.043$). In men (59 and 2 subjects) these figures were 15% and 18% respectively.

Symptomatology

49 patients (38%), (18 females/31 males) aged 57 ± 17 years (range 18–84), had had 1 syncope before the tilt test, and 79 (60%), (43 females/36 males) aged 49 ± 21 years

Table 1 Baseline characteristics related to outcome.

	Number	Recurrence	No recurrence	P value
Gender				
Female	N= 62 (47%)	27 (44%)	35 (56%)	< 0.001
Male	N= 69 (53%)	11 (16%)	58 (84%)	
Age (years)	53±19	48±21	54±19	0.255
≤ 25	18 (14%)	8 (44%)	10 (56%)	
26-49	38 (29%)	9 (24%)	29 (76%)	
50-74	61 (47%)	19 (31%)	42 (69%)	
≥ 75	14 (11%)	2 (13%)	12 (86%)	
Symptomatology				
1 syncope	49 (37%)	9 (18%)	40 (82%)	0.027
≥ 2 syncope	79 (60%)	29 (37%)	50 (63%)	
Smoking				
No smoking	104 (76%)	32 (31%)	72 (69%)	0.577
Smoking	24 (18%)	6 (25%)	18 (75%)	
Alcohol				
None	66 (50%)	18 (27%)	48 (73%)	0.537
Yes	62 (47%)	20 (32%)	42 (68%)	
Caffeine				
None	32 (24%)	8 (25%)	24 (75%)	0.503
Yes	96 (73%)	30 (31%)	66 (69%)	
Varicose veins				
None	92 (70%)	27 (29%)	65 (71%)	0.931
Yes	35 (27%)	10 (29%)	25 (71%)	
Medication				
None	61 (47%)	16 (26%)	45 (75%)	0.527
Vasoactive medication	31 (24%)	8 (27%)	23 (74%)	
Other	39 (30%)	14 (37%)	25 (64%)	
Positive fam history				
No	110 (84%)	33 (30%)	77 (70%)	0.848
Yes	18 (14%)	5 (28%)	13 (72%)	

Table 2 Tilt test characteristics (n=96).

	Number	Recurrence	No recurrence	P value
Time to positive tilt (min.)				
Passive tilt phase	18±10	19±9	19±10	0.916
Nitrate tilt phase	9±4	9±3	9±4	0.827
Hemodynamic pattern of a positive tilt (n=101)				0.353
Mixed (n)	66 (69%)	22 (33%)	44 (67%)	
Cardioinhibitory (n)	9 (9%)	1 (11%)	8 (89%)	
Vasodepressive (n)	22 (23%)	8 (36%)	14 (64%)	
Unknown (n)	5 (5%)

Figure 1 Risk of recurrence and predictive value of nitrate tilt testing.

Sens: Sensitivity, Spec: Specificity, PPV: Positive Predictive Value; NPV: Negative Predictive Value.

(range 15–87), had two or more. In 3 subjects this information could not be retrieved anymore, so the analysis was limited to 128 subjects. As could be expected, the recurrence rate was higher in the more symptomatic group: 29 (37%) vs. 9 (18%), $P=0.027$. In the male subjects no difference in recurrence could be detected between those with a first or repetitive syncope, 16% and 17% respectively. On the other hand, there was a striking increase of recurrence in the more symptomatic women compared to those with a first syncope, 54% vs. 17%, $P=0.025$.

Hemodynamic pattern

According to the VASIS classification, the hemodynamic response during a positive tilt test can be classified into: the mixed type (bradycardia and hypotension), cardioinhibitory (asystole) or a vasodepressive type (predominately hypotension).¹ Recurrence occurred in 22 (34%) out of 65 subjects with a hemodynamic mixed tilt response, in 1 out of 9 (11%) with a cardioinhibitory and in 8 out of 22 (36%) with a vasodepressor response. Subjects with a cardioinhibitory response tended to be younger than those with a mixed or vasodepressor response, 40 ± 16 years vs. 51 ± 19 years and 52 ± 23 years respectively. This difference, however, was not statistically significant. Cardioinhibitory tilt responses occurred in 1 subject during the passive tilt and in 8 during nitrate stimulation. Median duration of asystolic episodes was 11 seconds, (range 5–40 seconds).

Age

Patients with a recurrence of syncope ($n=38$) tended to be younger than those without: 49 ± 21 years (range 15–84) vs. 54 ± 19 years (range 16–87), but the difference was not statistically significant.

Injury

No deaths occurred during follow-up. Five patients, aged 63 ± 18 years, had syncope associated with injuries necessitating doctor's attention but not requiring hospitalisation. Three of them had a positive baseline test after nitrate stimulation, 1 had a positive passive tilt test and 1 a negative nitrate tilt test.

Vasoactive medication and recurrence

The use of vasoactive medications has been correlated with an increased susceptibility of vasovagal syncope.⁹ In the present study such medications were stopped at least 3 days before the tilt test. During follow-up 31 (24%) patients were on long-term

vasoactive medication, of whom 23 (74%) had a positive tilt test (8 passive and 15 during the nitrate tilt). The overall recurrence rate was 8 (26%). Without any therapy ($n=61$, 45%), the tilt test was positive in 47 subjects (77%), (12 passive and 35 during nitrates). In this group the overall recurrence rate was 16 (25%). Also the number with a more symptomatic history, ≥ 2 syncope, was comparable in the vasoactive group vs. the no therapy group, 18 (58%) and 38 (62%) respectively.

DISCUSSION

Our main finding is that both positive and negative passive tilt test results have a relatively low risk of recurrence (26% vs. 30%, $P=0.734$) making the test not useful for risk stratification. On the other hand, when analysing the overall test results, after the addition of sublingual nitrates, the test became a significant predictor ($P=0.031$) (Figure 1).

Risk factors for recurrence of syncope

In the univariate analysis, gender and symptomatology (number of syncopal spells pre-tilt test) were significant predictors of risk of recurrence of syncope (Table 1). Gender was a highly predictive independent risk factor ($P<0.0001$) for recurrence.

Prognostic value in other tilt studies

Few reports focus on the predictive value of passive and isoproterenol stimulated tilt protocols in patients with suspected vasovagal syncope without specific therapy.⁴⁻⁷ Besides the well known dilemmas of differences in patient selection and tilt protocol some only report on the value of a positive tilt test and not of a negative one.^{7,9}

Sheldon et al.⁷ evaluated risk factors for recurrence of vasovagal syncope in 101 relatively young patients (mean age 36 ± 16 years), with syncope and a positive isoproterenol stimulated tilt test. They found, after one year follow-up, a recurrence rate of 28%, with age (univariate), duration of symptoms and number of syncopal spells (multivariate) as significant clinical pre-test factors in predicting recurrence of syncope. Patients with recurrence were significantly younger (30 ± 19 vs. 38 ± 19 years, $P=0.01$) and more often females 21 (75%, $P=0.042$). Although the results of stimulated and passive testing separately were not specified, the overall result, including a positive isoproterenol test, was associated with a trend in predicting recurrence ($P=0.062$). Later, the same group reported in patients with a negative tilt test, using

the same protocol, a comparable outcome (recurrence rate 35%) after 1 year follow-up as we found.¹⁴

In our study, the passive tilt test was not a useful predictor of recurrence. However, it became so after the addition of nitrates. To the best of our knowledge no other reports exist demonstrating any predictive value of the tilt test on the risk of recurrence.^{4-7,14}

Natale et al.⁵ analysed the long-term outcome (follow-up 3 ± 1.5 years) of 54 patients (aged 48 ± 12 years) with unexplained syncope and a positive tilt test and no therapy. 39 (72%) had a positive passive test and 15 (28%) an isoproterenol-induced one. They found an overall recurrence rate of 28%. Although the results of the passive and stimulated test are not mentioned separately, the response of the combined tilt did not predict recurrence whereas the pre-test variables symptomatology and duration of symptoms did.

Grimm et al.⁶ found in 80 patients (aged 40 ± 16 years) with suspected neurally mediated syncope, after a 45 minutes passive tilt and a 2-years follow-up, an overall recurrence rate of 33%. No difference was found in recurrence rates between subjects with a positive vs. a negative tilt, (43% vs. 30%, ns) nor was there any influence of gender and age. The only predictor was the pre-test number of syncopes, 1 syncope vs. ≥ 2 syncopes (10% vs. 54%, $P=0.04$). Ruiz et al.⁴ evaluated the outcome of 56 patients (aged 39 ± 23 years) with suspected vasovagal syncope, after a 60 minutes passive tilt, and a 1.3-years follow-up. They found an overall recurrence rate of 9%. Recurrence rate in relation to the tilt result was 8% and 17% for a positive and negative test respectively. However, in that study a positive tilt test result and duration of symptoms, but not the pre-test symptomatology, were associated with recurrence of syncope.

In our study, despite a higher mean age, (53 ± 19 years), the patients had a comparable overall recurrence rate of 29%. As was also reported by Sheldon, Grimm and Natale, we found in the more symptomatic subjects (≥ 2 syncopes) a significant higher recurrence rate than in those who experienced a first syncope (18% and 37% respectively, $P=0.027$). This underscores the importance of clinical history in risk stratification.

Also based on these reports, and in agreement with our findings, is that a passive test result is not useful for prognostic implications. In contrast to the sparse follow-up studies, which used isoproterenol tilt tests, a nitrate stimulated test result may be an additional tool for risk stratification in patients with vasovagal syncope. Other demographic characteristics (Table 1), like smoking, use of alcohol and caffeine, presence

of varicose veins, positive family history of syncope and various medications including vasoactive ones, did not demonstrate any clinical relevance in predicting the risk of recurrence. Especially, the absence of increased risk in subjects with varicose veins is in contradiction with the presumed efficacy of elastic stockings in diminishing venous pooling in the lower extremities.⁸

Also, the use of vasoactive medication in patients with suspected vasovagal syncope seems less problematic than has been suggested by Gaggiolo et al.¹⁰ They reported in patients with unexplained syncope, with and without vasoactive medication, that the use of vasoactive medications increases the likelihood of a positive nitrate stimulated tilt test. They concluded that this test may identify those subjects in whom the contribution of vasoactive therapy is predominant in the development of vasovagal syncope and so could affect therapeutic strategy. In our study, we found no difference in outcome of patients taking chronic vasoactive therapy compared to those who did not.

Asystole

This hemodynamic tilt response can be found in 14% during passive and in 21% during nitrate stimulated testing.¹¹ Tilt induced asystole was previously thought to be a malignant variant of vasovagal syncope with adverse outcome.¹² However, recently published data show that the clinical outcome of tilt positive patients with or without asystole is similarly benign.¹¹⁻¹³ Whether nitrates induce more often asystole during tilt testing, remains controversial.

The low yield of the passive test and differences in stimulated and unstimulated protocols, such as table descent time, patient selection and the amount of vagal discharge at the moment of ending the test, are probably more important in the development of a cardioinhibitory response than the mode of stimulation.¹² In our study, the cardioinhibitory response occurred in 8 out of 78 (10%) patients with a positive nitrate test and in 1 out of 23 (4%) with a positive passive one. Clinical outcome in these patients was comparable with that in patients without an asystolic positive test result and, although statistically not significant, the recurrence rate tended to be even lower, (11% vs. 34% respectively). Thus, as with passive and isoproterenol-stimulated tilting, subjects with a nitrate induced asystolic tilt result seem to have a similarly good outcome as those without this response.

At any rate, according to the recently published ISSUE study, which used a implantable loop recorder in patients with unexplained syncope, there seems little

correlation between the heart rate behaviour during the tilt test and the spontaneously occurring episode.¹⁵ Concordance was found in only 28% of the subjects.

Study limitations

As done by other authors the test results were calculated after the passive phase and after the addition of nitrates as an overall result. Though it seems very acceptable that subjects with a positive passive test will be positive during nitrate stimulation too, no data exist confirming this presumption.

CONCLUSION

This study shows that the nitrate stimulated tilt test, in addition to the clinical factors gender and symptomatology, is predictive of the risk of recurrence of syncope. Although nitrate tilt test results are already used to guide therapy in clinical practice,¹⁶ the clinical relevance of our finding needs to await further prospectively designed studies, preferably combined with other, easily attainable and established clinical risk factors.

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CHAPTER 7

Venous pooling during nitrate stimulated tilt testing in patients with vasovagal syncope

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ABSTRACT

Aims: To investigate the importance of venous pooling and variation in venous tone during nitrate stimulated tilt testing in patients.

Methods: Ten patients with a history of vasovagal syncope underwent an upright tilt test after an injection of ^{99m}Tc -labeled albumin. A gamma camera was positioned at the level of the lower legs. The patients were tilted to 90° for 30 minutes or until symptoms developed. In those subjects who did not show any symptoms before the end of the 30-minutes period, isosorbide dinitrate (ISDN) 5 mg was given sublingually and the test was prolonged for a maximum of 15 minutes.

Results: Nine of 10 patients needed nitrate stimulation to develop symptoms, one patient remained free following ISDN administration. Measurement of radioactivity revealed no significant increase in calf volume after nitrate stimulation (the mean volume increase was 77% before ISDN stimulation, and a further 0.9% afterwards).

Conclusions: The higher sensitivity for vasovagal syncope during upright tilt testing after administration of sublingual ISDN is not due to an increase in venous pooling in the lower extremities.

INTRODUCTION

Tilt table testing has become a useful *diagnostic procedure for diagnostic evaluation* of vasovagal syncope.¹ During upright tilt testing, nitrates may be administered as an additional tool to provoke syncope. Nitrates are known to increase substantially the number of positive responses during upright tilt testing.^{2,3} Although, the precise mechanism of nitrate induced syncope remains to be investigated, it is thought that the venous dilating capacities of nitrates are responsible.⁴ It is postulated that increasing venous pooling in lower extremities will decrease the effective circulating blood volume, and thus by reducing venous return will lead to syncope.⁵ The purpose of this study was to investigate the importance of venous pooling during nitrate stimulated tilt testing in patients.

METHODS

The study population consisted of nine patients (4 females, 5 males; mean age 63 ± 11 years, range 46–78). These patients were referred because of syncope. The diagnosis of vasovagal syncope was made on history (prodromal symptoms such as nausea, sweating, pallor, dizziness, yawning, haziness, and tachycardia; induced by orthostatic stress), and after other causes of syncope were excluded by physical (including neurologic) evaluation, orthostatic blood pressure testing for 5 minutes, carotid sinus massage, 12-lead ECG, and routine laboratory measurements. Supplementary examinations, such as computed tomography of the brain, electroencephalogram testing and a 24-hour of Holter monitoring, were performed when clinically indicated. None of the patients had any overt cardiovascular pathology. All patients who were taking vasoactive medication were asked to stop taking it 2 days before the test. Before participating in the study, all patients gave informed consent.

The patients had a light breakfast on the morning of the study. All tests were performed between 8 am and noon. The patients were first positioned horizontally on an examination table. ^{99m}Tc -dimercaptopropionyl-human serum albumin (10 mCi) was injected in the right arm and was allowed to reach equilibrium over a period of 10 minutes. This agent is known to provide excellent image quality with almost no extravascular diffusion.⁶ Over the next 5 minutes, activity of venous calf volume was detected by a gamma camera (Siemens ZLC 3700), which was placed 5 cm in front of the legs while the patient was still in the supine position. Patients were asked not to move their legs during the study. Baseline recordings were made every 30 seconds over a 5-minutes period. The patients were then asked to stand up and walk to a set-up, where they could lean in a 90° vertical position. The gamma camera was immediately repositioned in front of the legs and recordings continued every 30 seconds. If the test remained negative after 30 minutes standing in the upright position, isosorbide dinitrate (ISDN) 5 mg was given sublingually and the test was prolonged for a maximum of 15 minutes. When symptoms of syncope or near syncope (sudden fall in blood pressure, bradycardia, loss of consciousness) occurred or the test remained negative, the subjects were brought back to the supine position, and isotopic recordings were made for another 5 minutes with a time interval of 30 seconds. This isotopic technique to measure the intravascular volume changes in the lower extremities has been validated by Rutlen et al. and provides a quantitative and reliable assessment of peripheral vascular capacity in man.⁷

Heart rate and rhythm were recorded continuously during the test with a three-lead monitor (IVY Biomedical systems inc., 101 patient monitor). Blood pressure was

measured by an automatic sphygmomanometer (Lohmeier B606) placed on the right arm. Blood pressure and heart rate were measured every minute. If symptoms developed, the recordings were repeated immediately.

RESULTS

Ten patients underwent this procedure. One patient was excluded because of pre-syncope before ISDN administration. Eight of nine patients experienced symptoms during the tilt test (89%). The mean duration to (near) syncope in subjects with a positive tilt test result was 38 minutes $\pm$ 3 minutes (range 34–43 minutes). Seven patients had a decrease in blood pressure and a concomitant increase in sinus rate, which occurs at the time of symptoms. One patient had both a heart rate slowing and blood pressure decrease (Table 1). The increase in venous volume (%) was derived by the formula: $(y-x)/x \times 100$, where x stands for the average number of counts at baseline, and y stands for the average number of counts at plateau⁴. The mean percentage increase in venous calf volume during 30 minutes of passive tilting, compared with the baseline venous calf volume whilst in the supine position, was 77 %, (SD $\pm$ 34 %, range 38–140 %). Between administration of ISDN and the moment of developing symptoms, there was a further increase of the mean percentage in venous volume of 0.9 % (SD $\pm$ 3 %, range -5 to +5 %) which is not significant. Only three patients showed a decrease in venous volume,

Table 1 Characteristics, haemodynamic results and symptoms of individual patients.

Patient	Sex	Age	Baseline BP	Baseline HR	Last upright BP	Last upright HR	End of upright position	Symptoms
1	F	67	150/92	68	125/80	100	36	Syncope
2	M	51	160/100	76	110/60	110	38	Pre-syncope
3	M	78	165/85	104	71/46	122	38	Pre-syncope
4	M	46	140/80	60	109/62	70	36	Pre-syncope
5	M	73	158/100	80	127/78	114	43	Pre-syncope
6	F	60	140/90	100	158/95	145	35	Pre-syncope
7	F	54	110/70	80	140/80	126		None
8	M	57	140/75	76	141/90	103	34	Pre-syncope
9	M	52	110/70	52	106/60	43	22	Pre-syncope
10	F	77	170/100	80	79/51	60	41	Syncope

Age = years; BP = blood pressure (mm Hg); HR = heart rate (beats/min.); End of upright position = minutes after start of upright position.

Figure 1 Calf volume during different stages of upright tilt.

A = mean nuclear counts in supine position; B = mean nuclear counts at plateau in standing position; C = last count before symptoms; D = mean nuclear counts in supine position after tilt test.

with a maximum fall of 5 %. The only symptom-free patient had an increase of 1.5 %. The results of venous response are shown in Figure 1.

DISCUSSION

Haemodynamic studies have suggested that nitrates may lower blood pressure by a predominant venodilator effect and a quantitatively lesser effect on arteriolar resistance vessels, inducing reduced cardiac output primarily by diminished ventricular pre-load⁸. This finding leads to the possibility that the increased sensitivity of nitrate stimulated tilt testing is due to excessive venous pooling whilst in the upright posture.

These results show that in subjects with vasovagal syncope, the addition of sublingual nitrate following passive tilt testing does not result in excessive venous pooling in the lower extremities. It seems that most patients already have a maximal or nearly maximal vasodilatation after a period of 30 minutes upright tilting in the lower extremities, and yet do not faint until the test is prolonged and ISDN is administered.

These findings suggest that other mechanisms are likely to be involved. Recently, a study was published evaluating the differential effects of captopril and nitrates on autonomic nervous system, measured by muscle sympathetic nerve activity. They found that nitrates strongly activated the sympathetic nervous system in supine position⁹. This could elevate the inotropic state and so stimulate the Bezold-Jarisch reflex.

The major limitation of the present study was the low number of patients, although the results were very consistent. Secondly, it was not possible to investigate a control group of normal volunteers to compare venous response during upright tilting. However, it has been shown that pharmacological provocation with ISDN elicits susceptibility to syncope, and the aim of the study was to investigate the importance of venous pooling and variation in venous tone in this group. Also, it was not possible for the authors to use a tilt table in their isotopic laboratory, but it has been shown in the literature that the standing test adopted can serve as an alternative to upright tilt testing.¹⁰ In theory, the 90° position could antagonize venous pooling due to greater leg muscle activity compared with 60–80°. Another limitation to be mentioned is the fact that although isotopic techniques have been validated in previous studies⁷, the real accuracy in the assessment of peripheral vascular capacity is not certain.

Finally, these results are of measurements where the camera was focused on the calf of the patients, not on other organs, although in one patient (not included in the study), the camera was focused on the splanchnic region, which showed no important increase in venous volume. It is possible that a very small increase in venous volume in the whole body is necessary to cross the critical limit.

Despite these limitations, the authors believe that vasovagal syncope precipitated by nitrate upright tilt testing is not merely due to an excessive venous pooling in the lower extremities. Other mechanisms of nitrate induced syncope need to be investigated to understand mechanism of action of nitrates in susceptible subjects.

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CHAPTER 8

Neurohormonal activation during nitrate
stimulated tilt testing in patients with clinically
suspected vasovagal syncope:
A pilot study

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ABSTRACT

Background: Nitrate stimulated tilt testing, for the diagnosis of vasovagal syncope, is often used to increase the diagnostic performance of the tilt test. However, the precise mechanism of nitrate tilt induced vasovagal syncope, has still not been entirely clarified.

Neurohormonal activation is believed to play a role in the development of vasovagal syncope. In this study we investigated the role of neurohormones during a positive nitrate stimulated tilt test in patients with clinically suspected vasovagal syncope.

Methods: 6 patients with one or more episodes of vasovagal syncope were studied. An intra-arterial catheter was introduced for neurohormonal sampling. We used a combined protocol consisting of a 30-minutes passive tilt phase at 70°, followed by a maximum period of 15 minutes during nitrate stimulation (0.4 mg nitroglycerin spray). Neurohormones were drawn at baseline, during the passive phase at 5 and 30 minutes, or sooner imminent to syncope and recumbence.

Results: The passive phase of the test was positive in two and the nitrate phase in four. A positive tilt occurred after 15 and 26 minutes of passive testing, and after 5–11 minutes in the nitrate phase. During the early passive tilt phase (5 minutes), arterial norepinephrine increased significantly compared to baseline values (from 1.08 ± 0.27 nmol/l to 2.44 ± 1.41 nmol/l, $P < 0.001$). None of the other neurohormones demonstrated important changes in plasma concentrations at this stage of the test. At the end of the passive phase, in those who remained asymptomatic ($n=4$), norepinephrine did not increase further but angiotensin II rose significantly compared to baseline values (from 3.96 ± 1.39 pg/ml to 7.56 ± 1.73 pg/ml, $P < 0.05$). This in contrast to the plasma levels of dopamine, vasopressin and endothelin-1 which failed to show important changes. Nitrate induced syncope was neurohormonally characterized by a further increase in the levels of norepinephrine as well as a striking surge of vasopressin (2.50 ± 0.20 pg/ml vs. 19.15 ± 4.05 pg/ml, $P=0.001$).

Conclusion: Sympathoadrenal activation, in patients with vasovagal syncope, occurs early during tilt testing and remains apparent throughout the test. Nitrate induced syncope is, compared to passive tilting, characterized by a striking surge of vasopressin. Whether this represents a causal or secondary phenomenon awaits further study.

INTRODUCTION

Nitrate stimulated tilt testing is a well-accepted and well-documented way of establishing a diagnosis of vasovagal syncope.¹ Not only does it have a significantly higher yield than that of the generally disappointing passive tilt test, it has also successfully reduced this time-consuming phase of the test.¹ If sublingual nitrates are employed, the test is even more practical for use in daily clinical practice. The cost of inducing syncope in patients has also been demonstrably reduced by a more frequent use of the test.² However, the precise mechanism of tilt induced vasovagal syncope, as well as that of spontaneous syncopal episodes, has still not been entirely clarified. Although nitrates are known to be potent venodilators, venous pooling may not be the sole mechanism in nitrate induced syncope as baroreceptor and neurohormonal activation also play a role.³

An abnormal neurohormonal response during orthostatic stress appears to be an essential precursor in the development of tilt induced syncope,⁴⁻⁸ but this does not necessarily influence nitrate induced syncope during upright posture. So far, an understanding of the way in which nitrates increase the yield of the tilt test still remains elusive.

Whereas several studies have investigated the role of neurohormones during passive tilt^{8,15,18,19,25,28,30}, only few have addressed this issue during isoproterenol drug challenge^{17,29,31} and virtually none when sublingual nitrates were used in patients with a high clinical likelihood of vasovagal syncope. Additionally, most studies used intravenous blood sampling. However, as demonstrated by others, results of intra-arterial sampling allow a more accurate assessment of sympathetic activity.⁹

In this observational pilot study we investigated the role of neurohormones during nitrate stimulated tilt testing in patients with clinically suspected vasovagal syncope who had had a positive tilt test.

METHODS

Six consecutive patients (3 female/3 male, median age 45 years) with a typical history of vasovagal syncope and an initial positive nitrate tilt test but no apparent other causes of syncope had a neurohormonal profile taken during repeat nitrate tilting. To exclude other causes of syncope, all patients had a full medical history and clinical (including neurological) examination, carotid sinus massage and orthostatic blood

pressure testing (defined as blood pressure measurements supine and standing for 5 minutes), 12-lead electrocardiogram and routine laboratory tests. Patients taking cardiovascular or vasodilating drugs were excluded. Supplementary examinations such as 24-hour Holter recording, echocardiogram, computed tomography of the brain and electroencephalogram were done when clinically indicated. On the day of testing an intra-arterial catheter was inserted into the radial artery. Subsequently, blood samples were taken at baseline (20 minutes after insertion of the intra-arterial catheter), and again after 5 and 30 minutes of passive tilt, or sooner when syncope was imminent and during recumbence. Blood samples were immediately centrifuged and stored at -80°C until time of assay. In all samples, we analyzed catecholamines (norepinephrine, epinephrine and dopamine), vasopressin, endothelin-1 and angiotensin II.

TILT PROTOCOL

Tests were performed between 9.00 and 12.00 am after an overnight fast. We used a motorized table with footboard support located in a quiet room with a constant temperature of 21°C Celsius. A 12-lead electrocardiogram (Marquette) was displayed continuously and blood pressure was measured every minute by an automatic device (Dinamap). The tilt table was lowered when the subject developed a positive response (syncope or presyncope). Syncope was defined as a transient loss of consciousness with spontaneous recovery. Presyncope was defined as a state of light-headedness accompanied by signs and symptoms such as nausea, sweating, vomiting, pallor or weakness suggesting imminent syncope. According to the hemodynamic profile, a positive response was classified as a mixed, vasodepressor or a cardioinhibitory reaction. A mixed response was defined as a decrease in heart rate of ≥ 20 bpm and a decrease in systolic blood pressure of ≥ 20 mm Hg. A vasodepressor response was defined as a decrease in blood pressure of ≥ 20 mm Hg but no significant reduction in heart rate. A cardioinhibitory response was defined as a sudden decrease in heart rate of ≥ 20 bpm without a preceding decrease of blood pressure. The protocol was approved by the hospital ethics committee and informed consent was obtained from all subjects.

RESULTS

Six consecutive patients with a positive nitrate tilt test entered the study. Although their initial nitrate tilt test had been positive, on the day that neurohormones were

Table 1 Plasma levels of neurohormones at different time intervals in patients with clinically vasovagal syncope.

	Baseline	5'	30'	Syncope	Test end
Norepinephrine nmol/l	1.08±0.27*	2.44±0.41*	2.45±1.24*	3.78±1.85*	1.40±0.54*
Epinephrine nmol/l	0.32±0.17	0.52±0.28	0.64±0.32	2.14±2.45	0.56±0.34
Dopamine nmol/l	0.28±0.23	0.24±0.09	0.30±0.08	0.40±0.11	0.33±0.06
Vasopressin pg/ml	2.50±0.20	3.48±1.15	3.60±2.34	19.15±4.05*,**	25.63±3.15
Endothelin-1 pg/ml	1.76±0.84	2.30±1.01	2.30±2.14	3.13±0.95	2.54±0.51
Angiotensin II pmol/l	3.96±1.39	3.86±1.69	7.56±1.73*	9.34±4.53	7.34±3.75

* = $P < 0.05$, compared to Baseline; ** = $P < 0.05$, compared to end of the passive test.

taken, the passive phase of the test was positive in only two and the nitrate phase in four. A positive tilt occurred after 15 and 26 minutes of passive testing, and after 5–11 minutes in the nitrate phase. The hemodynamic response was mixed in four cases, vasodepressor in one and cardioinhibitory in the final case. The results of the neurohormonal measurements during tilting are shown in Table 1.

During the early passive tilt phase (5 minutes), arterial norepinephrine increased significantly compared to baseline values (from 1.08 ± 0.27 nmol/l to 2.44 ± 1.41 nmol/l) ($P < 0.001$). None of the other neurohormones demonstrated important changes in plasma concentrations at this stage of the test.

At the end of the passive phase, in those who remained asymptomatic ($n=4$), norepinephrine did not increase further but angiotensin II rose significantly compared to baseline values, (from 3.96 ± 1.39 pg/ml to 7.56 ± 1.73 pg/ml) ($P < 0.05$). This in contrast to the plasma levels of dopamine, vasopressin and endothelin-1 which failed to show important changes.

Nitrate induced syncope was neurohormonally characterized by a further increase in the levels of norepinephrine, as well as a striking surge of vasopressin, (2.50 ± 0.20 pg/ml vs. 19.15 ± 4.05 pg/ml) ($P=0.001$).

The concentrations of endothelin-1 and angiotensin II, increased at syncope, but compared to baseline both increments failed to reach statistical significance. Only the levels of vasopressin were significantly higher at syncope compared to those at the end of the passive tilt, (3.60 ± 2.34 pg/ml and 19.15 ± 4.05 pg/ml) ($P < 0.05$).

After 15 minutes in recumbence levels of vasopressin remained significantly elevated, as did those of norepinephrine. No complications occurred during the test.

DISCUSSION

This pilot study was conducted to analyze the neurohormonal effects of passive and nitrate stimulated tilt testing. We found that at an early stage of the passive tilt, when subjects had been upright for 5 minutes, and were still hemodynamically stable, a significant increase of norepinephrine occurred with no changes in epinephrine, dopamine, vasopressin, endothelin-1 and angiotensin II. At the end of the passive tilt phase angiotensin II increased significantly with no alterations of the other hormones. At nitrate induced syncope, an impressive increase in the levels of vasopressin was seen. Whereas at this stage the levels of the other neurohormones did not differ significantly from the values obtained at the end of the passive tilt test, those of vasopressin did. However, whether this surge in vasopressin is the cause of vasovagal syncope or rather reflects a counteracting vasoconstrictor reaction secondary to impending hemodynamic instability needs to be addressed in further studies.

Our results suggest that an increase of sympathetic outflow, as assessed by neurohormonal activity, precedes or accompanies the development of vasovagal syncope.^{10,11} In our study, plasma levels of catecholamines at syncope increased compared to baseline, but only for norepinephrine this was statistically significant. Several reports^{6,7,10,14,31,32} mention a significant increase of epinephrine with subsequent stimulation of vasodilating β_2 -adrenergic receptors, as a presumed detrimental precursor of the development of vasovagal syncope. However, our study did not find a significant rise of epinephrine imminent to syncope. Wallbridge et al. found similar levels of epinephrine in patients with either a positive or negative tilt test, suggesting that other neurohormones or mechanisms must be involved in the development of vasovagal syncope.⁸ This is supported by the findings of Dietz et al.²⁰ They investigated in ten healthy subjects β_2 -adrenergic mediated vasodilation, measured by forearm vascular resistance, in response to lower body negative pressure-induced orthostatic stress. They found that vasodilation may still occur under circumstances where the β_2 -adrenergic receptor is blocked suggesting that other mechanisms must be involved in the vasodilation which precedes vasovagal syncope. These mechanisms may include the renin-angiotensin-aldosterone system, vasopressin and endogenous opioids.^{8,20}

Catecholamines during nitrate stimulated tilt testing

Only few data are available on the effects of nitrates on neurohormonal responsiveness occurring during orthostatic stress. Tatar et al. investigated the neurohormonal response during tilt in a healthy male group, after the administration of sublingual nitrates.¹⁴ They found a significant increase in epinephrine levels in nitrate tilt

responders (syncope), when compared to those who had a negative response. Norepinephrine levels also increased but this was not related to the development of syncope.

Sardina et al. investigated in a placebo-controlled, double-blind, randomized cross-over study the hemodynamic and humoral effects of nitrates in a group of ten healthy individuals.¹⁶ Nitrates were administered by a 24-hour isosorbide dinitrate (ISDN) infusion in incremental doses (1–6 mcg/kg/min) and four consecutive, very short, tilt tests (2 minutes, 70°) were performed after 1, 6, 12 and 24 hours of infusion.

Blood samples for measurements of plasma catecholamine concentrations and plasma renin activity were taken 1 hour pre- and post-tilt. The investigators found that, although nitrates induced a significant diurnal increase of plasma renin activity levels, no significant changes occurred in pre- and post-tilt values in both the nitrate stimulated and the placebo group. However, when epinephrine data from the first tilt test were analyzed separately, a remarkable increase as compared to baseline was found, which was no longer evident during the follow-up tilt tests. This is of interest since the authors mention that several members of the study population developed vagal symptoms during the initial tilt test but not during the follow-up tests. This suggests not only that during nitrate stimulated tilting, an increase in epinephrine may be involved in the development of vagal reactions but also that repeat exposure to orthostatic stress may result in inhibition of sympatho-adrenergic responsiveness.

Takase et al. investigated the role of catecholamines during nitrate and isoproterenol tilting in 43 patients with syncope of unknown origin and a control group of 16 subjects.¹⁷ They used a protocol with intravenous dosing and a tilt angle of 80°. They also found that baseline values of catecholamines did not differ between subjects with either a positive (n=23) or negative tilt test or in the control group. A clear activation of catecholamines was demonstrable at an early stage after upright tilt at two minutes. During nitrate stimulation norepinephrine levels significantly increased compared to baseline, but they did not discriminate between those with a positive or a negative test. This was in contrast to epinephrine, which significantly increased only during nitrate induced syncope. What was remarkable, however, was that plasma levels of epinephrine during either passive or nitrate tilt induced syncope did not differ significantly from one another. This indicates that the superior yield of nitrate tilt testing, when compared to the passive test, is not merely due to an excessive catecholamine surge. It also suggests that other neurohormones and hemodynamic factors may be involved in the development of nitrate induced syncope.

Relations of plasma catecholamines to hemodynamic changes preceding tilt induced vasovagal syncope

Benditt et al. very recently reported on the intriguing question of whether neurohormonal activation during tilt is a primary phenomenon or secondary to tilt induced hemodynamic instability.¹⁸ They found a significant increase of epinephrine in tilt positive patients with unexplained syncope (n=11) after 4–6 minutes of passive tilting, compared to those with a negative tilt test (n=11). This was in contrast to the increasing but non-discriminatory values of norepinephrine during the test. Most importantly, this phenomenon was apparent before any hemodynamic alterations (heart rate, blood pressure) were evident. This suggests that an exaggerated neurohormonal activation preceding vasovagal faint during upright tilt, especially of epinephrine, may be a cause rather than a consequence of hemodynamic instability.

Goldstein et al. investigated the neurohormonal response of a positive and a negative passive tilt in 13 predominantly female patients with a history of neurocardiogenic syncope.¹⁹ Sublingual nitrates were only used in two of the patients. Beside catecholamines, forearm vascular resistance (FVR), as a marker of vascular tone, was measured. They found that both epinephrine and norepinephrine increased significantly during tilt, compared to baseline. At syncope, plasma levels of epinephrine well exceeded those of norepinephrine (sympathoadrenal imbalance). Forearm vascular resistance correlated inversely to plasma epinephrine levels. In patients with a positive tilt test, FVR typically decreased after the onset of tilting, and decreased progressively at the onset of syncope. This was in contrast to the FVR pattern in those with a negative tilt, where it increased throughout the tilt test. They concluded that this sympathoadrenal imbalance plays a pathophysiological role in the hemodynamic instability preceding vasovagal syncope. There was however, no mention of whether the early fall in FVR in tilt positive subjects was related to alterations in neurohormonal and hemodynamic variables (heart rate and blood pressure). Therefore it may be that a subclinical decrease in FVR is the only vascular precursor to impending hemodynamic instability. In support of this hypothesis is the fact that even at low levels of tilt (10°–20°) a decrease in central venous pressure may occur without important changes in heart rate and blood pressure.¹² Also, in healthy control subjects, these changes in FVR may be sufficient to stimulate norepinephrine release.¹² It is not known whether tilt induced changes in FVR can occur without neurohormonal activation, or vice versa in patients with vasovagal syncope.

More detailed investigations are needed to reveal the initial trigger of vasovagal syncope and to ascertain, whether this is an abnormal neurohormonal or endothelial response or perhaps a combination of both.

Role of vasopressin

Vasopressin is a potent vasoconstrictor hormone, which is released by the neurohypophysis. Although it is known as an osmoregulator, it may also be involved in the regulation of blood pressure during orthostatic stress.¹² Aside from a baroreflex-mediated increase, vasopressin may also be modulated by angiotensin II.²⁵ In addition, increasing levels of endothelin may stimulate angiotensin secretion²⁶ and, thus, vasopressin as well. Finally experimental data have documented, vasopressin-induced enhancement of baroreflex sensitivity.³²

Asymptomatic baroreceptor stimulation during sitting, standing or tilting may produce small increases in plasma vasopressin. However, during syncope several studies reported an enormous surge of vasopressin either preceding syncope or immediately afterwards.¹² Although most reports indicate a striking increase of vasopressin when syncope is imminent,^{27-30,32} some found no difference between the levels of vasopressin in tilt positive or tilt negative responders.²⁵ In our study, we also found a striking increase of vasopressin, imminent to nitrate induced syncope. However, whether vasopressin release bears any causal relationship to the development of vagal faint remains unclear. Combined hemodynamic and neurohormonal investigation is required to clarify this matter. Whether nitrates stimulate vasopressin release directly or through baroreceptor stimulation remains unclear as well.

Role of endothelin-1

Kaufmann et al. studied levels of endothelin, vasopressin, norepinephrine and plasma renin activity in seven patients (mean age 38 ± 7 years) with clinically suspected vasovagal syncope who had had a positive passive tilt test (30 minutes, 60°), and five healthy control subjects (mean age 41 ± 14 years).²⁸ They found that endothelin, norepinephrine, renin and vasopressin increased significantly during upright tilt in both groups when compared to baseline. In the patient group, however, norepinephrine decreased significantly at the onset of hypotension whereas levels of vasopressin and endothelin increased further. Based on this pattern, the authors hypothesized the efferent mechanism of vasovagal syncope to be primarily due to inhibition of, noradrenergic, sympathetic outflow.

This is contradicted by the findings of White et al. These investigators evaluated changes in endothelin and catecholamine release in a healthy control group using passive tilt (30 minutes, 60°) without drug challenge.³⁰ They compared the neurohormonal profiles of subjects with a positive tilt test with those with a negative one in an asymptomatic population ($n=46$, aged 47 ± 3 years) with no prior history of

syncope. The data showed that both norepinephrine and epinephrine increased during upright tilt, but only epinephrine increased significantly at the onset of syncope. Dopamine increased significantly in both groups compared to baseline, but angiotensin II only in those with a negative tilt test. In contrast to the findings of Kaufman et al., endothelin did not increase in subjects with either a positive or negative tilt test at any time during the tilt. Intriguingly, in the study of White et al., three out of 12 subjects with tilt induced syncope showed an increase of endothelin before syncope, but there was no change or decrease in these levels in the other nine. In our study, we did not find a statistically significant change in the levels of endothelin-1 during the test either.

Role of nitric oxide

Aside from hypotension induced by arterial and venular dilatation during tilt testing, a paradoxical skeletal muscle vasodilatation has been identified as being involved in the development of vasovagal syncope.²⁰ The occurrence of this phenomenon is believed to be nitric oxide (NO) mediated. In addition, a synergistic action seems to exist with β_2 -mediated vasodilatation due to epinephrine release.^{20,21} Indeed, sparse preliminary results indicate that nitric oxide activity increases during tilt testing.²²

In a recent review, Dietz and Joyner stated that the release of NO was the principal mediator in the development of vasodilation in response to mental stress.²¹ In support of this idea are *in vivo* data indicating that this vasodilation can be reversed by intra-arterial administration of the nitric oxide synthase inhibitor N-monomethyl-L-arginine (L-NMMA).²⁰ Nitrates exert their vasodilating action through their transformation into nitric oxide.²³ Whether the effect of nitrate tilting is due to an excess of nitric oxide formation remains to be investigated, however.

Sarah Sangha et al. recently provided new data as to why, despite a pre-syncope and potentially counteractive vasoconstrictor neurohormonal surge, the development of a vasovagal response is not prevented.²⁴ They reported on hyporesponsiveness to norepinephrine in peripheral arteries of animals, induced by microgravity and reminiscent of the decreased orthostatic intolerance which may develop in astronauts after space flights. According to some investigators this 'cardiac deconditioning' on gravitational challenge may be due to stimulation of vascular nitric oxide. Whether such a finding is also relevant for the norepinephrine increase occurring during nitrate tilt stimulation awaits further investigation. Nevertheless, based on the findings of Sarah Sangha et al., one may hypothesize that this increase in NO is the reason why vasovagal syncope is not prevented, despite increasing plasma levels of norepinephrine.

Beneficial effects of pharmacological therapy on neurohormones

Based on the assumption that neurohormonal activation plays a causal role in the development of vasovagal syncope, numerous reports have addressed the efficacy of drugs, which are capable of suppressing neurohormonal activity. Roul et al. evaluated in 44 patients with unexplained syncope, the neurohormonal profile before and after β -blockade.³² In patients with an isoproterenol-positive tilt test they found a significantly greater increase in epinephrine and vasopressin compared to those with a negative tilt test. However, repeat tilt testing during aselective β -blocker therapy, 8 ± 4 months later, revealed similar neurohormonal patterns as in the baseline tests. Moreover, both groups, i.e. those with a positive as well as those with a negative follow-up tilt test, remained asymptomatic. It is questionable, therefore, whether β -blockers have any effect in vasovagal syncope. Indeed a recent meta-analysis showed that beta-blockers do not prevent vagal faint at all.

Zeng et al. demonstrated, in a randomized, placebo controlled trial, that by using an ACE-inhibitor (enalapril) a significant reduction of tilt induced vasovagal faint was attained when compared to placebo.³¹ This phenomenon was associated with a significant suppression of catecholamines, which was absent in the placebo group. During follow-up all patients on enalapril remained asymptomatic. However, it is unclear from this paper whether the follow-up phase of the trial was also placebo controlled. In any case, the authors are the first to report that suppression of neurohormonal activation by means of an ACE-inhibitor may be associated with a reversal of tilt induced vasovagal faint.

To date, no data are available on other drugs such as, endothelin-1 or vasopressin antagonists.

SUMMARY

Based on the data available, the concept of nitrate induced vasovagal syncope emerges as an intriguing cascade of hemodynamic abnormalities and activation of neurohormones, either primary or secondary to imminent hemodynamic instability. The precise mechanism by which nitrates induce neurohormonal activation remains elusive, however. Increasing levels of epinephrine and vasopressin seem to predispose to and to precede an eventual vagal faint during either passive or nitrate tilt. However, available data on this phenomenon indicate a similar magnitude of this neurohormonal response in nitrate and passive tilting induced syncope.

Further studies are needed to assess the potential role of other vasoactive hormones and peptides during nitrate stimulated tilt. In particular, this applies to nitric oxide. Lastly, more attention should be directed towards various therapeutic strategies.

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CHAPTER 9

Nitrate stimulated tilt table testing: A review of the literature

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INTRODUCTION

In clinical practice, upright tilt testing is frequently used to determine the etiology of syncope by trying to induce vasovagal reactions. The importance of the test is underscored by the fact that before the introduction of the test in 1986 by Kenny et al.¹, often very expensive cardiac examinations were performed without resulting in a clear diagnosis. The more frequent use of the passive unmedicated tilt test also revealed its practical limitations. Not only is the test time consuming, but also the sensitivity in unselected populations appears not to be as high as originally described.²

Therefore, a pharmacological stimulation with isoproterenol was introduced. This resulted in an important increase in sensitivity, even though specificity tended to decrease, especially at higher doses. The widespread use of isoproterenol as a provocative stimulus during tilt testing revealed also its limitations. Reports of supraventricular arrhythmias, variant angina pectoris, and even ventricular fibrillation, in patients with structural heart disease, during isoproterenol stimulated tilt testing, make the use less desirable in unselected patient groups.³ Also the intravenous cannulation itself may result in an important decrease in specificity.⁴ Therefore, an alternative was sought and found in nitrates. These compounds are well known for their ability to induce vasovagal syncope. Raviele was the first in 1993 to publish about the value of intravenous nitrates during head-up tilt testing in patients with syncope of unknown origin.⁵ Since then several authors reported about the use of, oral and intravenous, nitrates for stimulation during tilt testing.⁵⁻²¹

The aim of this article is to review the history and data on how nitrates provoke syncope and the present state of use of nitrates during tilt table testing.

HISTORY

Ascanio Sobrero, an Italian chemist, discovered nitroglycerin in 1846. Alfred Nobel then manufactured nitroglycerin in 1864 as a new explosive agent. The vasoactive effects of nitrate compounds were soon revealed when workers in nitroglycerin factories experienced typical vasoactive symptoms, e.g. headaches and vasovagal reactions.²² Nitroglycerin (NTG), isosorbide dinitrate (ISDN) and isosorbide 5-mono-nitrate are organic nitrate esters containing the $-ONO_2$ groups. Nitrates exert their vasoactive capacities through transformation into nitric oxide (NO) which activates the enzyme guanylate cyclase resulting in an increase in intracellular 3', 5'-monophosphate (cGMP) which induces vasodilation.²³ Although the mechanism

of action was unknown at that time, Sir Thomas Lauder Brunton introduced in 1867 the use of nitrates in cardiovascular medicine. The more widespread use of nitrate compounds in medicine revealed the nowadays well known ability to induce vasovagal symptoms in man. Several case reports describe typical vagal characteristics as severe bradycardia, third degree AV block, asystole and severe hypotension with the use of sublingual or oral nitrates for ischemic heart disease.²⁴ Later several investigators started to use nitrocompounds during tilt testing to investigate the hemodynamics of vasovagal syncope. In the nineteen-thirties, Weiss and his collaborators studied the nature of circulatory collapse induced by sodium nitrite.²⁵ Later, nitrate compounds were used by Weissler et al. to study cardiac output changes during vasovagal syncope.²⁶ Recently, several publications have described the use of intravenous or sublingual nitrates as an alternative for isoproterenol during upright tilt testing for the induction of vasovagal syncope. This new way of stimulation has the advantage of being relatively free of serious side effects (only headaches are reported) and holds the promise of resulting in a practical, rapid and accurate test. The increasing number of studies presented and published on the subject reflects the growing interest in this type of pharmacological stimulation.⁵⁻²¹

Pathophysiology of nitrate induced syncope during tilt testing

The exact pathophysiological mechanism of vasovagal syncope is still a matter of discussion, and the precise mechanism by which nitrates induce vasovagal syncope is equally speculative. Although nitrates were studied extensively for their hemodynamic and anti ischemic effects in patients with coronary heart disease and heart failure, little is known about the precise mechanism of nitrate induced syncope. Based on data, mainly derived from hemodynamical and in-vitro studies with nitrate compounds, we discuss several pathways by which nitrates may induce syncope.

Biochemical: According to latest insights, nitrates cause vasodilation by an indirect stimulation of cyclic GMP leading to vascular smooth muscle relaxation.²³ Nitrate induced venodilation results in pooling of blood into the lower extremities, splanchnic and mesenteric vascular beds. Arterial dilation is predominately responsible for a decrease of the systemic blood pressure. The combination of a shift of blood volume and arterial dilation may result in baroreceptor mediated stimulation with β_1 -mediated tachycardia, as well as systemic, α -mediated, vasoconstriction.²⁷

Hemodynamic: Although the hemodynamic effects of nitrate compounds are well studied in supine conditions, few have investigated the effects during tilt testing. Weissler et al. investigated the hemodynamic effects of nitrite induced vasodepressor syncope in normal subjects during 60° upright tilt position, and found a decrease of

peripheral resistance and a slight decrease in cardiac output as the main cause of vasodepressor syncope.^{26,28,44} The impressive effectiveness of antigravity suit inflation to reverse the syncopal reaction indirectly reinforced the important role of venous distension and diminished cardiac output due to the decrease of venous return.

Wortmann et al.²⁸ investigated in post-infarction patients and controls (with normal LV function) the cardiodynamic changes during a short passive tilt (90°, duration 2 minutes) and after use of sublingual nitroglycerin (0.8 mg). They found in the control group that sublingual nitrates induced a significant reduction of the end-diastolic volume index (EDVI) and increase ($+19 \pm 6/\text{min}$) of heart rate. Remarkable from this study is the finding of a comparable unloading capacity, in both passive tilting and nitrate stimulated tilting, based on a similar reduction in EDVI ($-18 \pm 7 \text{ ml/m}^2$ vs. $-12 \pm 4 \text{ ml/m}^2$). This suggests that, at least during a short tilt, there is no excessive pooling during the nitrate tilt compared to the passive one.

Autonomic tone: That nitrates may cause a baroreceptor-mediated stimulation of the sympathetic tone was recently demonstrated by Noll et al.²⁹ They analyzed the influence of oral nitrates on muscle sympathetic activity (MSA) in healthy controls in supine position. They found that isosorbide dinitrate led to a marked activation of sympathetic outflow, as measured by MSA, in the absence of changes in heart rate and blood pressure. An increase in sympathetic tone is considered to contribute to the development of vasovagal syncope by increasing contraction of the left ventricle and subsequently triggering of the intraventricular mechanoreceptors which initiate the Bezold-Jarish reflex.

Central acting: Also of interest is the possibility of a direct central action of nitrates may contribute to the development of syncope. This view is supported by in vitro studies from Ma and Long.³⁰ They directly microinjected nitroglycerin in the nucleus tractus solitarius in anaesthetized rats, inducing α_2 -adrenoreceptor stimulation which resulted in hypotension and bradycardia. Nitrates are lipid soluble and readily cross the blood-brain barrier in human, which makes central action potentially an additional pathway of nitrate induced syncope.

Neurohormonal: Several studies have demonstrated a role of catecholamines and other vasoactive hormones such as vasopressine, endotheline, serotonin and brain natriuretic peptide, during passive tilt testing preceding the vasovagal syncope.³¹

The role of neurohormones during nitrate stimulated tilt testing might therefore be an underestimated part in the syncope cascade. Little is known, however about the neurohormonal behaviour during nitrate stimulated tilt testing and its part in the development of vasovagal syncope.

Parker et al.³² investigated the tolerance effect of chronic nitrate therapy, in patients with coronary artery disease. They found in patients treated with continuous nitrate application a clear neurohormonal activation with elevation of plasma renin activity, norepinephrine, atrial natriuretic peptide and arginine vasopressine. Unknown is whether this phenomenon also occurs after administration of a short acting nitrate compound during a nitrate stimulated tilt test.

Very recently Takase et al. reported a different behaviour of the catecholamines epinephrine and norepinephrine in patients with unexplained syncope, during nitrate stimulated tilt testing.⁶ They found in patients and controls that, during tilting, norepinephrine increased significantly, irrespective if pharmacological stimulation was used or not, and that epinephrine only increased in patients with a positive response during both passive and nitrate tilting. However in a positive response, both passive or nitrate induced, the mean levels of epinephrine did not differ significantly and were even higher in the passive positive group than during nitrate stimulation (148 ± 118 pg/ml vs. 111 ± 45 pg/ml). The authors argued that a difference in age of the two groups might have influenced the results. They concluded that nitrate induced syncope might be partially due to an increase in epinephrine which results in β_2 mediated vasodilation and increased cardiac contractility. This finding suggests that nitrate induced syncope is not related to an excess in catecholamines and that other factors/hormones contribute to the capability of nitrates to increase the amount of positive responses during tilt testing.

Venous pooling: The venodilating effect of nitrate compounds and the subsequent decrease of venous return is generally assumed to be the main mechanism of nitrate induced vasovagal syncope.⁵ Using a radionuclide technique in patients with vasovagal syncope during tilt testing, we found no significant supplementary pooling occurring in the lower extremities when nitrates were given after 30 minutes of passive tilt testing. We hypothesized that nitrate induced vasovagal syncope is due not only to the vasodilating capacities of the drug, but to other factors like neurohormonal activation, direct or indirectly through the baroreflex, could contribute in the vasovagal cascade.³³

Therefore the precise mechanism by which nitrates increase the sensitivity of the tilt test might be more complex than merely the widely assumed venodilating phenomenon. Further studies are needed to understand the mechanism by which nitrates induce vasovagal syncope.

METHODOLOGY

As in tilt testing in general, either unmedicated or stimulated, there is no standardization for tilt test protocols, although the ACC Expert Consensus Document in 1996, provided guidelines for clinical practice.³⁴ Nitrate stimulated tilt testing has been studied using different nitrate formulations, preparations and dosages. Intravenous or sublingual (spray or tablet) nitroglycerin and isosorbide dinitrate have been studied (Table 1).

Intravenous testing

Intravenous testing has the important advantages of a rapid onset of action and the relatively constant plasma concentration, that can be achieved. Comparison of the pharmacokinetics of intravenous and oral nitrates (ISDN) show that only when dosing is done intravenously, a linear dose-concentration relation of ISDN kinetics is found over the range of the infusion rate and duration.³⁵ Also, first pass hepatic metabolism is avoided and constant plasma levels can be maintained at a constant infusion rate. In addition the effect disappears rapidly after cessation of the infusion. However, as shown by Morrison et al.,³⁵ there seems to be no linear correlation between plasma ISDN concentration and responses of heart rate and blood pressure. This finding might raise some doubts about the need for intravenous testing because of accurate dosing.

Therapeutic dosages of intravenous nitrates for unstable angina pectoris vary from 10–200 $\mu\text{g}/\text{min}$, with exceptional cases of requiring 400 $\mu\text{g}/\text{min}$.³⁶ Starting dose is usually 10 $\mu\text{g}/\text{minutes}$ increased by 10 μg every 5 minutes. The half-life of intravenous ISDN is longer (in most studies between 30–60 minutes) than nitroglycerin (4–5 minutes).³⁶

Raviele et al., the first to report on intravenous nitroglycerin stimulation during tilt testing, in patients with unexplained syncope, used a starting dose 1.72 $\mu\text{g}/\text{kg}/\text{hr}$ with successive increments, per stage of 10 minutes, of 0.86 $\mu\text{g}/\text{kg}/\text{hr}$ to a maximum dose of 5.16 $\mu\text{g}/\text{kg}/\text{hr}$ at the end of the test.⁵ In-between dose increments the tilt

Table 1 Diagnostic value of sublingual nitrate stimulated head up tilt test protocols.

Author	N	Tilt angle	Nitrate dose, formulation	Passive phase (min.)	Stimulated phase (min.)	Sens. (%)	Spec. (%)	Accuracy (%)
Raviele, 1995 ¹⁴	235	60°	300 µg NTG	45	20	51 (65) [‡]	94	56 (67) [‡]
Kurbaan, 1999 ¹⁷	102	60°	300 µg NTG*	45	20	72	na	na
Raviele, 2000 ¹⁵	71	60°	300 µg NTG	20	20	49	90	62
Del Rosso, 1998 ⁴³	202	60°	400 µg NTG	20	25	70 (74) [‡]	94 (82) [‡]	81 (83) [‡]
Natale, 1998 ¹²	33	70°	400 µg NTG	20	15	78	88	na
Foglia-Manzillo, 1999 ¹³	48	60°	400 µg NTG*	45	20	71	na	na
Oraili, 1999 ¹⁶	65	70°	400 µg NTG	45	20	69	90	na
Bartoletti, 1999 ¹⁰	84	60°	400 µg NTG*	5	20	35	96	na
Graham, 2001 ¹⁹	48	70°	800 µg NTG*	40	25	68	63	na
Aerts, 1997 ⁸	32	70°	5 mg ISDN	45	15	87	70	81
Ammirati, 1998 ⁹	73	60°	1.25 mg ISDN*	30	15	57 (71) [‡]	100	62 (75) [‡]
Hermosillo, 2000 ¹⁸	120	70°	5 mg ISDN	30	12	83	88	84

* = spray; NTG = nitroglycerin; ISDN = isosorbide dinitrate; ‡ = results including exaggerated response; na = not available.

Table 2 Diagnostic value of intravenous nitrates during head up tilt testing.

Author	N	Tilt angle	Nitrate	Start dose µg/kg/hr	Dosing µg/kg/hr	Passive phase (min.)	Nitrate phase (min.)	Sens. (%)	Spec. (%)	Accu. (%)
Raviele, 1993 ⁵	40	80°	NTG	0.86	0.86	60	50 [†]	53 [‡]	92	67
Aerts, 1999 ⁷	20	70°	ISDN	1	1	0	30 [‡]	95	26	58
Zeng, 2001 ²¹	37	80°	NTG	1.72	0.86	0	50 (15) [§]	68 (71) [§]	90 (95) [§]	na

= when including an exaggerated response, results for sensitivity, specificity and accuracy were 78%, 48% and 66% respectively; † = 5 stages of 10 minutes, with in-between lowering of the tilt table; ‡ = continuous tilting, no lowering of the tilt table in-between dose increments; § = results for the single stage, 15 minutes, head up tilt protocol, at a constant dose of 3.44 µg/kg/hr; NTG = nitroglycerin; ISDN = isosorbide dinitrate; na = not available.

table was lowered again for a period of 5 minutes. Mean dose of a positive result was $3.43 \mu\text{g/kg/hr}$.

We described, using a different protocol, the value of stimulation with intravenous isosorbide dinitrate in a population with clinically suspected vasovagal syncope. The test started with a dose of $1 \mu\text{g/kg/min}$ uptitrated every 5 minutes, with $1 \mu\text{g/kg/min}$, to a maximum of $6 \mu\text{g/kg/min}$ at test end.⁷ In this protocol the table was not lowered in-between dose increments. Mean dose of a positive result in this study was $3 \mu\text{g/kg/hr}$.

Very recently Zeng et al. compared a 15 minutes single stage intravenous nitroglycerin tilt test, with a continuous dose of $3.44 \mu\text{g/kg/hr}$ with a protocol as previously described by Raviele in patients with syncope of unknown origin.²¹ They found a comparable diagnostic value of the relative short, 15 minutes limited, protocol compared to the protocol using prolonged stimulation (sensitivity 71% vs. 68% respectively, excluding drug intolerance). The details of the protocols and diagnostic values are shown in Table 2.

Sublingual nitrate tablets/spray

Different galenic sublingual nitrate formulations nitroglycerin (NTG) and isosorbide dinitrate (ISDN) and dosages have been used for stimulation during upright tilt testing (Table 1). In contrast to intravenous testing, the bioavailability of sublingual tablets is known to be variable and incomplete. Morrison et al. found a bioavailability of only 59% (range 19–93%) with 5 mg of isosorbide dinitrate sublingual tablets.³⁵

An important cause of this variable absorption of sublingual tablets is the dryness of the mouth and a presystemic clearance of the drug, which should be less with the nitrate spray. Maximal plasma levels after administration of oral ISDN spray are achieved within 2 minutes compared to 2–5 minutes after oral ISDN sublingual tablets.^{36,37,42}

Marchionni et al.³⁸ compared the time-course of hemodynamic effects of 5 mg sublingual ISDN tablets and spray in patients with heart failure. They found that both formulations lowered pulmonary arterial end-diastolic pressure in the same magnitude but the effects of the spray were significantly more rapid, with a peak effect at 10 minutes for the spray and at 30 minutes for the tablet ($P < 0.01$). Nitroglycerin, the traditional formulation, has a shorter half-life than ISDN.^{36,42}

Fung et al.²³ found an elimination half-time of nitroglycerin of 1–3-minutes, although pharmacological effects may persist for up to 30 minutes after dose administration.⁷ Armstrong et al.³⁹ found a peak nitroglycerin plasma concentration after 5 minutes and a drop to 50% of maximal concentration after 7.5 minutes with undetectable plasma levels after 20 minutes.

Saito et al.⁴⁰ compared the hemodynamic effects of different nitrate preparations (0.3 mg NTG tablet, 2.5 mg ISDN spray and 5 mg tablets) during Swan-Ganz monitoring in patients with a myocardial infarction. They found that time of action of isosorbide dinitrate spray was comparable to that of sublingual nitroglycerin tablets (2.67 ± 2.4 minutes for the ISDN spray vs. 2.67 ± 1.90 minutes for the NTG tablet), but the duration of action of the isosorbide dinitrate formulations, spray and tablet, was significantly longer (NTG 11.4 ± 6.4 vs. 57.4 ± 42.1 , $P < 0.05$) with individual values of more than 120 minutes.

These findings imply that in prolonged tilt testing, to obtain similar plasma concentrations and hemodynamic effects, the short acting nitroglycerin spray or tablets should be dosed several times. However this is contradicted by the findings of Ducharme et al.⁴¹ who demonstrated in normal subjects that forearm dilation, after a single administration of 0.4 mg sublingual nitroglycerin, tablet or spray, was still apparent 15 minutes after administration. To our knowledge no other data are available comparing the two nitrate formulations, nitroglycerin and isosorbide dinitrate, for stimulation during tilt testing. It is questionable whether the pharmacokinetic differences between the tablet and spray has any clinical relevance. The results of protocols using sublingual nitrate formulations during tilt testing are shown in Table 1.

The tilt protocol

The tilt methodology used in the studies of nitrate stimulated tilt testing is as varied as it is in the unstimulated tilt test literature. As is shown in Table 1, the various tilt angles and durations of either passive, unmedicated, or stimulated tilt tests make a comparison between the protocols difficult. The studies using intravenous nitrates used a small starting dose with increments every 5 or 10 minutes up to a maximum dose. All sublingual studies used a single high dose at the beginning of the test without further administration during tilting. In the study by Raviele et al. patients were tilted back to supine position between different stages of the test.⁵ The optimal duration of the nitrate stimulated tilt test cannot be concluded from the published literature, but as the mean duration from nitrate administration to syncope varied between 5 ± 4 to 9 ± 4 minutes, a total duration of the stimulation of up to 15 minutes seems optimal when sublingual nitrates are used after a passive phase.^{8,9} The important decrease in

specificity and accuracy when prolonging the stimulation from 15 to 30 minutes is also noted in the intravenous study by Aerts et al.⁷ In this the accuracy increased to a maximum of 79% at 18 minutes, but decreased progressively to 58% at 30 minutes.

Tilt angle

As shown in Table 1, angles of 60° and 70° are used during nitrate stimulated tilt testing. Derived from non nitrate tilting, it is generally assumed that steeper tilt angles may increase the number of false positive responses.¹⁵ For this reason some authors prefer a less steep angle of 60°. No reports exist comparing the two angles in nitrate stimulated tilting. The cumulative mean values of sensitivity and specificity (excluding exaggerated responses) of used nitrate protocols (Table 1), show a higher sensitivity and lower specificity for the 70° angle (77% vs. 58% and 88% vs. 95% respectively). Both angles are recommended by the Task Force on Syncope of the European Society of Cardiology.⁴⁵

Duration of preceding passive tilt

A preceding unstimulated tilt period of 20 to 60 minutes was used in the studies with sublingual nitrate stimulation. In most protocols sublingual nitrate was administered in standing position without returning to a supine position, but in some the tilt table was lowered to restore baseline values of heart rate and blood pressure.^{12,18,19} Whether this difference in technique has any importance on test outcome has not been investigated before. One might hypothesize that the total amount of orthostatic stress is less in protocols which lower the table before doing administration.

The optimal duration of the passive or unmedicated tilt phase before the nitrate stimulated phase is not yet precisely determined. The ACC guidelines from 1996, advise an unmedicated tilt phase of 30 minutes, but recent studies have investigated the influence of the duration of the unmedicated phase preceding nitrate stimulation.

Bartoletti et al.¹⁰ compared, in patients with unexplained syncope (mean age 55 ± 22 years), the value of a conventional 45 minutes passive tilt phase (60° angle) vs. a very short one of 5 minutes preceding 20 minutes with sublingual nitrate stimulation. In this study the overall positive rate (after nitrates) of the protocol with the 45 minutes unmedicated tilt phase was significantly higher than in the one with a 5 minutes passive tilt (51% vs. 35%, $P=0.04$). They concluded that, compared to no preceding passive phase, a protocol with a prolonged unmedicated tilt phase is preferable.

The findings of Aerts et al.⁴⁶ differed however. They compared three protocols, 45 minutes, 30 minutes or no unstimulated phase preceding a 15 minutes nitrate phase (70° angle) in 54 consecutive patients (mean age 46 ± 16 years) selected by an typical history of vasovagal syncope and 60 healthy controls. We found a sensitivity of 87%, 77% and 76% respectively, an almost unchanged specificity of 83%, 83% and 82 % respectively, and a slight but not significant difference in accuracy, 78%, 80% and 71%.

These data suggest that the passive tilt phase has little additional value in head-up tilt testing potentiated with sublingual nitrates. The higher positive rate, with no preceding passive tilt phase, compared to the results of Bartoletti (sensitivity 79% vs. 35%), despite only minor differences in tilt protocol, could be explained by the difference in patient selection. Although speculative the true value of a tilt protocol might be more appropriately determined, in absence of a gold standard, in patients with a clinically strong suspicion of vasovagal syncope, as done by Aerts et al., and not in patients with negative examinations. A larger randomized study, comparing the performance of a protocol using direct nitrate stimulation with one incorporating an unstimulated phase is necessary to increase confidence in this very short and practical test. A stimulated tilt test of only 15 minutes would certainly make this test easier to perform in a busy clinical practice.

Hemodynamic response during nitrate stimulation

Nitrate stimulation typically results in an increase in heart rate and a slight decrease in blood pressure, especially in the upright position.^{28,44} During tilting, typical vasovagal reactions can be observed. Different hemodynamic responses have been described, which are comparable to the responses in passive tilt testing: vasodepressor, cardioinhibitory and mixed responses are all seen after nitrate stimulation.⁵⁻⁸ A response thought to be specifically due to the pharmacological effects of nitrates or isoproterenol stimulation is the "exaggerated response". This is defined by Raviele as the "gradual development of symptoms of pre-syncope resulting from a progressive and slow (occurring in > 5 minutes) decrease in systolic blood pressure with a concomitant compensatory tachycardia or with only slight bradycardia occurring after a very prolonged period of marked hypotension".⁵ This response was seen in 25 % of patients in the original publication, during either nitrate and isoproterenol stimulation, but 14 % of patients in a subsequent publication from the same group and from Ammirati et al.⁹

Del Rosso⁴³ described this response in 4% and Aerts et al. in 11%.⁸ The latter considered this reaction as a vasovagal response (vasodepressor type), and not merely a phar-

macological effect. According to the proposed European classification for definition of vasovagal response, the type 3 vasodepressor pre-syncope response closely resembles the exaggerated response.⁴⁷ Also as summarized by Kapoor et al.,² a vasodepressor response (hypotension only) during passive tilt testing, has been demonstrated in approximately 30% of 181 positive patients and in 37% when isoproterenol is used. As mentioned in the American College of Cardiology Expert Consensus in 1996, a positive response provoked by tilt testing may include a reaction of pre-syncope and hypotension alone, if according to the attending physician a true syncope is inevitable.³⁴

Diagnostic value of nitrate stimulated tilt protocols

The sensitivity, specificity and accuracy of a tilt test are difficult to calculate because no agreed gold standard exists for the diagnosis of vasovagal syncope. Only the exclusion of other etiologies by a thorough cardiological and neurological examination and/or the selection of patients with symptoms very typical for vasovagal syncope will allow the real sensitivity and accuracy of the test to be assessed. Curiously enough, only a minority of studies has been performed on patients selected through a clinical history of vasovagal syncope, as mentioned by Kapoor et al.² Interestingly, Klingenhoben et al. reported that sensitivity was three times higher in patients with a pre-tilt test likelihood for neurocardiogenic syncope.⁴⁸ Their classification score system is an attempt to standardise populations with unexplained syncope in whom diagnostic tilting is performed. The results of published nitrate stimulated tilt protocols studies are presented in Tables 1 and 2.

Combined nitrate isoproterenol tilt tests

The presumed different mechanisms of action of the two provocative drugs used for stimulation during tilt testing has led some investigators to develop a stimulated protocol combining nitrates and isoproterenol.

Zeng et al.¹¹ investigated in patients with syncope of unknown origin and a negative baseline tilt test (60 minutes in 80° upright posture) the value of a pre-treatment of 10 mg isosorbide dinitrate sl., during supine position, followed by an incremental (10 min/phase) intravenous infusion with isoproterenol (1–5 µg/min) during tilt. They found a sensitivity of 88% and a specificity of 67%. These findings included an exaggerated response (14%), minor symptoms in association with hypotension, and drug intolerance in 5.6%.

Natale et al.¹² investigated in elderly (> 60 years) patients, with syncope of unknown origin, the additional value of adding 0.4 mg sublingual nitrates after a negative shortened passive tilt phase (20 minutes) and stimulation with a increasing dose of intravenous isoproterenol (1–5 µg/min). If subjects remained negative sublingual nitroglycerin was administrated and the test was prolonged for 15 minutes. They found that nitroglycerin, after an incremental dose of isoproterenol, increased the positive rate from 34% to 79%. Remarkable in this study is that in another group of patients, after a negative passive tilt, underwent stimulation with sublingual nitrates alone, resulting in a sensitivity of 78%.

REPRODUCIBILITY

A high reproducibility of a tilt test result is a prerequisite when using a follow-up tilt test for evaluation of therapeutic interventions for prevention of syncope. It may also be useful for prognosis. Few studies have reported on the reproducibility of the nitrate tilt test.

Foglia-Manzillo et al.¹³ attained in 48 patients with unexplained syncope the reproducibility of a nitrate stimulated tilt test using a protocol of 45 minutes drug-free tilt at 60°, and a maximum period of 20 minutes after administration of sublingual nitroglycerin. The tests were done at an interval of 2 to 21 days apart (median 2 days). They found a reproducibility, of an initial positive result of 79% and 83% for a negative one. Delrosso et al.²⁰ evaluated the reproducibility of a nitrate stimulated tilt test (60°, 45 ± 20 minutes, 400 µg NTG spray) in 38 patients (age 50 ± 21 years) with unexplained syncope. The tests were performed within a 1 week interval. They found a reproducibility of 67% for an initial positive response and 87% for a negative one.²⁰ We found in a small study of 17 patients selected by a typical history of vasovagal syncope, and using a different protocol (70°, 30 + 15 minutes, 5 mg ISDN), also the two tilt tests one week apart, a reproducibility of 100% for a positive result and 94% for a negative one.⁴⁹ The results of reproducibility of nitrate stimulated tilt testing are comparable with the data obtained from passive and isoproterenol stimulated tilt studies.⁵⁰ The results of non-nitrate tilt testing show that the overall reproducibility of an initial negative tilt result seems to be higher than a positive one (85% to 94% vs. 31% to 93%).³

No reports of randomized trials exist comparing the reproducibility of nitrate and isoproterenol stimulated tilt testing. Also it is unknown whether the reported limitations of assessing the reproducibility of non-nitrate tilt protocols (the influence of the

time interval in-between two tests, protocol choice and patient selection), are also applicable for nitrate stimulated protocols.

Side effects

The most frequent side effect reported during nitrate stimulated tilt testing was headache. Atrial fibrillation may be induced after the onset of bradycardia,⁴³ which is probably a vagal effect and not specific for nitrates. No major arrhythmias or complications were described in any of the studies.

Bradycardia and asystole

As early as 1932 reports exist of the occurrence of bradycardia and hypotension after administration of sublingual nitroglycerin.⁵¹ Later several authors reported nitrate induced asystole in patients with and without coronary heart disease.^{52,53} The assumption that nitrate stimulation, during upright tilt, would cause more frequent or severe asystole is not supported by the literature.

Hence other factors may influence the occurrence of severe bradycardia or asystole. Delayed interruption of a tilt test and the use of a electromechanized table may influence the amount of parasympathetic discharge and induce more severe and longer bradycardia or asystole.⁴⁵

Prognostic and therapeutical considerations

It is commonly agreed that vasovagal syncope is usually a benign event with a good prognosis and requiring in most individuals no specific therapy.⁵⁴ Only a minority of patients will be disabled, despite educational and reassuring measures, in their daily life due to vagal susceptibility. Several pharmacological agents have been tested, based on their assumed interaction in the vasovagal faint.^{55,56} However, based on a positive tilt test, until now no medical therapy, has shown any clear beneficial long-term effects compared to placebo.⁵⁵⁻⁵⁸

Recently new data has become available about drug efficacy in preventing vasovagal syncope. In a placebo controlled randomized trial, paroxetine, a serotonin re-uptake inhibitor, significantly improved symptoms and reduced, during long-term follow-up (25 ± 8 months), the number of recurrences of syncope to 18% and 53% in the paroxetine and placebo groups respectively.⁵⁹ This beneficial effect is in agreement with several uncontrolled studies.⁵⁸ Also remarkable from this study is that a nitrate stimulated tilt result was used to guide therapy and that paroxetine not only

reduced symptoms during daily life, but also significantly reduced the number of positive responses during a follow-up tilt after 1 month (38% paroxetine vs. 62% placebo group respectively). However whether patients on therapy, with a negative follow-up nitrate stimulated tilt test, have a more advantageous outcome remains unclear.

Another category of drugs with potential beneficial effects in preventing vasovagal syncope is the group of alpha-adrenergic agonists. Midodrine, is a selective α_1 -adrenoreceptor agonist used in recent reports to diminish venous pooling in order to prevent development of vasovagal syncope.⁶⁰ Only very recently controlled data was published about the efficacy of midodrine in patients with vasovagal syncope. In this randomized study the other arm consisted of a strategy with extra fluid management, salt tablets and counselling. Midodrine was superior compared to the fluid-therapy group. During 6 months follow-up 81% remained asymptomatic in the midodrine group vs. 13% in the fluid-therapy group. Although in this study midodrine was well tolerated, reports of inconvenient side effects using alpha-adrenergic agonists (e.g. scalp itching, tachyphylaxis, urinary retention and supine hypertension), may damp its use as a first choice or as a long-term regimen in vasovagal syncope. Another point of consideration is that another adrenoreceptor agonist, etilefrine, was recently demonstrated in a placebo controlled trial to be of no benefit in the treatment of vasovagal syncope.⁶⁴ Hence the efficacy and tolerance of these new agents for the prevention of vasovagal syncope needs to be confirmed in more randomized and placebo controlled trials.

Whether tilt guided (passive or isoproterenol induced) therapy is useful remains controversial. The long-term consequences of a nitrate induced tilt test result remain to be determined. Decision to start therapy will be usually done on an individual basis and depends on factors as the symptomatology, risk of physical injury, impairments in lifestyle or employment.^{55,56}

Tilt guided therapy has become of great interest since the announcement of the data of the international VASIS (DDI pacing vs. control) and North American Vasovagal Pacemaker (DDD pacing vs. control) studies.^{61,62} In these studies the effects of pacing with rate hysteresis vs. no therapy were evaluated in patients with repeating neurally mediated suspected syncope and a positive tilt test (mixed or cardioinhibitory responses). The tilt test protocol consisted of 45 minutes of passive tilt (60°) followed by a maximum of 20 minutes after 0.3 mg sublingual nitroglycerin administration (VASIS study). This randomized study demonstrated a long-term beneficial effect of

DDI pacing in minimizing, but not abolishing recurrence of syncope during long-term follow-up.

Taking into consideration that the majority of vagal fainters are young and the consequences of a pacemaker implantation (follow-up, psychological, technical problems, risk of implantation) this aggressive non-pharmacological approach remains last choice among the therapeutic options.⁶³

CONCLUSION

The use of sublingual or intravenous nitrates has become an accepted way to increase the diagnostic accuracy of upright tilt testing for the diagnosis of vasovagal syncope. Nitrate induced vasovagal syncope is not merely a venodilating effect, but available data suggest a complex interaction of decreased venous return, baroreceptor and neurohormonal activation. There may also be a direct central acting effect of nitrates. Concerning the protocol, as with passive and isoproterenol stimulated tilt testing, wide variations exists. The ACC expert panel and Task force on Syncope recommend tilt angles of 60° or 70°. Although no studies exist investigating the two angles in nitrate stimulated tilt, the cumulative mean values indicate a higher diagnostic yield for the 70° angle. The contribution of the passive tilt, usually the most time consuming part with a low yield, remains controversial. For the time being most protocols incorporate a passive tilt phase of at least 20 minutes and the duration of stimulation should be limited to 15 or eventually 20 minutes after a passive phase of 30 minutes. Sublingual sprays and tablets may be used for stimulation. The spray has the theoretical advantage of more immediate and predictable absorption, though it remains unknown whether this has any clinical relevance. Tilt tests using the intravenous route are probably not superior to sublingual administration and are cumbersome; the cannulation itself may influence the test result. This is of course also applicable to protocols combining nitrate stimulation with isoproterenol, either simultaneous or sequential; the attained test results do not show a superiority to nitrate stimulation alone.

Whether nitrate stimulated tilt testing may be used for prognostic stratification or to guide therapy in patients with vasovagal syncope has to await further study.

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CHAPTER 10

Future perspectives

Vasovagal syncope is a frequently encountered problem in the general population. The condition has an excellent prognosis but in individual cases medical attention is advisable due to secondary injuries or the troublesome impact of the recurrent spells on daily life. In the majority of subjects, a proper diagnosis can be made based on the typical characteristic symptoms. When these are absent, however, the tilt table test has emerged as the first choice investigation in the evaluation of patients with unexplained syncope. The test can also be used for symptom recognition or as a guide to therapeutic strategy in clinically suspected vasovagal syncope.

Whether it can be used to evaluate therapeutic interventions, however, remains undetermined. The apparent low sensitivity of the passive (drug-free) tilt test made pharmacological provocation necessary. Known for their ability to induce vagal reactions in people, nitrates have been introduced as provocative agents in tilt testing. Although the precise mechanism of nitrates' ability to induce a vasovagal reaction has not been entirely clarified, the available data, as summarized in this thesis, suggest a complex interaction with venous pooling, baroreceptor stimulation and neurohormone activation. A central effect of nitrates has also been considered.¹

In this thesis we addressed the different aspects of nitrate stimulated protocols and the pathophysiological concept of nitrates' ability to provoke vasovagal syncope. Since its introduction, the nitrate stimulated tilt test has emerged as an excellent tool for eliciting a diagnosis of vasovagal syncope. It has not only successfully increased the diagnostic yield of the test, but has also provided a feasible way to shorten the duration of the test. A simplified protocol facilitates its utilization in a busy daily clinical practice and increases the likelihood of keeping up with the guidelines in patients evaluated for syncope. More patients may be diagnosed and subsequently therapy may be initiated in an earlier phase if necessary. Additionally, and no less importantly, in this era of cost-effectiveness policy, the use of the tilt test may prevent potentially unnecessary and often expensive investigations, whether or not it is incorporated in a syncope unit.² The importance of the nitrate tilt test is underscored by its implementation in both the American and European guidelines for the evaluation of patients with syncope.^{3,4}

As for either passive or drug-induced syncope in general, further studies focusing on the precise interaction and sequence of hemodynamic, autonomic and neurohormonal changes during upright posture and the development of symptoms are required. The tilt test provides an excellent clinical tool for simultaneously provoking and analyzing the contribution of these pathways in vasovagal syncope.

Recently introduced implantable devices monitor heart rate changes during spontaneous syncopal episodes, but lack the capability of measuring hemodynamic alterations.⁵ The precise role of these devices in the management of syncope and especially syncope of vasovagal origin awaits further studies. Yet these devices may provide new insights on heart rate behaviour during spontaneously occurring vagal spells, and thus contribute to the interpretation of those obtained during the tilt test.

Aside from the established uses of the tilt test, several other conditions exist which may also benefit from the utilisation of this test.

1. Misdiagnosis of epilepsy

Myoclonic activity during syncope may be a prominent misleading symptom leading to an erroneous diagnosis of epilepsy. However, as the use of the tilt test revealed, up to 90% of subjects with tilt induced vasovagal syncope may demonstrate seizure-like symptoms mimicking epilepsy.⁶ Up to 20–30% of patients with presumed epilepsy may have been misdiagnosed.⁷ A very recent report indicates that in 36% of patients with suspected epilepsy and apparent therapeutic failure of anti-seizure medication an alternative diagnosis may be made by performing a tilt test.⁸ The value of nitrate tilt testing in this area still awaits investigation.

2. Psychogenic syncope

Syncope-like symptoms, in the absence of any physiological alteration, may occur in psychiatric disorders and may mimic those of an epileptic origin. Preliminary results indicate a substantial proportion of psychiatric disorders in patients suffering from unexplained syncope. Therapy of their psychiatric condition effectively reduced the number of recurrent syncopes. However, in a diagnostic stimulation of syncope, differentiating the condition from epileptic attacks may be difficult. A few reports indicate that a passive tilt test may be useful in differentiating psychogenic from epileptic disorders.⁹ The value of the nitrate tilt test in this setting has not yet been addressed.

3. Evaluating syncope in the elderly

Although vasovagal syncope may occur at any age, several reports indicate a reduced vagal susceptibility in subjects older than 65 years.¹⁰ The etiology of syncope may be more complex in the elderly than in younger subjects, especially in patients without premonitory symptoms. For instance, structural heart disease is more likely to be present than in younger patients.

Future studies need to concentrate on the place of nitrates during tilt testing in the evaluation of syncope in elderly patients.

4. Presyncope and vertigo

Often extensive neurological and otolaryngological examinations are performed to evaluate presyncope and vertigo, but there is data to suggest that the tilt test may also be useful in establishing a vagal origin of presyncopal spells and idiopathic vertigo.¹¹ Presyncope and vertigo are frequently encountered by general health practitioners. The value and cost-effectiveness of the tilt test as a primary diagnostic tool in this setting awaits further study.

5. Peripheral neuropathies and dysautonomies

Autonomic failure, usually characterized by orthostatic hypotension, may be primarily due to specific neurological diseases such as M. Parkinson and multiple system atrophy. It may also occur as a result of a hereditary condition or metabolic and auto-immune diseases.¹² Pharmacotherapy with either central or peripheral vasoactive drugs probably accounts for the largest number of cases of acquired orthostatic hypotension. Orthostatic hypotension of this nature may force clinicians to weigh up the advantages and disadvantages of the medicines which are suspected to be the cause of the problem. Tilt testing in this setting, therefore, may not be of diagnostic value but offers the possibility of unmasking a potential vagal contribution to the syndrome. Recognizing this may be important for adjusting pharmacological treatment.¹³

6. To guide or evaluate therapy

Recognition of hemodynamic characteristics during tilt induced syncope may be useful in determining the appropriateness of therapy in an individual patient. Although only a few randomised placebo controlled trials addressed the long-term efficacy of drug therapy in the prevention of vagal syncope (efficacy measured by a reduction in symptom burden), the predictive value of a negative test during therapy remains less clear.¹⁴ A new era of interest for the use of the tilt test lies ahead due to the instruction and evaluation of recently introduced physical counteractive manoeuvres aimed at reducing vagal discharge during syncope.¹⁵

7. Sleep disordered breathing

Obstructive sleep apnea syndrome is related to an increased prevalence of cardiac arrhythmias.¹⁶ Bradycardia, asystole and episodes of non-sustained ventricular tachycardia have all been reported. In upper airway resistance syndrome, an increased prevalence of orthostatic intolerance has been described.¹⁷ In addition, a relationship between autonomic imbalance and sudden infant death syndrome has been suggested.¹⁸ The usefulness and predictive value of the tilt test in revealing susceptibility to these conditions and in the identification of those who require specific therapy should be subject for future study.

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CHAPTER 11

Summary

Vasovagal syncope is a frequently encountered phenomenon in the general population and is considered to occur at least once in the lifetime of half of the population. In contrast to patients with structural heart disease and syncope, vasovagal syncope has an excellent prognosis and is not associated with an increased risk of cardiovascular morbidity or mortality. Although most subjects experiencing a vagal faint do not seek medical attention, it is estimated that the syncope experienced by approximately 50% of the patients attending an emergency department is of vasovagal origin. The diagnosis is usually made after careful examination of a patient's medical history but may be difficult in patients lacking the typical premonitory signs and symptoms. These subjects in particular, classified as having syncope of unknown origin, often underwent expensive and low yielding investigations. The introduction of the tilt test not only successfully increased the number of diagnoses, but may also prevent the use of unnecessary examinations. However, the tilt test in its initial concept proved to be less sensitive than originally reported, and, no less importantly, very time consuming. This has prevented its widespread use in daily clinical practice. Consequently, pharmacological stimulation during tilt testing has been introduced to increase the yield of the test. It not only enhances the diagnostic performance but may also reduce the cumbersome nature and duration of the test. The use of sublingual nitrates during a tilt test provides an excellent tool for eliciting a diagnosis of vasovagal syncope.

The studies in this thesis evaluate the diagnostic value of different techniques of nitrate stimulation during tilt testing, the reproducibility of the test and the ability of nitrates to provoke vasovagal reactions. Given the absence of a true gold standard for the diagnosis, the merits of the tilt test may be more appropriately determined in patients clinically suspected of having vasovagal syncope. In the studies presented in this thesis, therefore, we investigated patients selected on the basis of their clinical history.

Chapter 1 describes the historical background, pathophysiological mechanism, epidemiology and the role of the tilt test in the diagnosis of vasovagal syncope. The importance of the diagnosis is further underscored by the section on the economical burden of investigating syncope. Finally, the aims and outlines of this thesis are presented in the last section.

In **Chapter 2** we assessed the diagnostic value of an intravenous nitrate protocol for pharmacological stimulation during tilt testing in patients with suspected vasovagal syncope. In this study isosorbide dinitrate was used at a starting dose of 1 $\mu\text{g}/\text{kg}/\text{min}$ utes to a maximum of 6 $\mu\text{g}/\text{kg}/\text{min}$ utes and no preceding passive tilt phase was performed. We found a sensitivity, specificity and accuracy of 95%, 26% and 58%

respectively at test end (30 minutes). Receiver operator characteristics analysis revealed a maximum accuracy of 79% at 18 minutes, giving a sensitivity and specificity of 80% and 78% respectively. We concluded that during tilt testing intravenous nitrate stimulation using incremental dosing was highly effective in confirming a diagnosis of vasovagal syncope. Limiting the test to a maximum duration of 18 minutes not only avoids a considerable loss in specificity but also makes the test more practical for use in daily clinical practice.

In **Chapter 3** we report on the use of sublingual nitrates as a provocative stimulus during tilt testing. In this study, we evaluated 32 patients with suspected vasovagal syncope and 20 healthy controls. A combined protocol of a 30-minutes passive phase, followed by a maximum stimulation duration of 15 minutes was used. Passive tilting performed poorly with a sensitivity of only 13%. Specificity, though, was 100%. The combined protocol including the nitrate phase attained a sensitivity of 87%, a specificity of 70% and an accuracy of 81%. We concluded that the administration of nitrates effectively increased the diagnostic yield of the tilt test, thereby making it an appropriate tool for eliciting vasovagal syncope.

Chapter 4. A high reproducibility of the test is essential when used for therapeutic interventions. Reproducibility should also be tested in controls to ensure correct interpretation of the specificity of the test. In this study, we addressed the reproducibility of a nitrate stimulated tilt test in 43 patients with vasovagal syncope and 18 healthy controls. In both patients and healthy subjects an excellent reproducibility (100%) was found of an overall positive nitrate tilt test (combined passive and nitrate tilt result). The results of the nitrate phase only, revealed a reproducibility of a positive test in patients of 91%. Fifty percent of the patients who had an initial negative tilt test had a positive second test and this suggests that it is justifiable, after an initial negative test, to perform a second test within a period of 1–2 weeks. We concluded that nitrate stimulated tilt testing has an excellent level of reproducibility when results are positive, but only a moderate level of reproducibility when results are negative.

Chapter 5. In agreement with other studies, we also found the passive tilt phase to have poor sensitivity. This led us to introduce the concept of a nitrate protocol omitting this phase in order to shorten the test, and to improve its applicability in clinical practice. In this study, a direct sublingual 30-minutes nitrate protocol was used, without a preceding passive tilt phase, in 38 patients with clinically suspected vasovagal syncope and 31 healthy controls. At the end of the test a sensitivity of 82%, a specificity of 84% and a accuracy of 83% was attained. A receiver operator charac-

teristics analysis revealed that a maximum accuracy of 83% was attained at 14 minutes, with a sensitivity and specificity of 79% and 87% respectively. We concluded that shortened (15 minutes) nitrate tilt testing was an effective and feasible method of provoking vasovagal responses in susceptible patients with a good diagnostic performance. By reducing the cumbersome nature of the test, its implementation into clinical practice may be facilitated, thereby providing a positive contribution to the current management of patients with syncope.

Chapter 5a and 5b. In these chapters we focus on the pitfalls of diagnostic tilt testing in vasovagal syncope. To date, no gold standard exists for the diagnosis of vasovagal syncope. Only in rare cases spontaneously occurring episodes can be clinically monitored to arrive at an accurate diagnosis. It is important to recognize that vasovagal syncope is not a disease but rather a susceptibility to a condition, which may occur, in any individual subject during their lifetime, due to various provocative circumstances. The similarity of tilt induced hemodynamic characteristics of vasovagal syncope in both patients and subjects with no previous syncopal experience supports this hypothesis. When establishing the diagnostic value of a tilt protocol, the occurrence of a positive response in controls should be interpreted in this context. Symptom recognition in tilt positive responders during the pre- or post-syncopal episode is considered to be an important marker of an accurate diagnosis, but may not be apparent in all cases.

Also for standardization of the tilt protocol, when addressing in future studies the diagnostic value of the tilt test, a better characterization of athletic status and prior experiences to prolonged orthostatic stress in control groups needs to be done.

Chapter 6 analyzes the predictive value of the passive and nitrate tilt test and other demographic characteristics on the risk of recurrence during one-year follow-up. Passive tilting was found not to be a useful predictor; recurrence rates after a positive and negative test were only 26% and 30% respectively. With the addition of sublingual nitrates the test became a significant predictor; recurrence rates of 34 (34%) with a positive tilt test and 4 (13%) with a negative one ($P = 0.031$). Univariate analysis of the clinical factors revealed that female gender and pre-test symptomatology (≥ 2 syncopes) were significant predictors of recurrence as well.

We concluded that the use of a positive tilt test with sublingual nitrates, together with the clinical factors gender and symptomatology, are predictors for the recurrence of syncope during a follow-up period of one year in patients with suspected vasovagal syncope.

Chapter 7. In this chapter we aimed to find an explanation of how nitrates induce vasovagal syncope. In this study we investigated the contribution of nitrates to venous pooling in the lower extremities of patients during a positive nitrate tilt test. In 10 patients with suspected vasovagal syncope we measured venous calf volume during the passive, drug free, tilt phase and compared these results with the ones obtained when nitrate induced syncope was imminent. We found that, compared to supine baseline values, venous calf volumes during asymptomatic passive tilting increased by $77\% \pm 34\%$. During nitrate induced syncope these values increased insignificantly by $0.9\% \pm 3\%$. We concluded that nitrates during tilt testing do not induce an excessive venous pooling in the lower extremities. These findings contradict the hypothesis that it is the venodilating effect of nitrates which leads to an increased sensitivity of the test when compared to the effects of passive tilt testing.

Chapter 8. In this chapter we describe the results of an observational study of neurohormonal activation during combined passive and nitrate stimulated tilt testing in patients with suspected vasovagal syncope. In six consecutive patients we measured catecholamines, vasopressin, dopamine, endothelin-1 and angiotensin II at baseline, early and at the end of the passive tilt phase and during nitrate stimulation when syncope was imminent and after 15 minutes in recumbence.

We found that during the early phase of the passive tilt, the levels of noradrenaline were significantly increased compared to baseline. At this phase of the test the other neurohormones demonstrated no important changes. At the end of the passive test, levels of noradrenaline were significantly increased, compared to baseline. An insignificant increase of endothelin-1 and angiotensin II occurred in parallel, whereas adrenaline, dopamine and vasopressin remained unchanged.

Measurements at the time when syncope was imminent revealed a striking increase of vasopressin, compared to the baseline as well as the end of the passive tilt phase values. Noradrenaline remained significantly increased compared to baseline, but did not substantially increase further during occurrence of syncope. The values of endothelin-1 and angiotensin II increased during nitrate induced syncope, but this rise failed to reach significance. Levels of dopamine and adrenaline remained unchanged during syncope.

We concluded that neurohormonal activation, by an increase of noradrenaline, occurs early after attaining the erect posture in patients with suspected vasovagal syncope, and remains so during prolonged orthostatic stress. In contrast to the other neurohormones, the onset of nitrate induced syncope is related to an excessive surge

of vasopressin. Whether these findings are a primary cause of the development of vasovagal syncope, or secondary due to hemodynamic instability when syncope is imminent needs to be clarified in future trials. Study of the sequence and interaction of hemodynamic and neurohormonal changes may provide also new insight into the development of a therapeutic regimen for the treatment of vasovagal syncope.

Chapter 9 presents a review of the literature on nitrate stimulated tilt testing. It includes the discovery and historical background of nitroglycerin, its pharmacological and therapeutic activity. Also, the introduction of nitrate compounds in hemodynamic tilt studies and their utilization for the diagnosis of vasovagal syncope is described. Reported studies on the diagnostic value of different nitrate protocols are summarized in an overview and different mechanisms of nitrate ability to induce vasovagal syncope have been highlighted.

CHAPTER 12

Samenvatting

Vasovagale syncope is een frequent voorkomende aandoening die in de helft van de bevolking kan optreden tijdens het leven. In tegenstelling tot patiënten met een structurele hartaandoening en syncope is de prognose van patiënten met een vasovagale syncope uitstekend. Ofschoon personen die ervaring hebben met een vagale wegraking in de meeste gevallen geen medische hulp zoeken, is naar schatting bij 50% van de patiënten die een eerste hulp bezoeken in verband met een wegraking sprake van een vagale oorzaak.

De diagnose kan meestal gesteld worden door een zorgvuldige anamnese gericht op de typische kenmerken van een vasovagale syncope. Bij patiënten waar deze typische kenmerken ontbreken, is het stellen van de diagnose minder eenvoudig. Juist deze patiënten – met een syncope van onbekende oorzaak – worden vaak geconfronteerd met dure onderzoeken die bovendien weinig of geen toegevoegde waarde bevatten. De introductie van de tilt test heeft er toe bijgedragen dat er vaker een diagnose kan worden gesteld bij patiënten met syncope en hierdoor wordt tevens het gebruik van onnodige en dure diagnostische onderzoeken voorkomen. De tilt test, zoals uitgevoerd in zijn eerste concept, bleek echter een minder gevoelige test te zijn dan verwacht en, niet minder belangrijk, zeer tijdrovend.

Hierdoor werd een uitgebreide toepassing in de dagelijkse cardiologische praktijk bemoeilijkt. Door introductie van farmacologische stimulatie werd de diagnostische waarde van de test verhoogd. Tevens beperkt farmacologische stimulatie voor een belangrijk deel de omslachtige aard en de duur van de test. Het gebruik van nitraten als provocatie tijdens de tilt test blijkt een uitstekende manier te zijn om de diagnose vasovagale syncope te stellen. Sublinguale toediening is eenvoudig toe te passen in een dagelijkse cardiologische praktijk.

De onderzoeken in dit proefschrift beoordelen de diagnostische waarde van verschillende nitraat tilt methodieken voor de diagnose van vasovagale syncope, de predictieve waarde van het test resultaat alsmede het mechanisme van nitraat geïnduceerde tilt collaps. Bij gebrek aan een gouden standaard voor de diagnose vasovagale collaps, anders dan het monitoren van een spontane aanval, kan de diagnostische waarde van de tilt test beter vastgesteld worden in een populatie met syncope die op basis van een typische anamnese een hoge pre-test waarschijnlijkheid heeft van een vagale origine. In de in dit proefschrift gepresenteerde onderzoeken hebben wij derhalve alleen patiënten geselecteerd op basis van hun typische anamnese.

Hoofdstuk 1. Hierin worden de historische achtergrond, pathofysiologie en epidemiologie van vasovagale syncope beschreven. Het gedeelte over de kosten die gemaakt worden bij een evaluatie van syncope onderbouwt het belang van de diagnose. Tenslotte worden in het laatste gedeelte de doelstellingen van ons onderzoek gepresenteerd.

Hoofdstuk 2. In dit hoofdstuk worden diagnostische waarde en optimale testduur van een intraveneus gestimuleerde nitraat tilt test bij patiënten met een verdenking van een vasovagale syncope en bij een controle groep beschreven. Twintig patiënten werden getest en 23 controle personen. Als nitraatpreparaat werd isosorbide dinitrate gebruikt, met een startdosis van $1 \mu\text{g/kg/min}$, en een optitratie van $1 \mu\text{g/kg/min}$ per 5 minuten, tot een maximum van $6 \mu\text{g/kg/min}$.

De diagnostische waarde van een 30 minuten durende intraveneuze nitraat tilt test toonde een sensitiviteit en specificiteit van respectievelijk 95% en 26% en een accuraatheid van 58%. Door middel van 'receiver operator characteristics' analyse vonden wij een maximale accuraatheid van 79% van de test na 18 minuten, met een sensitiviteit en specificiteit van respectievelijk 80% en 78%. Geconcludeerd kan worden dat een 30 minuten durende intraveneuze nitraat tilt test een effectieve manier is om de diagnose vasovagale collaps te stellen. Het limiteren van de testduur tot 18 minuten voorkomt niet alleen verlies aan specificiteit maar bevordert ook de toepasbaarheid van de test in een dagelijkse klinische praktijk.

Hoofdstuk 3. In dit hoofdstuk wordt de diagnostische waarde beschreven van een sublinguaal gestimuleerde nitraat tilt test. In de eerste studie werden 32 patiënten met verdenking op vasovagale syncope en 20 controle personen onderzocht. Het protocol bestond uit een passieve fase van 30 minuten gevolgd door een gestimuleerde fase van maximaal 15 minuten. In vergelijking met een passieve test gaf de nitraat tilt test een beter resultaat. De sensitiviteit van de nitraat tilt was hoger (87% vs. 13%), ten koste van een geringe daling van de specificiteit (70% vs. 100%). De accuraatheid van de nitraat gestimuleerde tilt test was 81% vs. 46% voor de passieve tilt alleen. Geconcludeerd kan worden dat voor het stellen van de diagnose van vasovagale syncope, een sublinguaal nitraat gestimuleerde tilt test een superieure methode is ten opzichte van de passieve test.

In **Hoofdstuk 4** wordt de reproduceerbaarheid van de nitraat tilt test beschreven. Bij de interpretatie van de diagnostische waarde van de tilt test is een hoge reproduceerbaarheid van het test resultaat – zowel bij patiënten als controles – essentieel. Dit geldt dienovereenkomstig ook ingeval de test wordt gebruikt voor de

evaluatie van de effectiviteit van een therapie. Bij 43 patiënten en 18 controles werd de reproduceerbaarheid van een nitraat gestimuleerde tilt test bestudeerd. Een positieve nitraat tilt test (passieve en nitraat test resultaat gecombineerd) bleek in 100% reproduceerbaar. Analyse van positieve test resultaten in de nitraatfase alleen, toonde een reproduceerbaarheid van 91%. Bij patiënten met een initieel negatieve nitraat tilt test bleek deze in 50% reproduceerbaar. Het is derhalve zinvol om bij een initieel negatieve nitraat tilt, een tweede test uit te voeren binnen een interval van 1-2 weken. Geconcludeerd kan worden dat slechts een positieve nitraat gestimuleerde tilt test een uitstekende reproduceerbaarheid heeft, maar dat deze reproduceerbaarheid matig is wanneer de resultaten negatief zijn.

In **Hoofdstuk 5** wordt de diagnostische waarde beschreven van een 'directe', sublinguale nitraat tilt test, zonder voorafgaande passieve fase met een maximale duur van 30 minuten. In deze studie werden 38 patiënten met verdenking op vagale syncope en 31 gezonde controles getest. Een sensitiviteit van 82%, een specificiteit van 84% en een accuraatheid van 83% werden gevonden. Door middel van een "receiver operator characteristics" analyse werd een maximale accuraatheid van 83% gevonden na een test duur van 14 minuten met een bijbehorende sensitiviteit en specificiteit van respectievelijk 79% en 87%. Geconcludeerd kan worden dat een verkorte nitraat tilt test, zonder voorafgaande passieve fase, een waardevol diagnosticum is voor de diagnose van vasovagale syncope. Een maximaal 15 minuten durend protocol is eenvoudig te implementeren en kan aldus een positieve bijdrage leveren aan de evaluatie van patiënten met syncope.

Hoofdstuk 5a en 5b beschrijven de mogelijke valkuilen bij het uitvoeren en interpreteren van een tilt test. Tot op heden is er geen gouden standaard voor de diagnose van vasovagale syncope. Alleen in die zeldzame gevallen dat een spontane aanval tijdens een klinische observatie kan worden geregistreerd, is een betrouwbare diagnose te stellen. Hierbij dient tevens te worden aangemerkt dat een vasovagale reactie geen ziektebeeld is maar louter een reflexmatig syndroom dat bij ieder willekeurig individu tijdens zijn leven kan optreden, afhankelijk van de provocerende omstandigheden bij die persoon. De juistheid van deze hypothese wordt onderbouwd door de fysiologische overeenkomsten tussen een tilt geïnduceerde vagale syncope bij een patiënt en een gezonde vrijwilliger die geen aanleiding tot flauwvallen gaf. Elk onderzoek dat tot doel heeft deze reflexmatigheid aan te tonen is op grond van vorenstaande een vorm van beschrijvende diagnostiek die de reactie en interactie van het baroreceptor en neurohormonale systeem aantoon op de diverse uitlokkende stressoren, zoals die in het dagelijks leven ervaren

kunnen worden. Dit is een alom geaccepteerde vorm van diagnostiek die onder andere ook wordt toegepast bij elektrofysiologische onderzoeken.

Bij het bepalen van de diagnostische waarde van een tilt test is het optreden van een positieve reactie in een controle persoon dan ook in deze context te plaatsen. Het herkennen van de symptomen, in de pre- en post-syncopale periode, bij een patiënt met een positieve tilt respons draagt in belangrijke mate bij aan die juiste diagnose, maar is niet in alle gevallen aanwezig.

Bij de standaardisering van tilt protocollen is het bij toekomstige studies over de diagnostische waarde van de tilt test essentieel, dat ook de gezonde vrijwilliger beter gekarakteriseerd wordt met betrekking tot zijn fysieke toestand. Hierbij moeten vroegere ervaringen met orthostatische belastingen in aanmerking worden genomen.

Hoofdstuk 6 beschrijft de predictieve waarde van de passieve en nitraat tilt test en de demografische karakteristieken om, gedurende een 1 jaar 'follow-up', de kans op een recidief te voorspellen. Zowel een positief als een negatief passief tilt test resultaat heeft een vergelijkbare kans op een recidief (26% vs. 30%). Hierdoor heeft deze test geen voorspellende waarde. Na de toevoeging van nitraten, bleek echter een positieve test een significante predictor (34% vs. 13%, $P=0.031$) te zijn op de recidief kans. Bij de basiskarakteristieken bleken bij univariate analyse, het geslacht (vrouw) en de symptomatologie (≥ 2 syncopes voor de test) significante voorspellers te zijn voor een recidief.

Concluderend kan gesteld worden dat gedurende een 'follow-up' van 1 jaar van patiënten met een verdenking op vasovagale syncope, een nitraat gestimuleerde tilt test alsmede het geslacht en de symptomatologie predictoren zijn voor een recidief.

Hoofdstuk 7 beschrijft een onderzoek voor de bepaling van de wijze waarop nitraten tijdens een tilt test een vagale syncope kunnen uitlokken. In deze studie wordt tijdens de tilt test - met behulp van een radionuclide techniek - de invloed van nitraten op de veneuze 'pooling' in de onderste extremiteiten onderzocht.

Bij 10 patiënten met een verdenking van vasovagale syncope werden volume metingen verricht van de veneuze capaciteitsvaten van de onderste ledematen. Dit gebeurde tijdens de passieve tilt en in de nitraatfase bij het begin van de syncopale reactie. Ten opzichte van de basiswaarden in liggende positie, toonden wij aan dat het aannemen van de rechtopstaande lichaamshouding tijdens de asymptomatische

passieve tilt test leidt tot een toename van de veneuze 'pooling' in de onderste extremiteiten, met $77\% \pm 34\%$. De metingen voorafgaande aan de vagale syncope tijdens nitraatstimulatie, toonden een niet significante toename van $0.9\% \pm 3\%$.

Geconcludeerd kan worden dat nitraat geïnduceerde syncope niet veroorzaakt wordt door een overmatige 'pooling' van het veneuze vaatbed in de onderste ledematen. Dit weerlegt de hypothese dat de verhoogde sensitiviteit van de nitraat tilt test, ten opzichte van de passieve test, veroorzaakt wordt door de vasodilaterende eigenschappen van nitraten.

In **Hoofdstuk 8** werd de invloed van neurohormonale activatie bij patiënten met verdenking van een vasovagale syncope tijdens de passieve tilt en nitraat gestimuleerde tilt syncope onderzocht. Bloedmonsters werden afgenomen in de rustfase (baseline), gedurende de passieve tilt en tijdens nitraatstimulatie op het moment, voorafgaande aan de vasovagale syncope en na 15 minuten in de herstelfase. Metingen van de catecholaminen, vasopressine, dopamine, endotheline-1 en angiotensine II werden verricht.

Aangetoond werd dat in het begin van de passieve tilt test de plasmaspiegel van noradrenaline significant stijgt ten opzichte van de baseline waarden. De andere hormonen toonden op dat moment van de test geen belangrijke veranderingen ten opzichte van de basiswaarden. Aan het einde van de passieve tilt test was de plasmaspiegel van noradrenaline significant gestegen ten opzichte van de basiswaarde. Tegelijkertijd was er een niet-significante stijging van de plasmaspiegels van endotheline-1 en angiotensine II, en onveranderde waarden van adrenaline, dopamine en vasopressine.

De metingen op het moment van de syncope toonden een significante stijging aan, ten opzichte van de basiswaarde, van de vasopressine plasmaspiegel. De plasmaspiegel van noradrenaline tijdens syncope was significant verhoogd, ten opzichte van de basiswaarde, maar niet ten opzichte van de waarde aan het einde van de passieve test. De plasmaspiegels van endotheline-1 en angiotensine II toonden een stijging tijdens de nitraat geïnduceerde syncope, maar het verschil was te gering om statistisch significant te zijn. De plasmaspiegels van adrenaline en dopamine bleven onveranderd op het moment van nitraat syncope.

Concluderend kan gesteld worden dat bij patiënten met een verdenking van een vasovagale syncope, er direct na het rechtekomen tijdens de tilt test, een stijging van noradrenaline door neurohormonale activatie ontstaat, welke ook tijdens langdurige

orthostatische stress aantoonbaar blijft. In tegenstelling tot de andere hormonen, wordt het ontstaan van de nitraat geïnduceerde syncope, gekenmerkt door een excessieve toename van de plasmaspiegel van vasopressine. Of deze bevindingen de oorzaak zijn van het ontwikkelen van een vagale syncope of een gevolg zijn van de hemodynamische instabiliteit die aan een syncope voorafgaat, kan hieruit niet worden afgeleid en dient in verder onderzoek geanalyseerd te worden. Onderzoek naar de effecten en interactie van de veranderingen in het cardiovasculaire en neurohormonale systeem zou ook een belangrijke bijdrage kunnen leveren in de ontwikkeling van een behandeling van vasovagale syncope.

Hoofdstuk 9. Hierin wordt een overzicht gegeven van de literatuur over de nitraat gestimuleerde tilt test. De introductie en historische achtergrond van het gebruik van nitroglycerine, en de farmacologische en therapeutische eigenschappen van dit middel worden beschreven. Verder beschrijven we de eerste toepassingen van nitraten tijdens hemodynamische tilt studies die verricht zijn in het kader van de diagnostiek van vasovagale syncope. In het overzicht wordt de diagnostische waarde van de verschillende nitraat tilt protocollen samengevat en wordt een ingegaan op het mogelijke werkingsmechanisme van nitraat geïnduceerde vasovagale syncope.

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Curriculum vitae

Arnaud Johannes Jacobus Aerts werd op 7 december 1958 geboren te Meerssen.

Na het behalen van het VWO diploma aan het St. Maartenscollege te Maastricht, begon hij in 1980 met de opleiding Geneeskunde aan de Universiteit Maastricht (de toenmalige Rijksuniversiteit Limburg).

Zijn interesse in de cardiologie werd groter naarmate zijn studie vorderde en in het bijzonder tijdens zijn stage fysiologie van hart en longen o.l.v. prof.dr. F. Bonke en prof.dr. M.A. Allesie. Op 30 mei 1986 werd hem het artsdiploma uitgereikt en in dat zelfde jaar begon hij als arts-assistent in het St. Jozef Ziekenhuis in Kerkrade (1986-1988). Vervolgens aanvaardde hij van 1988-1989 de positie van arts-assistent cardiologie (niet in opleiding) in het Ignatius Ziekenhuis te Breda (begeleider dr. P.H.J.M. Dunselman) en van 1990-1991 in het Academisch Ziekenhuis te Groningen (opleider prof.dr. K.I. Lie).

Op 1 januari 1992 startte hij met de opleiding cardiologie in het Academisch Ziekenhuis van de Vrije Universiteit Brussel, België (opleider prof.dr. P. Block). Hij werd gecertificeerd als cardioloog op 16 augustus 1996 en nam vervolgens deel aan de opleiding tot intensivist te Brussel (opleider prof.dr. L. Huyghens). Op 1 januari 1998 ontving hij hiervoor de aantekening.

In maart 1998 startte hij als cardioloog-intensivist in het De Wever Ziekenhuis te Heerlen. Vanaf maart 2002 is hij volledig als cardioloog werkzaam binnen de maatschap Cardiologie van het Atrium Medisch Centrum in Heerlen, met als aandachtsgebied syncope.