Review

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 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 pharmacologic 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 also revealed 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 of isoproterenol less desirable in unselected patient groups.3 In addition, 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 symptoms in humans. Several case reports describe typical vagal characteristics as severe bradycardia, third-degree atrioventricular (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 1930s, Weiss et al.25 studied the nature of circulatory collapse induced by sodium nitrite. Later, nitrate compounds were used by Weissler et al.26 to study cardiac output changes during vasovagal syncope. 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 pharmacologic 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 antiischemic 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, several pathways by which nitrates may induce syncope are discussed.

Biochemical

According to latest insights, nitrates cause vasodilation by an indirect stimulation of cGMP leading to vascular smooth muscle relaxation. Nitrate induced venodilation results in pooling of blood into the lower extremities, and the 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 β1 mediated tachycardia, and systemic, α mediated, vasoconstriction.

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 the 60-degree upright tilt position, and they found a decrease of peripheral resistance and a slight decrease in cardiac output as the main cause of vasodepressor syncope. The impressive effectiveness of anti-gravity 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. investigated, in postinfarction patients and controls (with normal left ventricular [LV] function), the cardiodynamic changes during a short passive tilt (90 degrees, duration 2 minutes) and after the use of sublingual NTG (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 ± 6/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 ± 7 mL/m2 vs −12 ± 4 mL/min). 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. They analyzed the influence of oral nitrates on muscle sympathetic activity (MSA) in healthy controls in the supine position. They found that ISDN 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 LV and subsequently triggering of the intraventricular mechanoreceptors which initiate the Bezold-Jarisch reflex.

Central Acting

Also of interest is the possibility that 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. They directly microinjected NTG in the nucleus tractus solitarii in anesthetized rats, inducing α2 adrenoreceptor stimulation that resulted in hypotension and bradycardia. Nitrates are lipid soluble and readily cross the blood to brain barrier in humans, which potentially makes central action an additional pathway of nitrate induced syncope.

Neurohormonal

Several studies have demonstrated a role of catecholamines and other vasoactive hormones, like vasopressin, endothelin, serotonin, and brain natriuretic peptide, during passive tilt testing preceding the vasovagal syncope. The role of neurohormones during nitrate stimulated tilt testing may, therefore, be an underestimated part in the syncope cascade. However, little is known about the neurohormonal behavior during nitrate stimulated tilt testing and its part in the development of vasovagal syncope.

Parker et al. 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 vasopressin. Unknown is if this phenomenon also occurs after administration of a short-acting nitrate compound during a nitrate stimulated tilt test.

Recently Takase et al. reported a different behavior of the catecholamines (epinephrine and norepinephrine) in patients with unexplained syncope during nitrate stimulated tilt testing. During tilting, they found in patients and controls that norepinephrine increased significantly,
irrespective of whether pharmacologic stimulation was used or not, and that epinephrine only increased in patients with a positive response during 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 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 may be partially due to an increase in epinephrine resulting in $\alpha_2$ 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. Using a radionuclide technique in patients with vasovagal syncope during tilt testing, this study found no significant supplementary pooling occurring in the lower extremities when nitrates were given after 30 minutes of passive tilt testing. The authors of the current review 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.

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 (unmedicated or stimulated) there is no standardization for tilt test protocols, although the American College of Cardiology (ACC) Expert Consensus Document in 1996, provided guidelines for clinical practice. Nitrate stimulated tilt testing has been studied using different nitrate formulations, preparations, and dosages. Intravenous or sublingual (spray or tablet) NTG and ISDN have been studied (Table I).

**Intravenous Testing**

Intravenous testing has 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 to a concentration relation of ISDN kinetics is provided.

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Tilt Angle</th>
<th>Nitrate Dose Formulation</th>
<th>Passive Phase (min)</th>
<th>Stimulated Phase (min)</th>
<th>Sens. (%)</th>
<th>Spec. (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raviele et al. 1995</td>
<td>235</td>
<td>60°</td>
<td>300 $\mu$g, NTG</td>
<td>45</td>
<td>20</td>
<td>51 (65)$^+$</td>
<td>94</td>
<td>56 (67)$^+$</td>
</tr>
<tr>
<td>Kurbaan et al. 1997</td>
<td>102</td>
<td>60°</td>
<td>300 $\mu$g, NTG*</td>
<td>45</td>
<td>20</td>
<td>72</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Raviele et al. 2000</td>
<td>71</td>
<td>60°</td>
<td>300 $\mu$g, NTG</td>
<td>20</td>
<td>20</td>
<td>49</td>
<td>90</td>
<td>62</td>
</tr>
<tr>
<td>Del Rosso et al. 1998</td>
<td>202</td>
<td>60°</td>
<td>400 $\mu$g, NTG</td>
<td>20</td>
<td>25</td>
<td>70 (74)$^+$</td>
<td>94 (82)$^+$</td>
<td>81 (83)$^+$</td>
</tr>
<tr>
<td>Natale et al. 1998</td>
<td>33</td>
<td>70°</td>
<td>400 $\mu$g, NTG</td>
<td>20</td>
<td>15</td>
<td>78</td>
<td>88</td>
<td>na</td>
</tr>
<tr>
<td>Foglia-Manzillo et al.</td>
<td>48</td>
<td>60°</td>
<td>400 $\mu$g, NTG*</td>
<td>45</td>
<td>20</td>
<td>71</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Orai et al. 1999</td>
<td>65</td>
<td>70°</td>
<td>400 $\mu$g, NTG</td>
<td>45</td>
<td>20</td>
<td>69</td>
<td>90</td>
<td>na</td>
</tr>
<tr>
<td>Bartoletti et al. 1999</td>
<td>84</td>
<td>60°</td>
<td>400 $\mu$g, NTG*</td>
<td>5</td>
<td>20</td>
<td>35</td>
<td>96</td>
<td>na</td>
</tr>
<tr>
<td>Graham, 2001</td>
<td>48</td>
<td>70°</td>
<td>800 $\mu$g, NTG*</td>
<td>40</td>
<td>25</td>
<td>68</td>
<td>63</td>
<td>na</td>
</tr>
<tr>
<td>Aerts et al. 1997</td>
<td>32</td>
<td>70°</td>
<td>5 mg ISDN</td>
<td>45</td>
<td>15</td>
<td>87</td>
<td>70</td>
<td>81</td>
</tr>
<tr>
<td>Ammirati et al. 1998</td>
<td>73</td>
<td>60°</td>
<td>1.25 mg ISDN*</td>
<td>30</td>
<td>15</td>
<td>57 (71)$^+$</td>
<td>100</td>
<td>62 (75)$^+$</td>
</tr>
<tr>
<td>Hermosillo et al. 2000</td>
<td>120</td>
<td>70°</td>
<td>5 mg ISDN</td>
<td>30</td>
<td>12</td>
<td>83</td>
<td>88</td>
<td>84</td>
</tr>
</tbody>
</table>

$^*$Spray NTG-nitroglycerin; ISON-isosorbide dinitrate; $^+$Results including exaggerated response. na = not available.

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**Table I. Diagnostic Value of Sublingual Nitrate Stimulated Head-Up Tilt Test Protocols**

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found over the range of the infusion rate and duration.\textsuperscript{36} In addition, first pass hepatic metabolism is avoided and constant plasma levels can be maintained at a constant infusion rate. The effect disappears rapidly after cessation of the infusion. However, as shown by Morrison et al.\textsuperscript{36} 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 \(\mu g/\text{min}\), with exceptional cases requiring 400 \(\mu g/\text{min}\).\textsuperscript{37} The starting dose is usually 10 \(\mu g/\text{min}\) increased by 10 \(\mu g\) every 5 minutes. The half-life of intravenous ISDN is longer (in most studies between 30 and 60 minutes) than NTG (4–5 minutes).\textsuperscript{37}

Raviele et al.\textsuperscript{,5} the first to report on intravenous NTG stimulation during tilt testing in patients with unexplained syncope, used a starting dose 1.72 \(\mu g/\text{kg per hour}\) with successive increments, per stage of 10 minutes, of 0.86 \(\mu g/\text{kg per hour}\) to a maximum dose of 5.16 \(\mu g/\text{kg per hour}\) at the end of the test. In between dose increments the tilt table was lowered again for a 5-minute period. Mean dose of a positive result was 3.43 \(\mu g/\text{kg per hour}\). The authors of this review described, using a different protocol, the value of stimulation with intravenous ISDN in a population with clinically suspected vasovagal syncope. 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 (\(P < 0.01\)).

NTG, the traditional formulation, has a shorter half-life than ISDN.\textsuperscript{37,39} Fung et al.\textsuperscript{23} found an elimination half-time of NTG of 1–3 minutes, although pharmacologic effects may persist for up to

| Table II. Diagnostic Value of Intravenous Nitrate During Head-Up Tilt Testing |

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Angle</th>
<th>Nitrate</th>
<th>Start Dose (\mu g/\text{kg/hr})</th>
<th>Dose Increments (\mu g/\text{kg/hr})</th>
<th>Passive Phase (min)</th>
<th>Nitrate Phase (min)</th>
<th>Sens. (%)</th>
<th>Spec. (%)</th>
<th>Accu. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raviele et al. 1993\textsuperscript{5}</td>
<td>40</td>
<td>80°</td>
<td>NTG</td>
<td>0.86</td>
<td>0.86</td>
<td>60</td>
<td>50\textsuperscript{†}</td>
<td>53\textsuperscript{v}</td>
<td>92</td>
<td>67</td>
</tr>
<tr>
<td>Aerts et al. 1997\textsuperscript{7}</td>
<td>20</td>
<td>70°</td>
<td>ISDN</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>30\textsuperscript{†}</td>
<td>95</td>
<td>28</td>
<td>58</td>
</tr>
<tr>
<td>Zeng et al. 2001\textsuperscript{21}</td>
<td>37</td>
<td>80°</td>
<td>NTG</td>
<td>1.72</td>
<td>0.86</td>
<td>0</td>
<td>50 (15)\textsuperscript{¶}</td>
<td>68 (71)\textsuperscript{§}</td>
<td>90 (95)\textsuperscript{§}</td>
<td>na</td>
</tr>
</tbody>
</table>

\#When including an exaggerated response, results for sensitivity, specificity, and accuracy were 78\%, 48\%, and 66\%, respectively. \(\dagger\) stages of 10 minutes with inbetween lowering of the tilt table. \(\ddagger\) Continuous tilting, no lowering of the tilt table in between dose increments 1 \(\mu g/\text{kg/min}\). \(\|^\text{§}\) Results for the single stage, 15 minutes, head-up tilt protocol, at a constant dose of 3.44 \(\mu g/\text{kg per hour}\). NTG-Nitroglycerin; ISDN-isosorbide dinitrate; na = not available.
30 minutes after dose administration. Armstrong et al. found a peak NTG 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. 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 (Baxter Healthcare Corp., Puerto Rico) monitoring in patients with a myocardial infarction. They found that the time of action of ISDN spray was comparable to that of sublingual NTG tablets (2.67 ± 2.4 vs 2.67 ± 1.90 minutes, respectively), but the duration of action of the ISDN formulations, spray and tablet, was significantly longer (NTG 11.4 ± 6.4 vs 57.4 ± 42.1, P < 0.05) with individual values > 120 minutes.

These findings imply that in prolonged tilt testing, to obtain similar plasma concentrations and hemodynamic effects, the short-acting NTG spray or tablets should be dosed several times. However, this is contradicted by the findings of Ducharme et al. who demonstrated in normal subjects that forearm dilation, after a single administration of 0.4 mg sublingual NTG (tablet or spray) was still apparent 15 minutes after administration. No other data are available comparing the two nitrate formulations, NTG and ISDN, 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 I.

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 I, the various tilt angles and durations of 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 the supine position between different stages of the test. 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. 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. 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 I, angles of 60 and 70 degrees are used during nitrate stimulated tilt testing. Derived from nonnitrate tilting, it is generally assumed that steeper tilt angles may increase the number of false-positive responses. For this reason some authors prefer a less steep angle of 60 degrees. 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 I), show a higher sensitivity and lower specificity for the 70-degree 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.

Duration of Preceding Passive Tilt

A preceding unstimulated tilt period of 20–60 minutes was used in the studies with sublingual nitrate stimulation. In most protocols sublingual nitrate was administered in the 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. Whether this difference in technique has any importance on test outcome has not been previously investigated. One might hypothesize that the total amount of orthostatic stress is less in protocols that 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. compared, in patients with unexplained syncope (mean age 55 ± 22), the value of a conventional 45 minutes passive tilt phase (60-degree angle) versus a 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-minute unmedicated tilt phase was significantly higher than in the one with a 5-minute 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.

However, the findings of Aerts et al. differed. They compared three protocols, 45 minutes, 30 minutes, or no unstimulated phase preceding a
Nitrate stimulation typically results in an increase in heart rate and a slight decrease in blood pressure, especially in the upright position. 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 the absence of a criterion 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 that compares the performance of a protocol using direct nitrate stimulation with one incorporating an unstimulated phase is necessary to increase confidence in this 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. Typical vasovagal reactions can be observed during tilting. Different hemodynamic responses have been described that are comparable to the responses in classical tilt testing: vasodepressor, cardioinhibitory, and mixed responses are all seen after nitrate stimulation. A response thought to be specifically due to the pharmacologic effects of nitrates or isoproterenol stimulation is the “exaggerated response.” This is defined by Raviele et al., as the “gradual development of symptoms of presyncope 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.” This response was seen in 25% of patients in the original publication, during nitrate and isoproterenol stimulation, but 14% of patients in a subsequent publication from the same group and from Ammirati et al.

Del Rosso et al. described this response in 4% and Aerts et al. in 11%. The latter considered this reaction as a vasovagal response (vasodepressor type), and not merely a pharmacologic effect. According to the proposed European classification for definition of vasovagal response, the type 3 vasodepressor presyncope response closely resembles the exaggerated response. Also as summarized by Kapoor et al., 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 ACC Expert Consensus in 1996, a positive response provoked by tilt testing may include a reaction of presyncope and hypotension alone, if according to the attending physician a true syncope is inevitable.

**Diagnostic Value of Nitrate Stimulated Tilt Protocols**

The sensitivity, specificity, and accuracy of a tilt test are difficult to calculate because no agreed criterion 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 typical for vasovagal syncope will allow the real sensitivity and accuracy of the test to be assessed. Curiously enough, only a minority of studies have been performed on patients selected through a clinical history of vasovagal syncope, as mentioned by Kapoor et al. Interestingly, Klingenhoven et al. reported that sensitivity was three times higher in patients with a pretilt test likelihood for neurocardiogenic syncope. Their classification score system is an attempt to standardize populations with unexplained syncope in whom diagnostic tilting is performed. The results of published nitrate stimulated tilt protocols studies are presented in Tables I and II.

**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. investigated in patients with syncope of unknown origin and a negative baseline tilt test (60 minutes in an 80-degree upright posture) the value of a pretreatment of 10 mg ISDN sl, during the supine position, followed by an incremental (10 min/phase) intravenous infusion with isoproterenol (1–5 ìg/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 (5.6%).

Natale et al. 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 NTG was administrated and the test was prolonged for 15 minutes. They found that NTG, 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 who after a negative passive tilt underwent stimulation with sublingual nitrates alone the resulting sensitivity was 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. attained in 48 patients with unexplained syncope the reproducibility of a nitrate stimulated tilt test using a protocol of a 45-minute drug-free tilt at 60 degrees and a maximum period of 20 minutes after administration of sublingual NTG. The tests were done at an interval of 2–21 days apart (median 2 days). They found a reproducibility of an initial positive result of 79% and 83% for a negative one.

Del Rosso et al. evaluated the reproducibility of a nitrate stimulated tilt test (60 degrees, 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. The authors of this review found, in a small study of 17 patients selected by a typical history of vasovagal syncope, and using a different protocol (70 degrees, 30 ± 15 minutes, 5-mg ISDN) and the two tilt tests 1 week apart, a reproducibility of 100% for a positive result and 94% for a negative one.

The results of reproducibility of nitrate stimulated tilt testing are comparable with the data obtained from passive and isoproterenol stimulated tilt studies. The results of nonnitrate tilt testing show that the overall reproducibility of an initial negative tilt result seems to be higher than a positive one (85–94% vs 31–93%).

No reports of randomized trials exist comparing the reproducibility of nitrate and isoproterenol stimulated tilt testing. In addition, it is unknown if the reported limitations of assessing the reproducibility of nonnitrate tilt protocols (the influence of the time interval 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, 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 NTG. Later, several authors reported nitrate induced asystole in patients with and without coronary heart disease.

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 an electromechanized table may influence the amount of parasympathetic discharge and induce more severe and longer bradycardia or asystole.

Prognostic and Therapeutical Considerations

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

Recently, new data has become available about drug efficacy in preventing vasovagal syncope. In a placebo-controlled randomized trial, paroxetine (a serotonin reuptake inhibitor) during long-term follow-up (25 ± 8 months) significantly improved symptoms and reduced the number of recurrences of syncope to 18% and 53% in the paroxetine and placebo groups, respectively. This beneficial effect is in agreement with several uncontrolled studies. 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 (36% paroxetine vs 62% placebo groups). 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 α1-adrenergic agonists. Midodrine is a selective α1-adrenoreceptor agonist used in recent reports to diminish venous pooling to prevent development of vasovagal syncope. Only recently controlled data were 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 counseling. Midodrine was superior compared to the fluid-therapy group. During a 6-month follow-up, 81% remained asymptomatic in the midodrine group versus 13% in the fluid-therapy group. Although in this study midodrine was well tolerated, reports of inconvenient side effects using α1-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. Hence, the efficacy and tolerance of these new agents for the prevention of vasovagal syncope need 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.

Tilt-guided therapy has become of great interest since the announcement of the data of the international Vasovagal Syncope International Study (VASIS) (DDI pacing versus control) and North American Vasovagal Pacemaker (DDI pacing versus control) studies. In these studies the effects of pacing with rate hysteresis versus 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 degrees) followed by a maximum of 20 minutes after 0.3 mg sublingual NTG 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 nonpharmacologic approach remains the last choice among the therapeutic options.

Conclusions

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, and 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 degrees. Although no studies exist investigating the two angles in nitrate stimulated tilt, the cumulative mean values indicate a higher diagnostic yield for the 70-degree 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 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 if 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 also applicable to protocols combining nitrate stimulation with isoproterenol, 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.

References


