Tilt training: A new challenge in the treatment of neurally mediated syncope

Tony REYBROUCK, Hugo ECTOR
Departments of Cardiovascular Rehabilitation and Cardiology, University Hospital Gasthuisberg and Department of Rehabilitation Sciences, University of Leuven (K.U.Leuven), Leuven, Belgium.

Clinical experience with repeated tilt testing and standing training has shown that this procedure can be used as a new therapy for the restoration of abnormal autonomic orthostatic reflexes. The introduction of tilt training therapy for neurally mediated syncope is a new and effective treatment. This new therapy has been used recently in several centres with excellent results. Since syncope is a severe social handicap for the patient, successful therapy will normalise the functional status and restore self-confidence. The use of tilt training can be considered as first-line therapy in this disorder. In the majority of the studies on tilt training, patients remain free of syncope during active treatment with this therapy. In about 50% of the patients with neurally mediated syncope already the second consecutive tilt test became negative. This therapeutic effect of in-hospital repeated tilt tests is sustained by continued standing training at home. (Acta Cardiol 2006; 61(2): 183-189)

Keywords: neurally mediated syncope – tilt table testing – tilt training – cardiovascular rehabilitation

Classification of the haemodynamic response to tilt testing in neurally mediated syncope

Neurally mediated syncope can be classified according to the response to a tilt table test. Originally, the response to tilt table testing was classified according to isolated or combined changes of heart rate and blood pressure. Sutton’s first classification referred to (i) a vasodepressor type, reflecting mainly a drop in blood pressure at the time of syncope without changes in heart rate, (ii) a cardioinhibitory type with a decrease in heart rate and/or asystole and, finally, (iii) a mixed type reflecting both a decrease in heart rate and blood pressure. Recently a new classification has been proposed by the European Task Force on Syncope. Four different haemodynamic types of syncope have now been described. Type 1, the mixed type, refers mainly to a combined decrease of heart rate and arterial blood pressure at the time of syncope but the ventricular rate does not fall below 40 beats per min or less than 40 beats per min for less than 10 s without asystole of less than 3 sec. Type 2A, cardioinhibition without asystole, reflecting a decreased heart rate below 40 beats per min but without asystole and 2B, cardioinhibition with asystole, reflecting a decrease of heart rate with asystole for more than 3 sec. Type 3, the vasodepressor type, refers to syncope with a decrease of blood pressure without a significant decrease of heart rate (> 10% of its peak value). These different haemodynamic patterns reflect the complexity of the mechanisms behind the clinical picture of neurally mediated syncope. Moreover, the haemodynamic type of syncope may vary from one moment to another.
Therapeutic options in the treatment of neurally mediated syncope

A review of the proposed therapeutic options is presented in table 2. These therapeutic options include vagolytic drugs, beta blocking agents, fludrocortisone (to enhance plasma volume), serotonin reuptake inhibitors, alpha constrictors, salt and water supplements, sleeping with the bed in a head-up tilt position and physical manoeuvres such as leg crossing to increase blood pressure3-7. Endurance training has also been advocated8. For patients with the cardioinhibitory type of syncope and asystole, pacemaker therapy has been used9-12.

However, both during short-term and long-term follow-up of patients with neurally mediated syncope who were treated with pharmacotherapy, a considerable number of patients still reported syncope recurrence. In a review of the literature Benditt et al.5 observed syncope recurrence in patients treated with pharmacotherapy during a period of 18.5 months, varying from 0 to 56%.

Pacemaker therapy in patients with the cardioinhibitory type of syncope and asystole, pacemaker therapy has been used9-12.

In our department we have observed that patients who underwent repeated tilt testing showed spontaneous improvement of the tilt tolerance both during tilt table testing and during daily life.

Table 1 – Studies on the reproducibility of tilt table testing

<table>
<thead>
<tr>
<th>Study</th>
<th>Time interval</th>
<th>N</th>
<th>Reproducibility of a positive tilt test (%)</th>
<th>Reproducibility of a negative tilt test (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Sagritta Sauleda25</td>
<td>1 week</td>
<td>127</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>2. Wu30</td>
<td>same day</td>
<td>123</td>
<td>53</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>(6 hours)</td>
<td></td>
<td>34</td>
<td>90</td>
</tr>
<tr>
<td>3. Kochiadis32</td>
<td>1 week</td>
<td>35</td>
<td>60</td>
<td>/</td>
</tr>
<tr>
<td>4. Pavri33</td>
<td>1 day</td>
<td>193</td>
<td>49</td>
<td>94</td>
</tr>
<tr>
<td>5. Ruiz34</td>
<td>9.8 ± 8.2 days</td>
<td>64</td>
<td>54.5</td>
<td>84.3</td>
</tr>
<tr>
<td>6. de Buitleir35</td>
<td>5 minutes</td>
<td>19</td>
<td>57</td>
<td>94</td>
</tr>
<tr>
<td>7. Brooks36</td>
<td>1 day</td>
<td>86</td>
<td>37</td>
<td>80</td>
</tr>
<tr>
<td>8. Raviele37</td>
<td>3 days</td>
<td>14</td>
<td>71</td>
<td>/</td>
</tr>
<tr>
<td>9. Fitzpatrick38</td>
<td>/</td>
<td>31</td>
<td>77</td>
<td>/</td>
</tr>
<tr>
<td>10. Blanc39</td>
<td>7 days</td>
<td>13</td>
<td>62</td>
<td>/</td>
</tr>
</tbody>
</table>

/ = not available
Reproducibility of a positive or negative tilt test: reproducibility of a positive or negative response between two tests.

Tilt training

In our department we have observed that patients who underwent repeated diagnostic tilt tests showed spontaneous improvement of the tilt tolerance both during tilt table testing and during daily life.
Therefore we have initiated a tilt training programme\textsuperscript{16}. The patients are put on a tilt table at 60° inclination (Westminster protocol) and fastened with chest straps. The technique of tilt table training is illustrated in figure 1. The patients perform serial tilt tests (one per day) until syncope, until signs of severe orthostatic intolerance occur or until a normal value of 45 min for the tilt test is reached. When the patients experience syncope during tilt training they are returned to the recumbent position and signs of orthostatic intolerance disappeared quickly. This therapy is continued every day until the patients are able to perform 2 consecutive negative tilt tests (\(= 45\) min duration). Thereafter the patients are discharged from the hospital and have to continue standing training at home. This therapy is usually initiated in the hospital. The patients are further followed in the outpatient clinic for syncope.

For safety reasons it is recommended that patients start the therapy in a clinical setting with monitoring of ECG and blood pressure. For standing training at home, the patients are instructed to stand with their feet 15 cm away from the wall and to lean with the upper back against the wall.

During the first 6 weeks, intensive tilt training therapy is required with 2 sessions per day. After 6 weeks a new tilt test is performed during an outpatient clinic visit. If this test is negative (normal duration 45 min) the patients have to continue the therapy at home but the frequency of the tilt training is reduced to one session per day. Other outpatient clinic visits with new tilt tests are planned 3 months after the first outpatient test, and later on 6 months and one year after the first tilt training session. After 1 year of tilt training therapy the frequency of tilt training can be reduced.

In the field of cardiovascular rehabilitation the treatment of neurally mediated syncope by repeated tilt testing is a new and fascinating therapy with promising results. In our initial series of 42 patients we have found a negative tilt table response in all patients after 3.2 \(\pm\) 1.5 (median 3) sessions\textsuperscript{16}. This was found in all types of neurally mediated syncope. During a follow-up period of 43 \(\pm\) 7.8 months on average, data were available in 38 patients. In 31/38 patients (82%) no syncope recurrence was reported\textsuperscript{17}. Seven patients had syncope recurrence. Six out of these 7 patients had discontinued the therapy at the time of syncope recurrence. Nevertheless, there was a remarkable improvement in the condition of the patients who became symptomatic again after early discontinuation of the tilt training therapy. We simply advised them to resume the tilt training programme and syncope disappeared again. In our cumulative experience with a total group of 222 patients who underwent tilt training therapy for neurally mediated syncope, we obtained a negative response to tilt testing in all patients.

Review of studies on tilt training in patients with orthostatic intolerance and neurally mediated syncope

Other investigators have also applied tilt training therapy in patients with neurally mediated syncope and have reported a therapeutic effect on syncope recur-

\begin{table}[h]
\centering
\caption{Test for therapeutic options in the treatment of neurally mediated syncope}
\begin{tabular}{|l|l|}
\hline
\textbf{Neurocardiogenic syncope: Therapeutic options} & \textbf{Neurocardiogenic syncope: Therapeutic options} \\
\hline
\textbullet\ Disopyramide & \textbullet\ Salt & fluid supplement \\
\textbullet\ Metoprolol, atenolol & \textbullet\ Prevent hypoglycaemia \\
\textbullet\ Fludrocortisone & \textbullet\ Blood pressure raising \\
\textbullet\ Theophylline, etilefrine & \textbullet\ manoeuvres: coughing, \\
\textbullet\ Ephedrine, etilefrine & \textbullet\ leg crossing, squatting, \\
\textbullet\ Serotonin reuptake & \textbullet\ muscle contraction \\
\textbullet\ inhibitors: fluoxetine, sertraline & \textbullet\ Endurance training \\
\textbullet\ Midodrine & \textbullet\ Avoid static position \\

Table 2. – Therapeutic options in the treatment of neurally mediated syncope

\end{tabular}
\end{table}
Table 3. – Review of studies on tilt training in patients with neurally mediated syncope.

<table>
<thead>
<tr>
<th>Author</th>
<th>Pat N</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Symptoms</th>
<th>Training regime</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hoeldtke et al.</td>
<td>1</td>
<td>54</td>
<td>M</td>
<td>Severe orthostatic hypotension</td>
<td>Tilt table training and isometric exercise - 1x/day - duration 45 min per session or until syncope - in hospital - continued at home - 5x/week - duration 10-50 min - 1/day in hospital - continued at home (2/day)</td>
<td>After 1 week of conditioning patient was able to walk Complete disappearance of syncope in all pts during TT</td>
</tr>
<tr>
<td>2. Ector et al.</td>
<td>13</td>
<td>39.5 ± 20.1</td>
<td>8M/5F</td>
<td>Positive TT recurrent syncope daily life</td>
<td>Syncope during TT: - 1/24 (4%) TTr group - 18/23(74%) C group</td>
<td></td>
</tr>
<tr>
<td>3. Di Girolamo et al.</td>
<td>47</td>
<td>16 ± 2.2</td>
<td>18M/29F</td>
<td>Recurrent syn. posit. TT (nitroglycerine potentiation)</td>
<td>- 1/day - duration 45 min - continued at home</td>
<td></td>
</tr>
<tr>
<td>4. Reybrouck et al.</td>
<td>42</td>
<td>42.4 ± 21.3</td>
<td>22M/20F</td>
<td>Posit. TT recurrent syncope</td>
<td>- 41/42 patients negative TT - 1pt persistent S - S disappeared during daily life</td>
<td></td>
</tr>
<tr>
<td>5. Numatha et al.</td>
<td>1</td>
<td>64</td>
<td>M</td>
<td>Recurrent syncope</td>
<td>Symptom free during follow-up 1 year</td>
<td></td>
</tr>
<tr>
<td>6. Abe et al.</td>
<td>24</td>
<td>34 ± 20</td>
<td>12M/12F</td>
<td>Recurrent syncope positive tilt test (isoproterenol)</td>
<td>- 2/day - 30 min/session - at home</td>
<td></td>
</tr>
<tr>
<td>7. Abe et al.</td>
<td>15</td>
<td>35 ± 14</td>
<td>6M/9F</td>
<td>Recurrent syncope drug refractory</td>
<td>- 2/day - 30 min per session - tilt table training started in hospital</td>
<td></td>
</tr>
<tr>
<td>8. Gajek et al.</td>
<td>40</td>
<td>36.6 ± 14.7</td>
<td>11M/29F</td>
<td>Recurrent syncope</td>
<td>- 33/40 pts (82%) remain free of S during follow-up of 18 ± 6.9 months no syncope 1 (6%) positive tilt table test</td>
<td></td>
</tr>
<tr>
<td>9. Hachul et al.</td>
<td>42</td>
<td>22.8 ± 8</td>
<td>13M/29F</td>
<td>Recurrent syncope</td>
<td>- 30 min tilt toleration of 33/40 pts (82%) remain free of S during follow-up of 18 ± 6.9 months no syncope</td>
<td></td>
</tr>
<tr>
<td>10. Gurevitz et al.</td>
<td>33</td>
<td>18</td>
<td>22M</td>
<td>Clinical diagnosis of syncope</td>
<td>- 3 months daily tilt training or no</td>
<td></td>
</tr>
<tr>
<td>11. Foglia-Manzillo et al.</td>
<td>35</td>
<td>40 ± 19</td>
<td>25M/43F</td>
<td>Recurrent syncope</td>
<td>- 3 weeks TT - 30 min/day - 6 days/week</td>
<td></td>
</tr>
<tr>
<td>12. Ector et al.</td>
<td>222</td>
<td>33.4 ± 21.2</td>
<td>107M/115F</td>
<td>Recurrent syncope</td>
<td>- 221/222 pts negative TT - 1 pt persistent S - S disappeared during daily life</td>
<td></td>
</tr>
</tbody>
</table>

C: controls, M = male, F = female, N = number, pos = positive, pts = patients, pat N = number of patients, TT = tilt test, TTr = tilt training; S = syncope.

rence19-24. For a review of these studies see table 3. A beneficial effect of tilt training on syncope disappearance has been observed in the majority of the studies. Only 2 studies22,23 showed that tilt training therapy was not superior to other lifestyle modifications such as increase in fluid and salt intake. However, in these 2 studies, a very low compliance to therapy was reported. In the study of Gurevitz et al.22 the patients were advised to perform daily tilt training, but the compliance to therapy had reduced to 53% after 2 months. Similarly, in the study of Foglia-Manzillo et al.23 only 34% of the patients performed all programmed sessions. This review shows that tilt training is very effective in patients who perform the prescribed tilt training therapy. The patients should be highly motivated and should continue the tilt training programme. Furthermore this also stresses the importance of regular outpatient visits and control tilt tests in this patient group. Moreover, in the study of Foglia-Manzillo23 the effect of tilt training was evaluated by performing...
nitroglycerin-potentiated tilt tests. It should be realised, however, that the specificity of the tilt test is considerably reduced for tilt tests with pharmacological provocation.26

In the ESC guidelines on syncope,3 the panel considers tilt training as a feasible treatment only for highly motivated patients. Because until now multiple randomised clinical trials are not yet available on this therapy, the panel ranks the usefulness and efficacy of this new therapy as level B (= data derived from single randomised clinical studies). However, a difficulty with many studies on tilt training therapy is the lack of formal control groups in the majority of the studies. Only 3 of the published studies21,23,24 had a control group to compare the effects of tilt training in patients with neurally mediated syncope. In the field of neurally mediated syncope, large prospective randomised controlled studies are difficult to undertake, due to the variable frequency of spontaneous symptoms and long periods of remission. Moreover, to be included in a study a positive tilt test is required at the initial assessment. The poor reproducibility of the tilt test (table 1) will occur upon tilt testing, the cerebral perfusion will be impaired and syncope will develop.27 This mechanism may explain the mixed type and cardioinhibitory type of syncope. In patients with the vasodepressor type of syncope, an excessive vasodilatation may induce a decrease in systemic arterial blood pressure with consequently critical impairment of the cerebral blood flow. This paradoxical response of the circulation to gravitational stress with low total peripheral resistance will lead to a fall in systemic blood pressure. If the decrease of total peripheral resistance, with excessive vasodilatation is the main result of a combined sympathetic withdrawal and excessive vagal tone, a vasodepressor type of syncope will occur.28 This review shows that although tilt testing is not able to identify the fixed pathological cause of syncope, it definitely uncovers an exaggerated susceptibility of the autonomous reflexes during gravitational stress.29 In this issue of the journal a heart rate variability study by Gajek et al.30 on 24 patients with vasovagal syncope, who were treated by a programme of tilt training, tries to explain some of the pathophysiological adaptive mechanisms during a tilt training programme. They found after a programme of 1 to 3 months of tilt training, a decreased sympathetic activation during the tilt test which may be sufficient to offset the trigger of the excess autonomic nervous activity which leads to neurally mediated syncope. We believe that the daily performance of a tilt training programme in patients with neurally mediated syncope may have a conditioning effect on these abnormal autonomic cardiovascular orthostatic reflexes.

**Physiological mechanisms of therapeutic effect of tilt training**

A general outline of the possible mechanisms explaining why tilt training improves the reduced orthostatic tolerance is difficult, since different types of neurally mediated syncope exist. The exact mechanism of the therapeutic effect of tilt training remains unknown. In patients with neurally mediated syncope orthostatic intolerance may be the result of an abnormal or excessive autonomic reflex activity. In individuals with impaired orthostatic tolerance, the assumption of a vertical position leads to a large gravitational shift of the central blood volume to the venous capacitance vessels. This leads to a reduced cardiac output and stroke volume with activation of the arterial baroreflexes and a reflex increase of the sympathetic nervous system. An excessive increase in heart rate is frequently observed in the period preceding syncope. This increase in heart rate is not accompanied by an increase in stroke volume as during physical exercise. Therefore, if venous return is not enhanced as during physical exercise, this increased heart rate response may lead to an insufficient increase in cardiac output. However, if the excessive vagal tone which develops during impending syncope will further decrease heart rate to critically low values, such as below 50 or even 40 beats per minute - as frequently observed during tilt testing - the cerebral perfusion will be impaired and syncope will develop. It should be realised, however, that the excessive vagal tone which develops during impending syncope will further decrease heart rate to critically low values, such as below 50 or even 40 beats per minute - as frequently observed during tilt testing - the cerebral perfusion will be impaired and syncope will develop. This mechanism may explain the mixed type and cardioinhibitory type of syncope. In patients with the vasodepressor type of syncope, an excessive vasodilatation may induce a decrease in systemic arterial blood pressure with consequently critical impairment of the cerebral blood flow. This paradoxical response of the circulation to gravitational stress with low total peripheral resistance will lead to a fall in systemic blood pressure. If the decrease of total peripheral resistance, with excessive vasodilatation is the main result of a combined sympathetic withdrawal and excessive vagal tone, a vasodepressor type of syncope will occur. This review shows that although tilt testing is not able to identify the fixed pathological cause of syncope, it definitely uncovers an exaggerated susceptibility of the autonomous reflexes during gravitational stress. In this issue of the journal a heart rate variability study by Gajek et al. on 24 patients with vasovagal syncope, who were treated by a programme of tilt training, tries to explain some of the pathophysiological adaptive mechanisms during a tilt training programme. They found after a programme of 1 to 3 months of tilt training, a decreased sympathetic activation during the tilt test which may be sufficient to offset the trigger of the excess autonomic nervous activity which leads to neurally mediated syncope. We believe that the daily performance of a tilt training programme in patients with neurally mediated syncope may have a conditioning effect on these abnormal autonomic cardiovascular orthostatic reflexes.

**Patient selection**

The therapeutic results obtained by tilt training are applicable to true neurally mediated syncope and not to all autonomic disorders and/or autonomic failure such as in other groups of dysautonomia, postural hypotension-induced disorders with peripheral neuropathy as can occur in diabetes and malignant disease. Also patients with psychiatric disorders may not respond to tilt training.

**Limitations of clinical studies**

The majority of the studies on tilt training were prospective, non randomised, single-centre studies.
without the inclusion of a formal control group\textsuperscript{6,16,20,22,42}. Neuromally mediated syncope is a fluctuating disorder with long periods of remission. Sometimes a trigger is required to induce syncope (e.g. dehydration, long standing, emotional stimuli, etc.). Moreover, to be included in a study a head-up tilt test is required to confirm the diagnosis. However, in our experience and also in earlier studies a poor reproducibility has been reported on repeated tilt testing (see table 1). This suggests some conditioning of the baroreflex activity. For all these reasons the first tilt test which is required to confirm the diagnosis of syncope is already an intervention. Therefore a comparison with a formal control group is difficult and has also major drawbacks.

It should be realised that the effect of tilt training as a beneficial therapy has only been shown for patients with neurally mediated syncope. For other types of loss of consciousness, due to autonomic failure, this therapy has not shown to be efficacious. Conditioning of the autonomic orthostatic reflexes is probably not feasible in this type of pathology. In these patients we recommend sleeping with the bed in a head-up tilt position. This has shown to reduce orthostatic hypotension during walking in earlier studies by MacLean and Allen\textsuperscript{43}. In selected cases we also obtained beneficial effects from this therapy (sleeping in head-up tilt position) in patients with severe autonomic failure.

Acknowledgment

The authors thank Mrs Ann Fort for assistance in the preparation of the manuscript.

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