Differential blood pressure behaviour as an early predictor of the outcome of the Head-Up Tilt-Table test among patients with neurally-mediated syncope

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Abstract
Neurocardiogenic syncope (NCS) is diagnosed by means of a head-up tilt table tests (HUTT). These are prolonged even knowing early outcome predictors.

Methods: We carried out a study among patients that were engaged in a syncope study protocol. We performed HUTT among all of them and compared the basal arterial pressure with the arterial pressure immediately after a 70° tilting.

Results: We performed 365 HUTT studies. Systolic blood pressure (SBP) raised 3.6% in the control group, 2.4% among patients with a negative test, meanwhile, patients with a positive HUTT showed a 1.7% decrease (p=0.04) in the same measurement. Diastolic BP (DBP) increased 5.4% in the control group, 17.5% among negative HUTT patients and 7.6% among patients with positive test (p=0.002). We found an odds ratio of 2.7 (95%CI: 1.3 – 5.8) for positive test when the combination of SBP decrease and mild DBP increase was present, according to the percentage of change and an OR of 13.6 (95% CI:1.8-101.5) for the combination of symptoms and haemodynamic changes.

Conclusions:
The combination of systolic BP reduction and diastolic BP mild elevation or decrease at the end of a 70° tilting, was associated with significantly higher chances of having a positive HUTT. When combined with nausea, diaphoresis and dizziness, this OR was higher.

INTRODUCTION
Neurally mediated syncope is a commonly diagnosed entity that results in an important number of visits to emergency departments. Its origin is related to a mild form of disautonomy with diverse changes in heart rate (HR) and blood pressure (BP).

The pathophysiology of syncope is somehow elusive, although the most widely accepted theory suggests a sympathetic-parasympathetic imbalance with sequential releases of adrenaline and acetylcholine that lead to a sudden drop of blood pressure, heart rate or both. Among certain varieties of syncope, these disautonomic reflexes are regional and are associated to localized vasomotor changes, such as the cerebral origin syncope.

The main diagnostic method is currently the Head-Up tilt Table Test (HUTT). This test has several limitations, and although it has been our main diagnostic tool, it is far from being a gold standard. Among its drawbacks, such as a low specificity, there is also the fact that it is a time-consuming test and it is also stressing for the patients. This fact has prompted the research for early physiologic test results' predictors.

Perhaps among the earliest predictors is the clinical presentation itself, which can be highly suggestive of a vagal origin of the patient's symptoms. In a previous work we reported that the combination of nausea, dizziness and diaphoresis is associated to a 25-fold increase in the risk of having a positive HUTT. Other studies have shown that early heart rate accelerations are another indicator of the
test's result, although there are recently published works that have reported contradictory results. In an attempt to add early prognostic data, we decided to evaluate if there was a distinct behaviour of BP immediately at the end of the tilting phase among patients with positive and negative HUTT tests. We hypothesized that the absence of changes in the BP measurements or a lowering of both systolic and/or diastolic recording would predict a positive HUTT test since those findings could be related to an abnormal autonomic response to tilt.

METHODS

We carried out a cross-sectional study with consecutive patients who were being studied because of syncope with a HUTT in a public academic hospital. The patients were candidates for a HUTT according to the criteria that we have previously described. The HUTT protocol is performed in a two stage mode if the first non-pharmacologic stage was negative, according to the 2004 European Syncope Guidelines, the patients were selected by two cardiologists for a HUTT according to their history. The day the test was performed, the patient had a 6 hr fast, and a 0.9% saline intravenous (I.V.) solution was installed on the antecubital fossa at a drip rate of 30 ml/hour to keep vein permeable. With a foot board and a thoracic restraint, the patient had a basal rest period of ten minutes in a dorsal decubitus position. At the end of the rest period, the patient’s heart rate and blood pressure were recorded by an ECG heart rate monitor and a non-invasive sphygmomanometer respectively. Subsequently, the patient was tilted to a 70° angle and the same measurements were again performed. The time elapsed from decubitus to 70° tilting is 10 seconds. The patient was kept in this position for twenty minutes or less if symptoms occurred earlier. If the passive tilting phase reached 20 minutes without symptoms, the patient was again positioned in decubitus and a 5 mg isosorbide dinitrate sublingual dose was administered. Ten minutes after the medication was given, we obtained new BP and HR values: If the HR had risen at least 20% compared to the basal value, the patient was again positioned at a 70° angle for an additional 20 minutes or until the occurrence of symptoms. The diagnostic criteria we used are the same described in previous works.

We included in the analysis the basal manual BP measurements and the BP registered immediately after finishing the tilting to a 70° angle, which we defined as minute 0 of the HUTT. The changes in BP were classified as categorical variables. That is, a decrease in systolic BP was considered as a positive finding and an increase in such a recording was considered a negative one. On the other hand, a decrease in diastolic BP or an increase equal or less of 7% of the diastolic BP basal record was considered as a positive finding, if DBP increased 7% or more compared to the basal DBP record, it was considered negative. The combination of SBP decrease and mild DBP elevation or decrease was also analyzed as a distinct categorical variable. All measurements were compared according to the result of the test: Positive against negatives and according to the positive test's “subtype” against negative results. A control group was composed of 14 patients without history of syncope and a negative HUTT test. Early heart rate (HR) changes were also analysed (basal against minute 0 HR) in order to correlate them with early BP changes. We finally analysed the presence in the patient's clinical history of a symptomatic triad composed of nausea, diaphoresis and dizziness associated to syncope (described in a previous work) to early BP changes in order to evaluate the combination's ability to predict a positive test result.

Continuous variables were expressed as mean standard deviation, and categorical variables were expressed as percentage. The differences between the basal and minute 0 measurements were analyzed by paired Student’s T test. To assess differences between groups we used analysis of variance. Logistic regression analysis was performed to calculate the risk of a positive HUTT result according to the combination of systolic BP (SBP) lowering and mild elevation of diastolic BP (DBP) or SBP and DBP decrease.

RESULTS

During a period of four years we have performed 365 HUTT tests. Two-hundred-fifty-two of them are female (69%) with a mean age of 42.09 18.9 years.

Forty-nine tests were negative (13.4%) and the remaining were positive. Among the later, 155 were of the vas depressor kind (42.5%), 131 were mixed (35.9%) and 23 were cardionhibitory (6.3%). We also found 5 cases of Postural Orthostatic Tachycardia Syndrome (POTS), two patients with autonomic failure and one psychogenic syncope that were excluded from further analysis. Sixty-three patients (17.3%) had a positive test result in the passive tilt phase, and 302 (82.7%) received pharmacologic stimulation.

The main basal SBP was 114.6 18.8 mmHg for the whole
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The mean basal heart rate was 66.6 for the positive test group, 65.06 for the negative test group and 66.7 for the control group (p=0.7). Upon completing tilting, the positive test group showed a HR increase to 75.6 beats per minute (bpm), the negative test to 74.1 and the control group to 74.6 (p=0.8).

We also found differences according to the test’s result regarding syncope subtypes, which are shown in table 2.

Figure 1
Table 1: Main results according to diagnostic group

<table>
<thead>
<tr>
<th>Diagnostic Group</th>
<th>Baseline</th>
<th>Mean ± SD</th>
<th>P Value</th>
<th>N (%)</th>
<th>Negative test</th>
<th>Mean ± SD</th>
<th>P Value</th>
<th>N (%)</th>
<th>Positive test</th>
<th>Mean ± SD</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>37.5 ± 11.3</td>
<td>NS</td>
<td>41 ± 17.5</td>
<td>NS</td>
<td>43 ± 19.4</td>
<td>NS</td>
<td>43 ± 19.4</td>
<td>NS</td>
<td>43 ± 19.4</td>
<td>NS</td>
<td>43 ± 19.4</td>
</tr>
<tr>
<td>Gender</td>
<td>Fem 6 (67.1%)</td>
<td>NS</td>
<td>Fem 27 (77.1%)</td>
<td>NS</td>
<td>Fem 216 (66.8%)</td>
<td>NS</td>
<td>Fem 216 (66.8%)</td>
<td>NS</td>
<td>Fem 216 (66.8%)</td>
<td>NS</td>
<td>Fem 216 (66.8%)</td>
</tr>
<tr>
<td>Basal HR (bpm)</td>
<td>65.5 ± 12.1</td>
<td>NS</td>
<td>65.6 ± 12.1</td>
<td>NS</td>
<td>65.9 ± 12.2</td>
<td>NS</td>
<td>65.9 ± 12.2</td>
<td>NS</td>
<td>65.9 ± 12.2</td>
<td>NS</td>
<td>65.9 ± 12.2</td>
</tr>
<tr>
<td>Minute 0 HR (bpm)</td>
<td>74.6 ± 17.3</td>
<td>NS</td>
<td>74.1 ± 17.6</td>
<td>NS</td>
<td>75.5 ± 15.06</td>
<td>NS</td>
<td>75.5 ± 15.06</td>
<td>NS</td>
<td>75.5 ± 15.06</td>
<td>NS</td>
<td>75.5 ± 15.06</td>
</tr>
<tr>
<td>Basal DBP (mmHg)</td>
<td>100.4 ± 11.2</td>
<td>NS</td>
<td>112 ± 18.00</td>
<td>NS</td>
<td>115.2 ± 19.1</td>
<td>NS</td>
<td>115.2 ± 19.1</td>
<td>NS</td>
<td>115.2 ± 19.1</td>
<td>NS</td>
<td>115.2 ± 19.1</td>
</tr>
<tr>
<td>Minute 0 DBP (mmHg)</td>
<td>113.5 ± 16.4</td>
<td>NS</td>
<td>114.17 ± 26.4</td>
<td>NS</td>
<td>112.9 ± 29.4</td>
<td>NS</td>
<td>112.9 ± 29.4</td>
<td>NS</td>
<td>112.9 ± 29.4</td>
<td>NS</td>
<td>112.9 ± 29.4</td>
</tr>
</tbody>
</table>
| Systolic BP showed a 3.6% mean elevation in the control group, a 2.7% mean rise among patients with a negative test and a reduction of 1.7% (p=0.04) among those with a positive one. Diastolic BP raised a 5.4% in the control group (p=0.4), 14.1% in patients with a negative test (p=0.002) and 7.6% in the one’s with a positive test (p=0.07) when compared to basal measurement. An increase in DBP of 7.6% or less was defined for analysis purposes as “mild increase”, compared to the 14% increase or “significant increase” in the negative test group. The mean BP measurements are compared in Figure 1.

Figure 2
Figure 1: Systolic and diastolic blood pressure changes according to diagnostic group.

The combinations of SBP decrease and mild DBP increase or SBP decrease and DBP decrease were considered as the same sort of haemodynamic behaviour. This combination was associated with a 2.7 odds ratio (OR) of having a positive HUTT result (CI 95%:1.3-5.8, p=0.007).

Regarding the presence of a specific clinical triad in the patient's history previously described, 273 patients had such symptoms (diaphoresis, nausea and dizziness), 42 did not have them, and the information was missing in 51. The number of patients with symptoms and positive test was 122, and the number of patients without symptoms and a negative test was 34.

The logistic regression analysis showed that the presence of symptoms was associated to an OR=3.9 (CI 95%:1.7-9.1, p=0.001) for a positive test. The combination of symptoms and BP changes showed an OR=13.6 (CI 95%: 1.8–101.5, p=0.01) for a positive HUTT (table 3).
Figure 4

Table 3: Logistic Regression Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coeff.</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Triad</td>
<td>1.3</td>
<td>3.0</td>
<td>1.7 – 9.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Combination of BP changes (SBP lowering and mild DBP elevation or SBP and DBP decrease)</td>
<td>1.01</td>
<td>2.7</td>
<td>1.3 – 5.8</td>
<td>0.007</td>
</tr>
<tr>
<td>Combination of Clinical triad and BP changes</td>
<td>2.6</td>
<td>13.6</td>
<td>1.8 – 101.5</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Correctly classified cases: 86.6%
CI: Confidence interval
SBP: Systolic blood pressure
DBP: Diastolic blood pressure
Sig: Significance

Changes in blood pressure showed a sensitivity of 47%, specificity 67%, a positive predictive value of 90% and a negative predictive value of 16%. When changes in blood pressure were combined with the triad of symptom, sensitivity was 21%, specificity 97.8%, positive predictive value was 98% and negative predictive value 15.6%.

DISCUSSION

Neurally mediated syncope (NMS) is considered as a mild form of disautonomic disease that has been thoroughly studied, but there are still some doubts about its pathophysiological origin, since several theories have inconsistencies. The observation of clinical phenomena and their correlation with physiopathological events could ease their understanding and possibly make the related diagnostic tests more efficient.

As we previously mentioned, early prognostic markers for the HUTT's result have been described. All of them are linked to an early sympathetic activity or stimulation. This sympathetic activity is supposed to trigger an abrupt parasympathetic response such as the Bezold-Jarish reflex that would be responsible for the changes in BP and heart rate. The measurements of catecholamines in peripheral blood have shown non-consistent results, so it should be necessary to look for more subtle regional changes in the catecholamine's concentrations. Previous studies showed that early heart rate changes (HR) could be a useful tool to predict the outcome of the test, but even if there is a trend that relates higher HR to positive tests, contradictory results lessen this parameter's usefulness. Our actual results do not contribute to define a relevant role of very early (minute 0) HR changes in the prediction of the test's outcome.

The physiological changes clinically detected without invasive methods, such as heart rate and BP could imply complex events or different behaviours among different groups of patients. A tendency for a differential behaviour of BP at the early stages of HUTT suggests that the patients with positive HUTT have a distinct neurohumoral profile. Our findings suggest that an increase in peripheral resistance correlates with the significant elevation of DBP, especially in negative HUTT's patients, possibly related to some sort of sympathetic “over-activity”. The absence of SBP changes could be explained considering that these negative-HUTT patients do not have very dramatic changes in intrathoracic volume since their compensatory mechanisms are very active. The control group shows a distinct behaviour regarding BP that shows that an intact autonomic regulation does not induce abrupt changes but perhaps rapidly progressing one's, that do not allow large intrathoracic volume changes during tilting. Patients with history of syncope but with a negative HUTT might have a more reactive sympathetic drive than those patients with positive HUTT, establishing perhaps different stages of the same disease, as was proposed by Grubb for the different haemodynamic classifications that we are currently using. Among patients with positive HUTT, the SBP drops slightly and DBP shows a mild elevation, suggesting a blunted sympathetic response, possibly due to an increased parasympathetic activity. An alternative explanation is the presence of a differential peripheral vascular response (increased venous compliance, perhaps) depending on local catecholamine concentrations, such as in Postural Orthostatic Tachycardia Syndrome (POTS) patients.

Although there is a very small number of patients with the POTS in our series, they show a distinct BP behaviour even when compared to the rest of patients with neurocardiogenic syncope. The explanation regarding local catecholamine concentrations goes in concordance with previous findings regarding the differential behaviour of HR. Patients with positive HUTT usually have higher early raises in HR, a finding that supports an increase in peripheral resistance by means of increased sympathetic stimulation, although we were unable to relate changes in BP to very early changes in HR. The reduction in SBP could be related to a proportionally greater loss of intrathoracic volume as a consequence of a deficient autonomic regulation.
Previous studies have evaluated the BP changes as predictors of the outcome of the test, but their measurements are longer and more complex. Therefore, our results concern a simple measure and are immediate to the beginning of the test. The ability to predict the result of the test is also enhanced by the patient’s history, as the positive predictive value calculation shows. On the other hand, even if sensitivity is low, specificity is high enough. It is important to recall that history’s relevance in the clinical assessment of syncpe patients cannot be overemphasized.

We have a high rate of positive HUTT that has been consistently reproduced among our patients, perhaps the explanation for such a phenomenon depends on the re-examination that the HUTT performing cardiologist does on every case prior to the test. The diagnostic criteria we use are the ones mentioned in the current guidelines, although some patients that meet them do not show a complete reproduction of symptoms; we classify them as having a positive HUTT test. Regarding the low figure of cardioinhibitory syncope patients, we had also found a tendency that confirms an early observation in our laboratory, that is, patients with this variety of NMS are usually young men. This tendency continues to be present since young males are a small percentage of our studied population (6.4% of men under 25 years of age, among them, 36% had cardioinhibitory NMS syncope).

Our study’s main limitation is the size of the population, and thus, thorough comparisons between NCS groups are not precise, although they reflect interesting tendencies that could deserve further evaluation. This could also explain the low sensitivity and positive predictive value.

Considering the pathophysiological complexity of neurally mediated syncope and the lack of a gold standard, a better option to achieve lesser HUTT delays could be the implementation of a good history establishing the vagal origin of symptoms, and support it with the observation of early changes in BP.

CONCLUSION

The association of a mild raise in DBP with a drop in SBP or a drop in both SBP and DBP correlates with an increased risk of having a positive HUTT. Blood pressure apparently has a differential behaviour among patients with neurally mediated syncope with positive HUTT. Although such behaviour could be correlated to specific pathophysiological changes, its interpretation remains complicated.

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