Changes in the transthoracic impedance signal predict the outcome of a 70° head-up tilt test

Elisabeth BELLARD*, Jacques-Olivier FORTRAT*, Daniel SCHANG†, Jean-Marc DUPUIS‡, Jacques VICTOR‡ and Georges LEFTHERIOTIS*

*Laboratoire de Physiologie - UPRÉS EA 2170, Faculté de Médecine, rue haute de Reculee, 49035 Angers cedex, France,
†Ecole Supérieure d’Electronique de l’Ouest, 4 rue Merlet de la Boulaye, P.O. Box 926, 49009 Angers cedex 01, France,
and ‡Département de Cardiologie, Centre Hospitalier d’Angers, rue Larrey, 49033 Angers cedex, France

ABSTRACT

We determined whether early changes in central haemodynamics, as determined by transthoracic impedance, induced by a 70° head-up tilt (HUT) test could predict syncope. Heart rate, arterial blood pressure and central haemodynamics [pre-ejection period and rapid left ventricular ejection time (T1), slow ejection time (T2) and dZ/dtmax (where Z is thoracic impedance), assessed by the transthoracic impedance technique], were recorded during supine rest and during a 45 min 70° HUT test in 68 patients (40 ± 2 years) with a history of unexplained recurrent syncope. We found that 38 patients (42 ± 3 years) had a symptomatic outcome to 70° HUT (fainters) and 30 (39 ± 2 years) had a negative outcome (non-fainters). When measured between 5 and 10 min of 70° HUT, T2 had increased significantly only in the fainters, and a change in T2 of > 40 ms from baseline predicted a positive outcome with a sensitivity of 68% and a specificity of 70%. During supine rest prior to 70° HUT, the fainters exhibited a shorter T2 than non-fainters (183 ± 10 compared with 233 ± 14 ms; P < 0.01), and a T2 of < 199 ms predicted a positive outcome to 70° HUT with a sensitivity of 68% and a specificity of 63%. Incorporation of the changes that occurred from rest to 70° HUT in other haemodynamic variables (heart rate > 11 beats/min, systolic pressure < 2 mmHg, diastolic pressure < 7 mmHg and pulse pressure < 3 mmHg) increased the specificity to 97% and the positive predictive value to 93%. Thus transthoracic impedance could detect differences in central haemodynamics between fainters and non-fainters during supine rest and during the initial period of 70° HUT with a consistent sensitivity and specificity when combined with peripheral haemodynamic variables.

INTRODUCTION

Neurally mediated syncope, characterized by sudden hypotension associated with bradycardia [1], is a frequent cause of hospital admissions. Diagnosis is currently based on the reproduction of symptoms, in combination with hypotension and bradycardia, induced by a 45 min 60–70° head-up tilt (HUT) test [2]. Since syncope is thought to result from excessive activation of the cardiac mechanoreceptors in response to the emptying of the heart (the Bezold–Jarisch reflex) [3], continuous recording of central haemodynamics could be helpful in improving the interpretation of HUT outcome. However, the haemodynamic variables usually collected during HUT remain limited to ECG and arterial pressure [4–6] because of technical and ethical limitations. Few studies have attempted to record cardiac haemodynamics during HUT in order to detect early abnormalities. Recordings of stroke volume by impedance cardiography during 80° HUT showed no significant difference between patients and controls [7]. Similarly, echocardiographic recordings of cardiac volume failed to confirm a

Key words: predictive indexes, syncope, transthoracic impedance.
Abbreviations: CI, contractility index; HUT, head-up tilt; RI, resistance index; Z, thoracic impedance.
Correspondence: Professor G. Leftheriotis (e-mail geleftheriotis@chu-angers.fr).
progressive cardiac emptying prior to syncope [7]. In contrast, distinct haemodynamic profiles, as assessed by transthoracic impedance variables, were reported in control subjects and patients with a positive response to passive HUT and pharmacologically sensitized HUT [8]. That study, however, reported substantial variability among subjects. Because of these discrepancies, and the limited amount of data, no firm conclusion could be drawn from these previous studies.

The purpose of the present study was to determine in a large group of patients whether early changes in central haemodynamic variables, derived from transthoracic impedance signals recorded at rest and early in a 70° HUT test could predict the outcome of a 70° HUT test in patients with recurrent unexplained syncope.

**METHODS**

**Patients**

A total of 71 patients (35 males/36 females; body weight 65 ± 2 kg; height 168 ± 1 cm), with a mean age of 41 ± 2 years (range 18–73 years), were referred to our laboratory for evaluation of unexplained recurrent syncope. All patients had experienced syncopal and/or near-syncopal episodes at least twice within the last 3 months. Neurological illness, structural heart disease, metabolic disease and psychiatric illness were excluded on the basis of physical examination and additional investigations (blood tests, ambulatory 12-lead ECG, transthoracic echocardiography, endocavitary investigations and carotid sonography) where necessary. The patients were included in the study only when results from all tests were negative. Medication that could interfere with the test (diuretics, vasodilators, β-blockers) was discontinued for a period corresponding to at least five half-lives before the study. The patients were asked to eat a light meal and refrained from alcohol, tobacco and caffeine within the 2 h prior to testing. The local ethics committee approved the protocol, and all patients gave written informed consent to participate.

**Recorded variables**

Cardiac haemodynamics were assessed using a computerized thoracic impedance technique (Physioflow; Manatech Bomedical, Macheren, France). Thoracic impedance (Z) was recorded via four ECG-type electrodes, with two electrodes placed on the neck and two over the xiphoid process (Ag/AgCl electrodes, 40493E; Agilent Technologies, Böblingen, Germany). Two additional electrodes were placed to record lead I derivation for impedance signal gating. Heart rate was monitored continuously using a 12-lead surface ECG (MAC vu; Marquette, Milwaukee, WI, U.S.A.). Instantaneous arterial blood pressure was recorded by digital servo plethysmography (Finapres 2300; Ohmeda, Englewood Cliffs, NJ, U.S.A.) with the cuff placed on the left arm. An estimate of the amount of blood pooled into the legs was determined by the relative changes in calf circumference, expressed in ml/100 ml and measured using a mercury-in-silastic strain gauge (Periven; Janssen Instruments). The gauge was placed on the right calf, and the heel was elevated 10 cm from the tilt table to prevent contact of the calf with the tilt table, but without exceeding the level of the heart. The calf gauge bridge amplifier was equilibrated to set the resting value before the measurements. All signals were digitized (sample rate 500 Hz) and recorded continuously by a computerized data acquisition system (Labview 5.1; National Instruments, Austin, TX, U.S.A.) for off-line analysis.

**HUT table test protocol**

The experiment was performed between 14.00 and 17.00 hours in a quiet, temperature-controlled room (24–25 °C) with dimmed lighting. The subjects wore their underwear, and were placed in supine position on a motorized tilt table (FGCK; Couverchel, Draveil, France) equipped with a footboard. Knee and abdominal straps prevented falling. After 10 min in the supine position, the patients were subjected to HUT at an angle of 70° for a maximum period of 45 min [2]. If symptoms occurred, the subjects were returned to the supine position and the test was ended. The table tilt test was considered to have a positive outcome if syncopal (loss of consciousness and postural tone) or near-syncopal (pallor, nausea, dizziness, light-headedness, sensation of imminent syncope) symptoms occurred and were associated with hypotension (fall in systolic blood pressure of > 60% from baseline value or an absolute value of < 80 mmHg) alone or in combination with bradycardia (fall in heart rate of > 30% from baseline value, an absolute value of < 40 beats/min or asystole [6]). According to the outcome of the HUT test, the patients were divided into two groups: non-fainters (negative response to a 45 min 70° HUT test) and fainters (positive response to 70° HUT).

The reproducibility of the transthoracic impedance measurements was determined in a subgroup of 26 patients in whom a second 70° HUT test was performed 10 ± 3 days after the first. The effect of a mild central hypovolaemia on the transthoracic impedance variables was tested in another subgroup of patients (n = 26).
Their venous return was reduced by inflating large congestive pneumatic thigh cuffs at a sub-diastolic pressure for 15 min while the patients were subjected to a 10° HUT test.

Data analysis
All signals were analysed off-line using specific software programmed with Labview 5.1 (National Instruments). RR intervals were determined from the ECG, and recordings with excessive artifacts (i.e. ectopic heartbeats, patient movement, etc.) were excluded from the analysis after a visual check by a trained operator (E.B.). Systolic, diastolic, mean and pulse arterial blood pressures were determined beat-by-beat. Pulse pressure was calculated as systolic minus diastolic blood pressure. For all of these variables, the beat-by-beat series was averaged over the last 5 min of horizontal supine rest, between the 5th and 10th min of 70° HUT, and during the last 5 min of 70° HUT. Spontaneous baroreflex sensitivity was calculated from systolic blood pressure and heart rate time series using the sequence technique [9] on the same periods.

Impedance waveform analysis
Transthoracic impedance waveforms were analysed using a specific algorithm developed for the study. The algorithm calculated a mean waveform of the first derivative (dZ/dt) of the thoracic impedance signal for each measurement period of the protocol (i.e. supine rest, 5–10 min of 70° HUT and final 5 min of HUT). One beat was selected on a visual basis by the experimenter (E.B.) as a reference template for the dZ/dt waveform [10]. Each subsequent beat of the selected 5-min period was re-sampled at the same length as the dZ/dt reference template, and the mean squared error between the template and the dZ/dt waveform of each beat was computed (Figure 1). A dZ/dt waveform was excluded from the analysis if its mean squared error exceeded the mean +1 S.D. of all mean squared errors of the selected 5-min period. The dZ/dt values of the remaining beats were compared again (using the same algorithm) to the reference template to provide a mean dZ/dt waveform with a reduced number of artifacts [10]. These averaged dZ/dt waveforms were computed for each patient and for each selected period of the study. The average dZ/dt value was also normalized at a mean RR interval to eliminate the effects of individual differences in heart rate [11].

The analysis algorithm detected two specific events on the averaged dZ/dt waveform: time interval $T_1$ (in ms) between the Q wave of the ECG and dZ/dtmax, and time interval $T_2$ (in ms) between dZ/dtmax and the nadir following dZ/dtmax. We also measured the amplitude of the peak deflection of dZ/dt (in $\Omega \cdot s^{-1}$). Since dZ/dtmax is considered to be proportional to the left ventricular stroke volume [12–15], a contractility index (CI; Heather index) was determined as (dZ/dtmax)/$T_1$ (in $10^{-3} \times \Omega \cdot s^{-2}$) [16]. The ratio of mean blood pressure/(dZ/dtmax, heart rate) was taken as an index of vascular resistance [resistance index (RI), in mmHg $\cdot \Omega^{-1} \cdot s^2$].

The position of the nadir following dZ/dtmax and the end of the left ventricular ejection time indicated by the second heart sound were determined in five healthy volunteers. Simultaneous recording of the apex phonocardiogram (EMT 25C; Siemens-Elema AB) and the transthoracic impedance signal (Figure 2) were performed at rest and during the last 5 min of a 10-min 70° HUT.

Statistical analysis
All data are expressed as means ± S.E.M. If the data were normally distributed, between-group comparisons were performed using Student’s t test for unpaired data; if not, the Mann–Whitney U test was used. Within-group statistical comparisons between supine rest and the last 5 min of thigh cuff inflation were performed using
Student’s t test for paired data. Comparisons between values during supine rest and the initial and final 70° HUT periods were made by means of repeated-measures ANOVA (SPSS software version 9.0; SPSS, Chicago, IL, U.S.A.). When appropriate, post hoc t tests for paired data with the Bonferroni correction were performed. Reproducibility was determined using Pearson’s test and the coefficient of variation. The cut-off point for a positive 70° HUT was determined, using receiver-operating curves [17], as the optimal value that maximizes sensitivity and specificity, i.e. minimizes the quantity [(1 – sensitivity)² + (1 – specificity)²]¹/². For all statistics, a P value of < 0.05 was considered significant.

RESULTS

Three patients were excluded from the analysis because too many artifacts were present on their impedance signal recordings (due to numerous unwanted movements or coughing). Of the 68 remaining patients, 38 (age 42 ± 3 years; 21 males) had a positive outcome to the initial 70° HUT (fainters; mean time to symptoms 19 ± 2 min), and 30 (age 39 ± 2 years; 14 males) had a negative outcome (non-fainters).

Haemodynamic parameters during supine rest

During supine rest, \( T_2 \) was significantly shorter in fainters compared with non-fainters (\( P < 0.01 \)) (Table 1), whereas all other variables were not statistically different between fainters and non-fainters (Table 2). A \( T_2 \) value of < 199 ms during supine rest predicted a positive outcome to the 70° HUT test with a sensitivity of 68%, a specificity of 63%, a positive predictive value of 63% and a negative predictive value of 68%.

![Figure 2](image)

**Figure 2** Averaged waveforms of the first derivative (dZ/dt) of the thoracic impedance signal and of the phonocardiogram on a cardiac cycle for a period of 5 min in one patient. \( T_1 \), \( T_2 \) and \( dZ/dt_{max} \) are indicated on the mean dZ/dt waveform.

### Table 1  Thoracic impedance variables assessed in response to 70° HUT

<table>
<thead>
<tr>
<th>Variable</th>
<th>Supine rest</th>
<th>70° HUT 5–10 min</th>
<th>Syncope or end of HUT</th>
</tr>
</thead>
<tbody>
<tr>
<td>( T_1 ) (ms)</td>
<td>Non-fainters: 200 ± 5, Fainters: 292 ± 9***</td>
<td>324 ± 9***</td>
<td>324 ± 10***</td>
</tr>
<tr>
<td>( T_2 ) (ms)</td>
<td>Non-fainters: 260 ± 6, Fainters: 299 ± 11***</td>
<td>324 ± 10***</td>
<td>324 ± 10***</td>
</tr>
<tr>
<td>( dZ/dt_{max} ) (( \Omega \cdot s^{-1} ))</td>
<td>Non-fainters: 542 ± 37, Fainters: 510 ± 29</td>
<td>496 ± 33</td>
<td>405 ± 24†</td>
</tr>
<tr>
<td>( 10^{-3} \times CI ) (( \Omega \cdot s^{-2} ))</td>
<td>Non-fainters: 2.76 ± 0.20, Fainters: 1.76 ± 0.11***</td>
<td>1.56 ± 0.12***</td>
<td>1.30 ± 0.10***</td>
</tr>
<tr>
<td>( RI ) (mmHg · ( \Omega^{-1} \cdot s^{-1} ))</td>
<td>Non-fainters: 0.184 ± 0.019, Fainters: 0.172 ± 0.015</td>
<td>0.176 ± 0.022</td>
<td>0.178 ± 0.014</td>
</tr>
</tbody>
</table>

**Effects of central hypovolaemia**

Inflation of thigh cuffs in a subgroup of patients (\( n = 26 \)) increased calf plethysmographic volume significantly in both groups (non-fainters, 3.77 ± 0.30%; fainters, 3.58 ± 0.47%; no significant difference between groups). \( T_1 \) increased, while \( dZ/dt_{max} \) and CI decreased, in both groups. \( T_2 \) decreased and RI increased significantly only in the non-fainters (Table 3).

**Effects of 70° HUT**

Between 5 and 10 min of the 70° HUT period, haemodynamic variables increased significantly in both groups, except that systolic pressure did not increase significantly in the fainters. Baroreflex sensitivity decreased significantly in both groups (Table 2). Changes in heart rate of > 11 beats/min, in systolic pressure of < 2 mmHg, in diastolic pressure of < 7 mmHg and in pulse pressure of < −3 mmHg predicted a positive outcome to the HUT test with a sensitivity of 62%, 84%, 81% and 70% respectively, and with a specificity of 40%, 50%, 37% and 60% respectively. Values of \( dZ/dt_{max} \) and RI did not change significantly during 70° HUT, whereas CI decreased significantly in both groups. \( T_3 \) increased significantly only in the fainters (Table 1). A change in \( T_2 \) of > 40 ms from baseline predicted a positive outcome to the HUT test with a sensitivity of 68%, a specificity of 70%, and positive and negative predictive values of 68% and 70% respectively. A combination of at least five out of six criteria within the 5–10 min period of 70° HUT (\( T_3 \) at rest < 199 ms; change in \( T_2 > 40 \) ms; change in...
Table 2  Haemodynamic variables assessed in response to 70° HUT
Data are means ± S.E.M. Calf volume changes are expressed in comparison with values during supine rest. Statistical differences: *P < 0.05, **P < 0.01, ***P < 0.001 for 70° HUT compared with supine rest; ††P < 0.01 for fainters compared with non-fainters.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Supine rest</th>
<th>5–10 min</th>
<th>Syncope or end of HUT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-fainters</td>
<td>127 ± 2</td>
<td>136 ± 5</td>
<td>134 ± 4</td>
</tr>
<tr>
<td>Fainters</td>
<td>133 ± 4</td>
<td>131 ± 4</td>
<td>118 ± 4††</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-fainters</td>
<td>71 ± 2</td>
<td>86 ± 3††</td>
<td>89 ± 3***</td>
</tr>
<tr>
<td>Fainters</td>
<td>76 ± 2</td>
<td>86 ± 3‡</td>
<td>79 ± 3††</td>
</tr>
<tr>
<td>Mean blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-fainters</td>
<td>89 ± 2</td>
<td>101 ± 3**</td>
<td>104 ± 3***</td>
</tr>
<tr>
<td>Fainters</td>
<td>93 ± 2</td>
<td>99 ± 3*</td>
<td>90 ± 3††</td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-fainters</td>
<td>56 ± 3</td>
<td>51 ± 3‡</td>
<td>45 ± 3***</td>
</tr>
<tr>
<td>Fainters</td>
<td>57 ± 3</td>
<td>45 ± 3**</td>
<td>39 ± 2***</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-fainters</td>
<td>67 ± 2</td>
<td>83 ± 3***</td>
<td>90 ± 3***</td>
</tr>
<tr>
<td>Fainters</td>
<td>68 ± 2</td>
<td>87 ± 3**</td>
<td>89 ± 3***</td>
</tr>
<tr>
<td>Calf volume change (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-fainters</td>
<td>–</td>
<td>3.31 ± 0.24</td>
<td>4.68 ± 0.39</td>
</tr>
<tr>
<td>Fainters</td>
<td>–</td>
<td>3.23 ± 0.26</td>
<td>3.85 ± 0.24</td>
</tr>
<tr>
<td>Baroreflex sensitivity (ms · mmHg⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-fainters</td>
<td>15.0 ± 2.1</td>
<td>6.5 ± 1.0‡‡</td>
<td>4.7 ± 0.5***</td>
</tr>
<tr>
<td>Fainters</td>
<td>13.0 ± 1.2</td>
<td>5.8 ± 0.7**</td>
<td>5.6 ± 0.8***</td>
</tr>
</tbody>
</table>

heart rate > 11 beats/min; change in systolic pressure < 2 mmHg, change in diastolic pressure < 7 mmHg and change in pulse pressure < −3 mmHg) had a sensitivity of 50%, a specificity of 97%, and negative and positive predictive values of 67% and 93% respectively. In fainters, all haemodynamic variables changed significantly during the 5 min that preceded syncope, except for diastolic pressure and mean pressure. T₁ had increased significantly from the value at supine rest in the non-fainters when measured during the last 5 min of the 70° HUT test. However, this increase in T₁ compared with baseline in the non-fainters was smaller than that in the fainters prior to syncope (39 ± 16 and 88 ± 13 ms respectively; P < 0.05).

Reproducibility of impedance measurements
For the 26 patients who underwent repeated 70° HUT, T₁ (r = 0.615, P < 0.01), dZ/dtmax (r = 0.808, P < 0.01) and CI (r = 0.777, P < 0.01), but not T₂, were significantly correlated between the rest periods preceding the first and the second 70° HUT tests. Values obtained between 5 and 10 min of 70° HUT showed correlations between the two tests for T₁ (r = 0.817; P < 0.01), T₂ (r = 0.628; P < 0.01), dZ/dtmax (r = 0.818, P < 0.01) and CI (r = 0.770, P < 0.01). The coefficients of variation for T₁, T₂, dZ/dtmax and CI were 6.1%, 14.7%, 14.2% and 15.8% respectively at rest, and 7.2%, 14.6%, 13.0% and 14.5% respectively during 70° HUT.

DISCUSSION
The novel finding of the present study is that specific changes in central haemodynamic parameters during the first 10 min of a 70° HUT test in patients were able to predict a positive outcome to the test (i.e. syncope or near-syncope). Significant differences between fainters and non-fainters were observed during horizontal supine rest prior to the HUT test. Central haemodynamics were determined using the transthoracic impedance technique, with characteristic variables extracted from the first derivative of the impedance waveform. The maximum of the first positive deflection (i.e. the dZ/dtmax peak) occurs simultaneously with peak aortic flow velocity [13,18], and its amplitude is correlated with left ventricular stroke volume [12–15]. Prior to syncope, the decrease in dZ/dtmax in fainters became obvious in comparison with non-fainters (Table 1), suggesting a higher rate of decrease in stroke volume and thus in ventricular filling volume in the former group, as described in a previous study [19]. These findings are in accordance with echocardiographic studies [20,21], but not with a previous study using transthoracic impedance, in which the decrease in stroke volume was similar between fainters and control subjects and a further decrease was not observed in fainters before the onset of syncope [7].

Table 3 Haemodynamic and thoracic impedance variables assessed in response to thigh cuff inflation (n = 26)
Data are means ± S.E.M. Statistical differences: *P < 0.05, **P < 0.01, ***P < 0.001 for thigh cuff inflation compared with supine rest.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Supine rest</th>
<th>Thigh cuff inflation</th>
</tr>
</thead>
<tbody>
<tr>
<td>T₁ (ms)</td>
<td>196 ± 7</td>
<td>217 ± 8***</td>
</tr>
<tr>
<td>Fainters</td>
<td>184 ± 10</td>
<td>202 ± 9**</td>
</tr>
<tr>
<td>T₂ (ms)</td>
<td>259 ± 12</td>
<td>201 ± 23*</td>
</tr>
<tr>
<td>Fainters</td>
<td>216 ± 13</td>
<td>165 ± 13</td>
</tr>
<tr>
<td>dZ/dtmax (L² · s⁻¹)</td>
<td>620 ± 43</td>
<td>549 ± 36**</td>
</tr>
<tr>
<td>Fainters</td>
<td>555 ± 67</td>
<td>492 ± 58*</td>
</tr>
<tr>
<td>10⁻³ × CI (L² · s⁻³)</td>
<td>3.24 ± 0.26</td>
<td>2.59 ± 0.20***</td>
</tr>
<tr>
<td>Fainters</td>
<td>3.01 ± 0.32</td>
<td>2.47 ± 0.29*</td>
</tr>
<tr>
<td>R (mmHg · L² · s⁻³)</td>
<td>0.147 ± 0.017</td>
<td>0.172 ± 0.023*</td>
</tr>
<tr>
<td>Fainters</td>
<td>0.178 ± 0.025</td>
<td>0.202 ± 0.028</td>
</tr>
</tbody>
</table>
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A decrease in the ventricular filling volume prior to syncope may be due to excessive pooling [22] of the blood in the subdiaphragmatic capacitance vascular beds, and may trigger the Bezold–Jarisch reflex [3]. The time interval between the Q wave of the ECG and the $dZ/dt_{\text{max}}$ peak (i.e. $T_z$) was chosen to reflect the pre-ejection and rapid left ventricular ejection time [13,18]. An increase in the pre-ejection time is influenced in part by changes in venous return [23,24], as demonstrated by the increase in $T_z$ when venous return is decreased by congestive thigh cuffs [25] or during HUT. In the present study, the increase in $T_z$ was similar in the two groups during the initial 5–10 min of HUT, and probably resulted from a similar decrease in venous return induced by fluid shifting towards the lower body, as indicated by the lack of significant differences in calf volume changes.

Excessive cardiac contractility can trigger syncope via exaggerated activation of the myocardial mechano-receptors [26]. During 70° HUT and prior to syncope, CI decreased significantly compared with that during supine rest in both groups. This finding is not in agreement with the hypothesis of increased contractility prior to syncope [27], but is in accordance with echocardiographic studies, in which contractility was shown to decline continuously during HUT in fainters [19,21]. Furthermore, peak endocardial acceleration, an intracardiac index of ventricular contractility, indicated that tilt-induced syncope could occur at both low and high levels of left ventricular contractility [28].

The nadir of the first negative deflection of $dZ/dt$ has been reported to occur synchronously with the aortic component of the second heart sound [29] and with aortic valve closure as measured by echocardiography [14]. Therefore the time interval ($T_z$) between the peak aortic flow velocity (i.e. $dZ/dt_{\text{max}}$) and aortic valve closure (i.e. the nadir) would theoretically represent the late part of systole (i.e. the slow left ventricular ejection time, $T_z$). Unlike in non-fainters, $T_z$ increased significantly in the fainters between supine rest and the initial 5–10 min of 70° HUT, but did not change further prior to syncope. In contrast, $T_z$ had increased significantly in the non-fainters only at the end of the 70° HUT test period (i.e. not after 5–10 min). The reasons for these changes are not clear. $T_z$ was not influenced by the occurrence of syncope; however, the value obtained during horizontal supine rest could predict patients with a positive outcome to the 70° HUT test.

A shorter $T_z$ at rest could result from several factors, including changes in cardiac pre-load, after-load, contractility and heart rate [23,30]. During supine rest the influence of pre-load should be negligible, since there is only a small venous pressure gradient between the peripheral vasculature and the heart. Similarly, there were no significant differences at rest in stroke volume or myocardial contractility between the fainters and non-fainters. Normalizing $T_z$ by a mean RR interval in all patients [11] eliminated the possible influence of differences in heart rate within and between patients. Possible differences in after-load resulting from peripheral resistance could be discounted, in view of insignificant differences at rest. This leaves the possibility of lower arterial compliance in the fainters during horizontal supine rest, as observed by others [31]. This difference disappeared during 70° HUT, so that $T_z$ reached similar values in the fainters and non-fainters, suggesting an increase in arterial compliance in the fainters. This pre-existing alteration in arterial compliance, as estimated from $T_z$ during supine rest, could contribute to the genesis of syncope [26] by altering cardiac baroreflex sensitivity [32]. However, no significant differences in baroreflex sensitivity were found between fainters and non-fainters during either supine rest or HUT.

The end point of the slow left ventricular ejection time ($T_z$) that we determined in the control group of five healthy volunteers by thoracic impedance ($dZ/dt$ nadir time: $318 \pm 30$ ms) and by phonocardiogram (second heart sound time: $516 \pm 49$ ms) showed a significant difference at rest between the two techniques ($P < 0.01$). This difference suggests that $T_z$ determined by thoracic impedance is greatly influenced by other factors, such as the reflective waves travelling along the aorta that could have significantly altered the impedance waveform [33]. These differences disappeared during 70° HUT ($dZ/dt$ nadir time, $509 \pm 39$ ms; second heart sound time, $581 \pm 35$ ms; not significant). Therefore it is likely that the shorter $T_z$ measured during supine rest in fainters resulted from unmeasured haemodynamic factors that are a function of vascular compliance and which appear to correlate with a positive outcome of the HUT test. The prediction of a positive outcome based on $T_z$ measured during supine rest or on the change in $T_z$ between rest and 70° HUT had limited sensitivity (both 68%) and specificity (63% and 70% respectively). However, combination with the changes from rest to 70° HUT in the other haemodynamic variables (heart rate > 11 beats/min, systolic pressure < 2 mmHg, diastolic pressure < 7 mmHg and pulse pressure < $-3$ mmHg) increased the specificity to 97% and the positive predictive value to 93%.

The transthoracic impedance technique is suitable for the continuous and non-invasive recording of central haemodynamics. However, the use of this method has several limitations. Determination of the nadir of $dZ/dt$ is difficult, as exemplified in studies with extremely ill patients and during exercise [18], and this could explain inaccurate determinations of stroke volume and thus cardiac output [33–36]. At rest, the reproducibility test for our transthoracic impedance variables performed in a subgroup of the studied population did not show a significant correlation in $T_z$ values between the first and
second 70° HUT tests, due to the variability of the studied pathology. However, the coefficient of variation was within the acceptable range for physiological variables. Although the quality of the impedance signal is highly dependent on the instrumentation and on patient co-operation, the signal could be collected reliably in more than 96% of our patients. The absence of a healthy control group had a limited impact on our findings, since our goal was to determine the variables that could predict the outcome to a 70° HUT test in a susceptible population. However, the lack of a control group probably contributed to the relatively small differences between the groups.

In conclusion, transthoracic impedance recorded at rest and during a 70° HUT test was able to detect early specific changes in central haemodynamics in patients with a positive outcome to 70° HUT. These findings are based on the absolute resting values and the range of changes in \( T_R \), although the mechanistic origin of these changes remains to be elucidated. The ability to predict the outcome of 70° HUT on the basis of \( T_S \) values alone was limited, but could be greatly improved when other peripheral haemodynamic variables were added. These results contribute to a new approach to the early detection of a positive outcome, and thus could help to reduce the duration of 70° HUT as a clinical test.

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