Failure of propranolol to prevent tilt-evoked systemic vasodilatation, adrenaline release and neurocardiogenic syncope

Basil A. ELDADAH*, Sandra L. PECHNIK*, Courtney S. HOLMES*, Jeffrey P. MOAK†, Ahmed M. SALEEM* and David S. GOLDSTEIN*

*Clinical Neurocardiology Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD 20892-1620, U.S.A., and †Department of Cardiology, Children’s National Medical Center, Washington DC 20010-2970, U.S.A.

ABSTRACT

In patients with neurocardiogenic syncope, head-up tilt often evokes acute loss of consciousness accompanied by vasodilatation, increased plasma adrenaline and systemic hypotension. Since hypotension increases adrenaline levels and adrenaline can produce skeletal muscle vasodilatation by activating β₂ receptors, adrenaline might induce a positive feedback loop precipitating circulatory collapse. We hypothesized that propranolol, a non-selective β-blocker, would prevent adrenaline-induced vasodilatation and thereby prevent syncope. Eight subjects with recurrent neurocardiogenic syncope and previously documented tilt-induced syncope with elevated plasma adrenaline levels participated in the present study. Subjects underwent tilt table testing after receiving oral propranolol or placebo in a double-blind randomized crossover fashion. Haemodynamic and neurochemical variables were measured using intra-arterial monitoring, impedance cardiography, arterial blood sampling and tracer kinetics of simultaneously infused [3H]noradrenaline and [3H]adrenaline. The occurrence of tilt-induced neurally mediated hypotension and syncope, duration of tilt tolerance, extent of the decrease in SVRI (systemic vascular resistance index) and magnitude of plasma adrenaline increases did not differ between the propranolol and placebo treatment phases. SVRI was inversely associated with fractional increase in plasma adrenaline during both phases. One subject did not faint when on propranolol; this subject’s response is discussed in the context of central effects of propranolol. In this small, but tightly controlled, study, propranolol did not prevent tilt-induced vasodilatation, syncope or elevated plasma adrenaline.

INTRODUCTION

Neurocardiogenic syncope (also known as vasovagal syncope, neurally mediated hypotension and the common faint) is the most common cause of acute reversible loss of consciousness [1,2]. Neurocardiogenic syncope has been classified into three types: cardioinhibitory, vasodepressor and mixed, based on changes in heart rate at the time of syncope during upright tilt table testing [3]. All three types feature acute large-magnitude decreases in blood pressure leading to loss of consciousness.

Mechanisms underlying the hypotension attending neurocardiogenic syncope have been considered for several decades [4]. It is now clear that vagally induced bradycardia cannot account completely for the decreased blood pressure. Neither atropine nor cardiac pacing consistently prevents hypotension or syncope [5,6]. Moreover, syncope can occur in heart transplant...
Table 1 Characteristics of the subjects

<table>
<thead>
<tr>
<th>Subject number</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>Phase</th>
<th>Dose</th>
<th>Syncope type</th>
<th>Placebo</th>
<th>Propranolol</th>
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<tr>
<td>#1</td>
<td>45</td>
<td>Female</td>
<td>76</td>
<td>163</td>
<td>A</td>
<td>20 mg every 5 h</td>
<td>3, 1</td>
<td>36</td>
<td>16</td>
</tr>
<tr>
<td>#2</td>
<td>36</td>
<td>Female</td>
<td>64</td>
<td>168</td>
<td>B</td>
<td>40 mg every 6 h</td>
<td>1, 3</td>
<td>31</td>
<td>16</td>
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<tr>
<td>#3</td>
<td>63</td>
<td>Female</td>
<td>73</td>
<td>157</td>
<td>B</td>
<td>60 mg every 6 h</td>
<td>3, 1</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>#4</td>
<td>31</td>
<td>Female</td>
<td>60</td>
<td>165</td>
<td>A</td>
<td>20 mg every 6 h</td>
<td>?, none</td>
<td>2</td>
<td>40</td>
</tr>
<tr>
<td>#5</td>
<td>18</td>
<td>Male</td>
<td>70</td>
<td>177</td>
<td>A</td>
<td>20 mg every 8 h</td>
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<td>19</td>
<td>18</td>
</tr>
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<td>#6</td>
<td>46</td>
<td>Female</td>
<td>54</td>
<td>166</td>
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<td>40 mg every 8 h</td>
<td>1, 3</td>
<td>13</td>
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<td>#7</td>
<td>50</td>
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<td>92</td>
<td>162</td>
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<td>60 mg every 6 h</td>
<td>3, 1</td>
<td>13</td>
<td>32</td>
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<tr>
<td>#8</td>
<td>25</td>
<td>Female</td>
<td>52</td>
<td>157</td>
<td>B</td>
<td>40 mg every 6 h</td>
<td>2B, 2B</td>
<td>19</td>
<td>28</td>
</tr>
</tbody>
</table>

*Syncope type is according to the modified VASIS (Vasovagal Syncope International Study) classification [3] as follows: 1, mixed; 2B cardioinhibition with asystole; 3, vasodepressor. Types are listed for placebo and propranolol phases respectively.

recipients in whom cardiac innervation has been severed [7].

Systemic vasodilatation without a compensatory increase in cardiac output may explain the hypotension attending syncopal reactions in at least some patients [8–12]. Such vasodilatation probably accounted for the observation in 1793 by the English surgeon John Hunter that the colour of venous blood from a syncopal patient was ‘a fine scarlet’ [13], as skeletal muscle vasodilatation probably arterialized the patient’s venous blood. Several mechanisms probably underlie vasodilatation, including withdrawal of sympathetic nervous system outflow [14–17] and high circulating adrenaline levels [18–22].

Adrenaline stimulates vasodilatory β2 receptors on skeletal muscle vascular cells, and inhibition of adrenaline at these receptors might prevent hypotension and syncope. Consistent with this theory, a meta-analysis of 24 trials of β-blockers for neurocardiogenic syncope showed that non-selective blockers were more effective than β1-selective blockers in preventing syncope [23]. Conversely, hypotension is well known to increase circulating adrenaline levels [24]. Therefore inhibition of adrenaline might prevent a neurocirculatory positive feedback loop, where adrenaline would cause vasodilatation and hypotension that, in turn, would lead to further adrenaline release. In the present study, we tested the hypothesis that oral administration of the non-selective β-blocker propranolol would attenuate decreases in systemic vascular resistance and thereby preserve systemic blood pressure and prevent tilt-induced neurocardiogenic syncope.

METHODS

Study subjects

The subjects were eight patients with a history of recurrent syncope and previously documented tilt-induced neurocardiogenic syncope associated with elevated plasma adrenaline levels. Prior evaluation excluded primary cardiac or neurological causes of syncope. Sym pathetic neurocirculatory failure was excluded by the absence of persistent consistent orthostatic hypotension and by a normal pattern of beat-to-beat blood pressure associated with performance of the Valsalva manoeuvre [25]. Table 1 lists other clinical characteristics.

Caffeine-containing beverages, cigarettes and alcohol were not allowed during the study. All potentially interfering medication, such as non-investigational β-blockers, midodrine, and certain antidepressants, were tapered and discontinued prior to entering the study; all other medication continued without changes in dosing.

This study was approved by the Institutional Review Board of the National Institute of Neurological Disorders and Stroke and was in accordance with the principles outlined in the Declaration of Helsinki. Each subject gave informed written consent prior to participation.

Study protocol

Subjects first underwent a dose-finding period with escalating doses of propranolol administered orally. Supine blood pressure and heart rate were measured prior to, and 2 h after, each dose of propranolol. Dosage was increased after each 24 h period to allow enough time to achieve steady-state plasma concentrations (mean half-life of propranolol in plasma is 3–4 h [26]). The target dosing schedule was determined by a 10% decrease in supine resting heart rate from baseline (Table 1).

After a washout period lasting at least 2 days, subjects began receiving propranolol or placebo in randomized double-blind fashion at the target dosing schedule. Administration continued for 72 h. At 1–2 h after the last dose, subjects underwent upright tilt table testing (described below). After a washout period of at least 2 days, subjects received propranolol or placebo in a crossover fashion, and administration of the second treatment continued for another 72 h at the target dosing schedule. At 1–2 h after the last dose, subjects underwent a second tilt table test.
**Tilt table testing**

Subjects attended the clinical laboratory in the morning after fasting for \(\geq 6\) h. Peripheral intravascular catheters were placed in a brachial or radial artery and two antecubital veins. Baseline blood was sampled through both arterial and intravenous catheters at least 15 min after catheter insertion for analysis of catecholamine concentrations. In seven subjects, \(L\)-[ring-2,5,6-\(^3\)H]noradrenaline and \(L\)-[\(N\)-methyl-\(^3\)H]adrenaline (PerkinElmer) were infused intravenously at approx. 0.4 \(\mu\)Ci/min for the duration of testing to calculate catecholamine clearance and spillover [27]. In the present study, spillover calculated from arterial plasma values is termed ‘total body spillover’.

Subjects were tilted upright to 70° on a motorized tilt table (Colin Medical Instruments) for 40 min or until syncope or pre-syncope developed. Blood pressure was measured continuously through the arterial catheter. Arterial and venous blood was sampled approximately every 4 min and at the time of syncope or pre-syncope. ECG and heart rate were recorded through an analogue-to-digital converter (PowerLab 16SP; ADInstruments). Forearm vascular resistance was measured by strain gauge plethysmography (Hokanson). Stroke volume was continuously measured non-invasively by impedance cardiography (CardioDynamics) [28], which has been validated previously [29]. Systemic vascular resistance was calculated according to the formula: (MAP – central venous pressure)/(stroke volume × heart rate), where MAP is mean arterial pressure. Central venous pressure was assumed to be 6 mmHg. SVRI (systemic vascular resistance index) was calculated by multiplying systemic vascular resistance by body surface area [30].

**Study variables**

Study variables included haemodynamic measurements, such as blood pressure, heart rate, stroke volume and forearm blood flow, and neurochemical measurements, including plasma adrenaline and noradrenaline concentrations. Derived variables included cardiac output, SVRI, forearm vascular resistance, catecholamine clearance and catecholamine spillover. Assays of plasma catecholamine concentrations were performed by HPLC with electrochemical detection after batch alumina extraction [31]. \(^3\)H-labelled catecholamines were quantified by assaying \(^3\)H content in the chromatographic fractions corresponding to the retention time with noradrenaline and adrenaline standards [32,33]. Noradrenaline and adrenaline spillover values were estimated according to methods described previously [32].

**Data analysis and statistics**

Each subject was his/her own control in this crossover study. Haemodynamic and neurochemical data were analysed in terms of mean absolute values (Table 2) and as mean normalized data (Figures 1, 2 and 4). Normalization was performed for each parameter by expressing each subject’s results during upright tilt in either phase as a percentage of that subject’s results at baseline on placebo. Values are means \(\pm\) S.E.M. Statistical significance was assessed using paired two-tailed Student’s t tests.

**RESULTS**

Of the eight subjects, seven had tilt-induced syncope or pre-syncope during both propranolol and placebo treatments. One subject (#4) had a negative tilt table test when on propranolol (Table 1). Across all subjects, the mean duration of tolerated tilt did not differ between placebo and propranolol phases (19 \(\pm\) 4 min compared with 21 \(\pm\) 4 min respectively).

MAP, SVRI and stroke volume were significantly lower at the end of tilt table testing than at baseline (Figure 1 and Table 2). The extents of these decreases were similar between the placebo and propranolol phases.

Cardiac output at end-tilt on propranolol was a smaller percentage of the baseline value than that on placebo (63 \(\pm\) 10 % compared with 81 \(\pm\) 13 % respectively; \(P = 0.03\)). Baseline and peak heart rates were significantly lower on propranolol (Figure 1 and Table 2).

Plasma adrenaline and noradrenaline increased significantly at end-tilt compared with baseline in both phases (Figure 2 and Table 2). There was a trend towards a greater increase in adrenaline during propranolol compared with placebo, which was statistically significant when only subjects with positive tilt tests were considered (3317 \(\pm\) 624 % compared with 1332 \(\pm\) 472 % respectively; \(P = 0.04\)).

With the exception of subject #4 (discussed in more detail below), there was an inverse relationship between SVRI and fractional change in plasma adrenaline during both placebo and propranolol phases (Figure 3).

Baseline clearance from arterial plasma of both adrenaline and noradrenaline significantly decreased during propranolol (Figure 4, upper panels). There were further significant decreases in clearance at end-tilt on propranolol (Figure 4, upper panels). During placebo treatment, clearance remained stable during and at the end of upright tilting (Figure 4, upper panels).

Total body spillovers of adrenaline and noradrenaline had an upward trend from baseline during upright tilt in both phases (Figure 4, lower panels). Noradrenaline increases were statistically significant while upright in both placebo and propranolol treatments.

Patient #4 was the only one who did not develop syncope during upright tilt while taking propranolol (Table 1). Her MAP was maintained during upright tilt, heart rate increased by 33 beats/min, SVRI and respiratory rate were stable, and there was a steady increase in arterial plasma adrenaline from 0.45 nmol/l at baseline to 1.44 nmol/l at end-tilt. In contrast,
while taking placebo, her heart rate increased by 90 beats/min and respiratory rate increased by more than 70 breaths/min during the first minute of tilting. She became unresponsive after 2 min; however, her blood pressure remained stable and SVRI exceeded the baseline value. Despite the absence of hypotension, her plasma adrenaline increased from 0.42 to 12.43 nmol/l.

Patient #8 had asystole leading rapidly to syncope during both treatment phases (Table 1). While she was on placebo, asystole lasted 20 s, whereas, on propranolol, asystole lasted 44 s. During the screening tilt table test, this subject did not have bradycardia or asystole.

Forearm blood flow was measured by strain gauge plethysmography. Because of artifactual effects of subject movement and rapid changes in directly recorded intra-arterial pressure at the time of syncope, compared with the relatively long time required for blood flow measurements, we did not have sufficient confidence in the calculated values of forearm vascular resistance to report them in the present study.

**DISCUSSION**

In the present study, oral propranolol had no effect on systemic vasodilatation, hypotension, plasma adrenaline levels or duration of tolerance to upright tilt in patients with previously documented tilt-induced neurocardiogenic syncope with elevated plasma adrenaline. The findings did not support the hypothesis that propranolol would attenuate tilt-induced acute vasodilatation and thereby prevent syncope in such patients.

SVRI fell significantly at the time of syncope (Figure 1B), consistent with a vasodepressor mechanism, and SVRI was inversely associated with a fractional change in plasma adrenaline concentration (Figure 3). These observations would be consistent with the notion that circulating adrenaline causes vasodilatation; however, in seven of the eight patients, inhibition of \( \beta \)-receptors failed to attenuate either tilt-induced vasodilatation or increased circulating adrenaline (Figures 1B, 2A and 3B). The vasodilatation attending neurocardiogenic syncope in this setting appears to reflect processes independent of vasodilatory \( \beta_2 \) receptors. Studies have evaluated other mediators of vascular tone in syncope, including sympathoneural outflow, vasopressin, endothelin-1, angiotensin II and nitric oxide [4]. None of these mediators, however, can account completely for the vasodilatation observed in syncope.

Withdrawal of sympathoneural outflow leads to decreased vascular resistance, and propranolol would not be expected to prevent sympathoinhibition. Indeed, in healthy volunteers, propranolol does not affect peroneal nerve sympathetic outflow [34]; however, it is not known whether \( \beta \)-receptor inhibition acts similarly in patients with neurocardiogenic syncope. Furthermore, as there...
Table 2 Summary of the haemodynamic and neurochemical data from tilt table tests during placebo or propranolol phases

Data are means ± S.E.M. at baseline and end-tilt respectively, except for heart rate data, which are listed for baseline, peak while upright and at end-tilt respectively. * P < 0.05 and ** P < 0.01 compared with baseline within phase; † † P < 0.01 and † † † P < 0.001 compared with placebo at the respective time point.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Peak</th>
<th>End-tilt</th>
<th>Propranolol</th>
<th>Peak</th>
<th>End-tilt</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mmHg)</td>
<td>101 ± 3</td>
<td>67 ± 9**</td>
<td>97 ± 5</td>
<td>62 ± 6**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate (min⁻¹)</td>
<td>76 ± 5</td>
<td>97 ± 23</td>
<td>75 ± 4</td>
<td>58 ± 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>73 ± 4</td>
<td>47 ± 9**</td>
<td>64 ± 6*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVRI (dyn · s⁻¹ · cm⁻⁵/m²)</td>
<td>2580 ± 176</td>
<td>1524 ± 319*</td>
<td>2771 ± 122</td>
<td>1838 ± 323**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac output (litres/min)</td>
<td>5.5 ± 0.4</td>
<td>5.3 ± 0.8</td>
<td>4.7 ± 0.4†††</td>
<td>4.0 ± 0.3*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noradrenaline (nmol/l)</td>
<td>1.31 ± 0.22</td>
<td>4.54 ± 1.43*</td>
<td>5.16 ± 1.82</td>
<td>5.16 ± 1.82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adrenaline (nmol/l)</td>
<td>0.28 ± 0.07</td>
<td>4.45 ± 1.53*</td>
<td>9.80 ± 5.45</td>
<td>9.80 ± 5.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noradrenaline spillover (µmol/min)</td>
<td>3.10 ± 0.95</td>
<td>8.50 ± 3.40</td>
<td>6.60 ± 3.24</td>
<td>6.60 ± 3.24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adrenaline spillover (µmol/min)</td>
<td>0.76 ± 0.32</td>
<td>14.54 ± 7.85</td>
<td>16.71 ± 11.36</td>
<td>16.71 ± 11.36</td>
<td></td>
<td></td>
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<tr>
<td>Noradrenaline clearance (ml/min)</td>
<td>2018 ± 307</td>
<td>1644 ± 161</td>
<td>1868 ± 142</td>
<td>1868 ± 142</td>
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<td></td>
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<tr>
<td>Adrenaline clearance (ml/min)</td>
<td>2244 ± 356</td>
<td>2409 ± 615</td>
<td>2131 ± 192</td>
<td>2131 ± 192</td>
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<td></td>
</tr>
</tbody>
</table>

It may be argued that the failure of propranolol to prevent systemic vasodilatation resulted from sufficiently high plasma adrenaline levels overcoming β₂-receptor inhibition by propranolol. Plasma adrenaline concentrations were indeed remarkably elevated at the time of syncope. In addition, increases in adrenaline levels had a higher trend in subjects on propranolol than on placebo, a relationship that was statistically significant when only subjects who had positive tilt table tests were considered. Nevertheless, the affinity of propranolol at β₂-receptors is over 900 times that of adrenaline [37]. Furthermore, we retrieved frozen plasma samples from five of the eight subjects in the present study and had the samples assayed for propranolol levels. Propranolol ranged from 80–1100 nmol/l, which is several times the mean peak concentration of adrenaline in the present study. Moreover, across all subjects, heart rate, cardiac output and catecholamine clearance were significantly reduced in subjects on propranolol (Figures 1 and 4). As such, propranolol in this study was probably sufficient to confer significant β-antagonism.

The present findings are consistent with those in a prospective randomized crossover study by Flevari et al. [38], who evaluated the non-selective β-blockers propranolol and nadolol. The results are inconsistent, however, with other studies showing a relatively greater benefit of non-selective β-blockers over selective β-blockers [23]. Propranolol is known to reduce plasma clearance of [³H]noradrenaline [39] and unlabelled adrenaline [40]. The present results fit with this literature, as propranolol administration was associated with an approx. 20% decrease in clearance of both catecholamines from arterial outflow and changes in circulating noradrenaline levels [35], changes in arterial plasma noradrenaline may not be an accurate reflection of sympathetic nerve activity, particularly in such a dynamic condition as syncope [36].
plasma at baseline (Figure 4). Previous studies have not evaluated arterial plasma clearance of [3H]adrenaline with propranolol. In the present study, propranolol reduced the clearance of adrenaline from arterial plasma at baseline, and a further reduction in clearance occurred during upright tilting.

The pattern of haemodynamic, respiratory and neurochemical changes in the single subject who responded to propranolol (#4) differed from those of the other subjects. On placebo, she lost consciousness within approx. 2 min after tilting. At this time, she had remarkable tachycardia without hypotension or systemic vasodilatation. SVRI did not decrease, despite a large increase in plasma adrenaline (Figure 3A). In addition, her respiratory rate increased dramatically from 12 breaths/min at baseline to 85 breaths/min at the end of tilt. In line with Grubb’s concept of ‘cerebral syncope’ [41], hyperventilation may have led to hypocapnia, cerebrovascular constriction and loss of consciousness without neurally mediated hypotension. Cerebral blood flow was not measured in the present study, however, so other mechanisms besides cerebral syncope may have played a role. For example, this subject may have had pseudosyncope, an apparent loss of consciousness, without transient global cerebral hypoperfusion that is typically associated with underlying psychiatric disease [42]. Indeed, subject #4 had been treated previously for depression; however, although consistent with pseudosyncope, a history of depression certainly does not rule out true syncope. In fact, psychiatric disorders are common in subjects with tilt-induced vasovagal syncope [43].

We speculate whether the apparent efficacy of propranolol in subject #4 reflected a central effect of the drug. Propranolol is useful in the treatment of essential tremor [44] and performance anxiety [45,46], suggesting that propranolol may act through other mechanisms in addition to its peripheral β-receptor inhibition effects. These mechanisms may include central anti-adrenergic effects or a general placebo effect. Although the present study was a double-blinded one, it was difficult to blind subjects completely to the central effects of propranolol, particularly in situations of presumed anxiety such as a tilt table test. Furthermore, in the case of subject #4, the negative tilt table test during the first phase might have led her to conclude that placebo would be the second phase. We did not record formally whether subjects in the present study correctly guessed the propranolol and placebo phases; however, our retrospective impression is that several, although not all, did identify both phases accurately.

**Study limitations and future directions**

The present study has several limitations. First, there were too few subjects studied to make valid generalizations about the clinical efficacy of non-selective β-receptor inhibition in neurocardiogenic syncope. Secondly, the extent of β-receptor inhibition was not formally tested; therefore it would be incorrect to assert that the present study tested the effects of β-blockade. Thirdly, it is difficult to blind subjects adequately on propranolol because of its central effects.

It remains possible that propranolol may benefit a subgroup of patients, such as subject #4 in the present study. Future studies should evaluate the extent to which propranolol is helpful in such subjects and the degree to which central compared with peripheral effects of the drug are involved. Caution should be exercised in future studies though, because prolonged asystole can occur with syncope in patients treated with β-blockers, as with subject #8 in the present study and reported by...
Data for each subject were normalized to the baseline placebo condition of that subject. Values are means ± S.E.M. at supine rest (baseline), at 3–5 min prior to end-tilt (tilt) and at end-tilt. *P < 0.05 and **P < 0.01 compared with baseline within phase, †P < 0.05 and ††P < 0.01 compared with placebo at the respective time point.

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