Carotid-Cardiac Baroreflex Function Does Not Influence Blood Pressure Regulation during Head-Up Tilt in Humans

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Abstract: The influence of the carotid-cardiac baroreflex on blood pressure regulation was evaluated during supine rest and 40° head-up tilt (HUT) in 9 healthy young subjects with and without full cardiac vagal blockade. The carotid baroreflex responsiveness, or maximal gain (GMAX), was assessed from the beat-to-beat changes in heart rate (HR) and mean arterial pressure (MAP) by the variable neck position and suction technique ranging in pressure from +40 to ~80 Torr, with and without glycopyrrolate (12.0 ± 1.0 µg/kg body weight; mean ± SE). In the supine position, glycopyrrolate increased the HR to 91 ± 3 bpm, from 54 ± 3; MAP to 89 ± 2 mmHg, from 76 ± 2; and cardiac output to 6.8 ± 0.3 l/min, from 4.9 ± 0.3 (P < 0.05). The GMAX of the carotid baroreflex control of HR was reduced to −0.06 ± 0.01 bpm mmHg−1, from −0.30 ± 0.02 (P < 0.05) with no significant effect on the GMAX of the carotid baroreflex control of MAP. During HUT the carotid baroreflex control of MAP was unchanged, though the GMAX of the carotid baroreflex control of HR was increased (P < 0.05). During HUT, central blood volume, assessed by electrical thoracic admittance, and total vascular conductance were decreased with and without glycopyrrolate. Furthermore, glycopyrrolate reduced GMAX of the carotid baroreflex control of HR during HUT (P < 0.05) with no significant effect on GMAX of the carotid baroreflex control of MAP. These data suggest that during supine rest and HUT-induced decreases in central blood volume, the carotid baroreflex control of HR is mediated primarily via parasympathetic activity. Furthermore, the maintenance of arterial blood pressure during postural stress is primarily mediated by arterial and cardiopulmonary reflex regulation of sympathetic activity and its effects on the systemic vasculature.

Key words: arterial blood pressure, baroreflex, central blood volume, heart rate.

The balance between the contribution of the carotid-cardiac and the carotid-vasomotor reflex arms to the carotid baroreflex (CBR) responses to changes in arterial pressure is altered during upright seating compared to the supine position [1]. This change in balance identified that the major adjustment to changes in posture primarily involved the carotid-vasomotor arm of the reflex [1]. This finding confirmed earlier work involving reflex adjustments to reductions in central blood volume (CBV) induced by lower body negative pressure (LBNP) [2]. Furthermore, in average healthy and fit young adults the maximal gains (GMAX) of the carotid-cardiac and the carotid-vasomotor arms of the CBR were augmented during decreases in CBV [3, 4] induced by head-up tilt (HUT) or LBNP [5, 6].

However, patients who exhibit parasympathetic dysfunction during an orthostatic challenge also exhibit decreased vasomotor responsiveness [7–9], indicating that a dysfunction of the carotid-vasomotor arm may be the underlying mechanism of the postural syncope despite the parasympathetic dysfunction. These findings raise the question of whether parasympathetic dysfunction is indeed an underlying etiology of the arterial baroreflex regulation of blood pressure during orthostatic stress.

We hypothesized that by interrupting the carotid-cardiac arm of the CBR, using complete cardiac vagal blockade during HUT, the relative functional importance of the carotid-cardiac arm of the CBR to the maintenance of arterial pressure would be identified. We tested this hypothesis in young healthy subjects by measuring the CBR function of the carotid-cardiac and carotid-vasomotor arms, using the variable neck pressure (NP) and neck suction (NS) technique as well as estimates of heart rate and blood pressure variability. We used power spectral analysis during 40° HUT with and without full cardiac vagal blockade.

MATERIALS AND METHODS

The nine subjects (4 men and 5 women) who participated in the study were active but not participating in any regular exercise training and were free of cardiovascular and
pulmonary disorders and not using prescribed or over-the-counter medication. Their mean age was 27 years (range 21–36), height 183 cm (168–198), and weight 77 kg (57–97). All subjects provided written informed consent, which conformed to the Declaration of Helsinki and was approved by the Ethics Committee of Copenhagen (KF 01-369/97). They were requested to abstain from caffeinated beverages for 12 hours and from strenuous physical activity and alcohol for at least 24 hours before the experiment.

Procedure. The subjects were placed supine on a tilt-table, and at least 10 min after being instrumented, the CBR function was determined; they were then exposed to 40° HUT for 12 min. They were requested to abstain from leg movement to reduce muscle pump activity. During the last two minutes of HUT, the CBR function was again obtained. Following one hour of recovery in the supine position, the protocol was repeated after an administration of repeated small (0.2 mg) intravenous doses of glycopyrrolate until there was no further increase in HR (group average dose of 12.0 ± 1.0 µg/kg body weight; range of 8.6–16.9 µg/kg body weight). We used glycopyrrolate to affect cholinergic blockade instead of the more commonly used atropine sulphate because atropine sulphate crosses the blood-brain barrier and influences central muscarinic receptors [10, 11], confounding the interpretation of responses exhibited in the systemic circulation [12, 13].

Measurements. A catheter (1.2 mm ID, 18 gauge) was inserted into an antecubital vein for the administration of glycopyrrolate. An additional catheter (1.1 mm ID, 20 gauge) was placed in the brachial artery of the nondominant arm for a determination of arterial blood pressure with a Bentley transducer (Uden, the Netherlands) positioned at the level of the right atrium and connected to a Dialogue 2000 monitor (IBC-Danica, Copenhagen, Denmark). The mean arterial pressure (MAP) was derived by electrical integration. The arterial pulse pressure (PP) was calculated as systolic minus diastolic pressures. The heart rate (HR) was monitored using a lead II electrocardiogram connected to the monitor (Dialogue 2000) interfaced with a personal computer equipped with customized data acquisition software for beat-to-beat recordings. Stroke volume (SV) and cardiac output (Q) were calculated off-line from the blood pressure waveform by using the Modelflow program that was included in the BeatScope version 1.0 software incorporating age, sex, height, and weight (TNO-TDP, Biomedical Instrumentation, Amsterdam, The Netherlands) and validated against the changes in a thermodilution estimate during HUT [14]. Total vascular conductance (TVC) was calculated as Q divided by MAP. To assess changes in the CBV during HUT, electrical thoracic admittance (TA) was measured using 200 µA at 1.5 kHz (C-guard, Danmeter, Odense, Denmark) [15, 16]. A malleable lead neck collar that encircled the anterior 2/3 of the neck of each subject was used for the application of NP and NS [1, 17]. During a supine rest, a random-ordered 5 s pulse of NP and NS at +40, +20, 0, –20, –40, –60, and –80 Torr was used during a 10–15 s breath hold at end-expiration. The application of each pressure was separated by 45 s. Three to four NP and NS were performed at each of the six pressures. The modeled CBR function curve [18], its GMAX, and latency (time-to-peak response) were determined from the HR and MAP responses to the NP and NS stimuli. Because the time required to complete this protocol during the supine rest was approximately 20 min, we used the rapid pulse train of variable neck pressures during HUT [4]. Three to four rapid pulse train protocols were also performed. The two approaches have been found to provide identical information for the evaluation of CBR [19].

Data analysis. Hemodynamic data were obtained by averaging a 3-min beat-to-beat value at the end of each condition. CBR function was calculated from the carotid-cardiac (carotid-HR) and carotid-vasomotor (carotid-MAP) baroreflex responses from plotting the peak changes in HR and MAP against the estimated carotid sinus pressure (ECSP). The ECSP was calculated as MAP minus neck chamber pressure. Each carotid baroreflex stimulus-response curve was mathematically fitted to the logistic model of Kent et al. [1, 17, 18, 20]. The gain was calculated from the first derivative of the logistic function, and the GMAX was used as the index of carotid baroreflex responsiveness. Moreover, the HR and MAP variability was quantified by fast Fourier Transform analysis. A 3-min steady-state segment was then linearly interpolated and resampled at 2 Hz for spectral analysis. Spectral power was calculated in the very low frequency (VLF; 0.02–0.07 Hz), low frequency (LF; 0.07–0.20 Hz), and high frequency (HF; 0.20–0.30 Hz) ranges. However, because the blood pressure fluctuations in the HF range are primarily a mechanical consequence of respiration-induced increases in venous return [21], and in the LF range they are independent of the respiratory frequency [22], we used the LF range of the MAP variability to identify the dynamic effect of arterial baroreflex function on blood pressure regulation.

Statistical comparisons of the steady-state hemodynamic variables and the gain of the carotid-HR and carotid-MAP baroreflexes were made utilizing a repeated measures two-way analyses of variance (ANOVA) with a 2 × 2 design (vagal blockade × HUT). A Student-Newman-Keuls test was employed post hoc when interactions were significant. Data were expressed as mean ± SE, and a P value of 0.05 was considered to represent statistical significance.
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RESULTS

Hemodynamic changes—Supine

In the supine position, glycopyrrolate increased the HR to 91 ± 3 bpm, from 54 ± 3 (P < 0.05), and MAP was increased to 89 ± 2 mmHg, from 76 ± 2 (P < 0.05) (Table 1). The Q increased to 6.8 ± 0.3 l·min⁻¹, from 4.9 ± 0.3 (P < 0.05), and SV decreased to 75 ± 5 ml, from 94 ± 7 (P < 0.05). Moreover, PP decreased to 50 ± 1 mmHg, from 56 ± 2 (P < 0.05), and TVC was increased to 76.4 ± 3.3 ml·min⁻¹·mmHg⁻¹, (P < 0.05), from 65.0 ± 4.7, but TA was unchanged.

CBR responsiveness—Supine

The GMAX of the carotid-HR baroreflex was reduced with glycopyrrolate to –0.06 ± 0.01 bpm·mmHg⁻¹, from –0.30 ± 0.02, and the change in HR across the NP and NS stimuli became linear rather than curvilinear (Fig. 1). Also, the HR responses during NP and NS were slower; i.e., the time-to-peak change in HR at each chamber pressure increased to 5.6 ± 0.2 s, from 3.1 ± 0.0 (P < 0.05). However, glycopyrrolate had no significant influence on the carotid-MAP baroreflex function; i.e., the time-to-peak change in MAP was unchanged (6.7 ± 0.4 s versus 7.1 ± 0.4 s, P > 0.05).

Hemodynamic changes—Head-up tilt

During 40° HUT, the TA decreased similarly with and without glycopyrrolate (Table 1). However, HUT did not significantly affect MAP with or without glycopyrrolate. From the supine position, HR increased +13 ± 3 bpm (P < 0.05), but the increase was attenuated by glycopyrrolate to +7 ± 2 bpm (P < 0.05). The SV, Q, TVC, and PP were reduced by HUT with glycopyrrolate (P < 0.05). However, HUT did not significantly change Q, MAP, or TVC without glycopyrrolate, although TA decreased.

CBR responsiveness—Head-up tilt

Even though HUT increased the GMAX of the carotid-HR baroreflex from supine (P < 0.05) without glycopyrro-

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Table 1. Hemodynamic variables at supine rest and during 40° HUT with and without glycopyrrolate.

<table>
<thead>
<tr>
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<th>Supine</th>
<th>HUT</th>
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<tr>
<td></td>
<td>Control</td>
<td>Vagal blockade</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>54 ± 3</td>
<td>91 ± 3*</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>76 ± 2</td>
<td>89 ± 2*</td>
</tr>
<tr>
<td>PP (mmHg)</td>
<td>56 ± 2</td>
<td>50 ± 1*</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>94 ± 7</td>
<td>75 ± 5*</td>
</tr>
<tr>
<td>Q (l/min)</td>
<td>4.9 ± 0.3</td>
<td>6.8 ± 0.3*</td>
</tr>
<tr>
<td>TA (S·10⁻³)</td>
<td>14.5 ± 0.8</td>
<td>14.0 ± 0.9</td>
</tr>
<tr>
<td>TVC (ml/min/mmHg)</td>
<td>65.0 ± 4.7</td>
<td>76.4 ± 3.3*</td>
</tr>
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</table>

Values are means ± SE; HR, heart rate; MAP, mean arterial pressure; PP, arterial pulse pressure; SV, stroke volume; Q, cardiac output; TA, thoracic admittance; TVC, total vascular conductance. Thoracic admittance is 1/TI; S, siemens. *P < 0.05 vs. control, †P < 0.05 vs. supine position.
late (Figs. 1 and 2), the \( G_{\text{MAX}} \) of the carotid-HR baroreflex was unchanged from supine to HUT with glycopyrrolate \((-0.06 \pm 0.01\) versus \(-0.09 \pm 0.02\) bpm-mmHg\(^{-1}\)). The \( G_{\text{MAX}} \) of carotid-MAP baroreflex was unchanged during HUT with and without glycopyrrolate.

**HR and MAP variabilities**

The LF and HF spectral power of HR decreased to 0.04 ± 0.01 and 0.14 ± 0.11 bpm\(^2\), from 2.73 ± 0.95 and 2.29 ± 0.81 bpm\(^2\), respectively, after the administration of glycopyrrolate (Fig. 3 and Table 2). Although the LF spectral power of HR increased to 3.96 ± 1.47 during HUT, from 2.73 ± 0.95, without glycopyrrolate, it decreased to 0.34 ± 0.11 and 0.02 ± 0.01 bpm\(^2\), respectively, in both LF and HF ranges after the administration of glycopyrrolate. In contrast, the LF spectral power of MAP was unchanged with glycopyrrolate blockade in the supine position (1.22 ± 0.36 versus 0.25 ± 0.06 mmHg\(^2\)) or during HUT (2.84 ± 0.76 versus 3.54 ± 0.88 mmHg\(^2\)). However, MAP variability was increased from the supine to HUT with \((P = 0.002)\) and without \((P = 0.080)\) glycopyrrolate (Table 2).

**DISCUSSION**

The data of the present investigation identified that despite an interruption of the vagal function of the carotid-cardiac arm of the CBR during 40° HUT, arterial blood pressure was well maintained and the function of the carotid-vasomotor arm was unchanged. These findings indicate that the maintenance of arterial blood pressure during postural stress is primarily mediated by arterial and cardiopulmonary reflex regulation of sympathetic activity and its effects on the systemic vasculature.

Orthostatic hypotension and its more life-threatening clinical sequel of postural syncope are prevalent in elderly populations [23, 24], patients with diabetic autonomic neuropathy [25], and patients with cardiac disease [26]. Each of these populations exhibits parasympathetic dysfunction, which is consistent with altered arterial baroreflex control of the heart [27–31]. In the present investigation, however, complete cardiac vagal blockade did not disturb the baroreflex control of arterial blood pressure during HUT, and arterial blood pressure was well maintained. Furthermore, patients with autonomic dysfunction who have postural syncope are more likely to have an impaired reflex control of vasomotion [7–9] as well as an impaired control of the heart. Therefore impaired orthostatic tolerance in patients with parasympathetic dysfunction is
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Table 2. Group-averaged spectral power of HR and MAP in low- and high-frequency ranges with and without glycopyrrolate at supine rest and during HUT.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Vagal blockade</th>
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<tr>
<td></td>
<td>Supine</td>
<td></td>
<td>HUT</td>
<td></td>
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<tr>
<td>HR (bpm&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>2.73 ± 0.95</td>
<td>0.04 ± 0.01*</td>
<td>3.96 ± 1.47</td>
<td>0.34 ± 0.11*</td>
</tr>
<tr>
<td>HF (bpm&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>2.29 ± 0.81</td>
<td>0.14 ± 0.11*</td>
<td>1.17 ± 0.40</td>
<td>0.02 ± 0.01</td>
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<tr>
<td>MAP (mmHg&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>1.22 ± 0.36</td>
<td>0.25 ± 0.06</td>
<td>2.84 ± 0.76</td>
<td>3.54 ± 0.88†</td>
</tr>
<tr>
<td>HF (mmHg&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>0.13 ± 0.04</td>
<td>0.35 ± 0.05</td>
<td>0.49 ± 0.11</td>
<td>1.23 ± 0.32†</td>
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</table>

Values are means ± SE; HR, heart rate; MAP, mean arterial pressure; LF, low-frequency range; HF, high-frequency range. *P < 0.05 vs. control, †P < 0.05 vs. supine position.

very likely to be related to an impaired reflex control of vasomotion.

A general belief is that during HUT, it is the reduction in pulse pressure mediating the arterial baroreceptor disengagement, despite the maintenance of MAP, that activates the arterial baroreflex withdrawal of the vagus and the subsequent increase in HR [32]. However, HR increases during LBNP were unchanged by vagal blockade [33], while during 40 min of 50° HUT the increase in HR required sympathetic activation [34]. In contrast, during LBNP the increases in HR mediated via vagal withdrawal have been identified using linear dynamic analysis of HR variability [31]. In the present investigation, the 25% increase in HR from the supine to the HUT position decreased to 8% after the vagal blockade (Table 1), suggesting that the HR increase during the 12 min of HUT was a result of a combination of vagal withdrawal and sympathoexcitation. Similar conclusions can be drawn from the HR response during the initial 10 min of 50° HUT comparing control conditions with selective cardiac blockade using metoprolol or propranolol [34]. However, as the time of the 50° HUT progressed to 40 min, the progressive decrease in central blood volume probably exacerbated the sympathoexcitation [2, 35, 36] and was reflected by increases in HR. Collectively, these data suggest that during HUT the initial HR increase is a result of a predominant vagal withdrawal and a modest sympathoexcitation; however, as HUT is prolonged, the further increases in HR are primarily a result of increased sympathetic activity.

Glycopyrrolate in both supine and HUT positions resulted in an increase in Q. This increased Q may be related to an enhancement of venous return because cholinergic blockade increased splanchic (mesenteric) vascular resistance [37]. Furthermore, large increases in HR were not entirely counteracted by the reduction in SV during cholinergic blockade. MAP increased during cholinergic blockade in both supine and HUT positions. This result is consistent with previous studies [31, 37] and might result from the increase in Q.

Vagal blockade did not alter the G<sub>MAX</sub> of the carotid-MAP baroreflex despite the reduction of carotid-HR baroreflex sensitivity (Figs. 1 and 2). This finding suggests that the contribution of the carotid-cardiac reflex arm to the CBR control of blood pressure was minimal and confirms previous reports identifying the selective roles of the carotid-cardiac and carotid-vasomotor arms of the CBR [1, 20]. For example, the reflex response to carotid baroreceptor stimulation at rest and during exercise was a result of peripheral vasoconstriction with no change in cardiac output [20]. Moreover, the major carotid baroreflex response during the upright position was a result of changes in total vascular conductance [1].

In the present investigation, the G<sub>MAX</sub> of the carotid-MAP function tended to increase during HUT with and without vagal blockade (Figs. 1 and 2). However, there was no significant statistical difference between the supine and HUT positions. In contrast, others have found an increased sensitivity of the carotid-vasomotor reflex during HUT and suggested that the increased baroreflex sensitivity of the reflex contributed to the maintenance of blood pressure during orthostatic stress [3, 4]. One possible reason for these differences in the findings between studies is that the carotid-MAP baroreflex gain did not increase in the present investigation because a lower degree of HUT was utilized. For example, during HUT of less than 40° enhancement of the carotid-HR baroreflex, G<sub>MAX</sub> appeared to be more critical for the control of blood pressure. However, during HUT of greater than 40°, when the carotid-MAP baroreflex G<sub>MAX</sub> was enhanced [4], the effect of the carotid-HR baroreflex on blood pressure control was reduced [1].

Besides the static examination of the roles of the carotid-cardiac and carotid-vasomotor reflex arms in the regulation of blood pressure during HUT, data from the present investigation provide a novel insight into the contribution of dynamic baroreflex regulation. The low frequency (LF) power of MAP variability increased during HUT with and without vagal blockade (Fig. 3 and Table 2). These findings support early work using HUT [38] and LBNP [31]. Furthermore, they identify a primary role of the carotid-vasomotor reflex in the regulation of arterial blood pressure during HUT, because increases in the LF MAP variability indicate a disengagement of the arterial...
and cardiopulmonary baroreflex and consequent increases in sympathetic activity [31].

During supine rest the blood pressure variability tended to decrease after vagal blockade (Fig. 3 and Table 2). This finding was consistent with the studies that used atropine sulphate to induce vagal blockade [31, 39]. Atropine sulphate crosses the blood barrier [10, 11], blocking central muscarinic cholinergic receptors, which results in the removal of its central inhibitory influence on muscle sympathetic nerve activity [13, 40]. However, the LF power of blood pressure variability was not related to the muscle sympathetic nerve activity [41], but the LF pulse interval variability and the LF power of the blood pressure variability were correlated [31, 42]. Thus the LF power of the blood pressure variability may decrease in relation to the reduced LF power of the HR variability during supine rest with glycopyrrolate.

Symptoms of parasympathetic activation, such as vagally induced bradycardia, sweating, and nausea are usually absent in patients with parasympathetic dysfunction that present with a sudden onset of postural syncope [23–26]. In the present study, complete cardiac vagal blockade did not disturb the baroreflex control of arterial blood pressure during HUT. These findings indicate that the maintenance of arterial blood pressure during postural stress is primarily mediated by arterial and cardiopulmonary reflex regulation of sympathetic activity and its effects on the systemic vasculature. Thus parasympathetic dysfunction in patients with orthostatic intolerance may prove to be a comorbidity and not the underlying etiology of the orthostatic intolerance. Patients with autonomic dysfunction who have postural syncope are more likely to have impaired reflex control of vasomotion [7–9], as well as impaired control of the heart.

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