Baroreflex Control of Blood Pressure During Hypoglycemia

Jacqueline K. Limberg, Jennifer L. Taylor, Michael T. Mozer, Simmi Dube, Aninda Basu, Rita Basu, Robert A. Rizza, Timothy B. Curry, Michael J. Joyner, Erica A. Wehrwein

Abstract—Hypoglycemia results in a reduction in cardiac baroreflex sensitivity and a shift in the baroreflex working range to higher heart rates. This effect is mediated, in part, by the carotid chemoreceptors. Therefore, we hypothesized hypoglycemia-mediated changes in baroreflex control of heart rate would be blunted in carotid body–resected patients when compared with healthy controls. Five patients with bilateral carotid body resection for glomus tumors and 10 healthy controls completed a 180-minute hyperinsulinemic, hypoglycemic (≈3.3 mmol/L) clamp. Changes in heart rate, blood pressure, and spontaneous cardiac baroreflex sensitivity were assessed. Baseline baroreflex sensitivity was not different between groups \((P>0.05)\). Hypoglycemia resulted in a reduction in baroreflex sensitivity in both the groups (main effect of time, \(P<0.01\)) and responses were lower in resected patients when compared with controls (main effect of group, \(P<0.05\)). Hypoglycemia resulted in large reductions in systolic \((-17±7 \text{ mm Hg})\) and mean \((-14±5 \text{ mm Hg})\) blood pressure in resected patients that were not observed in controls (interaction of group and time, \(P<0.05\)). Despite lower blood pressures, increases in heart rate with hypoglycemia were blunted in resected patients (interaction of group and time, \(P<0.01\)). Major novel findings from this study demonstrate that intact carotid chemoreceptors are essential for increasing heart rate and maintaining arterial blood pressure during hypoglycemia in humans. These data support a contribution of the carotid chemoreceptors to blood pressure control and highlight the potential widespread effects of carotid body resection in humans. (Hypertension. 2015;65:1365-1371. DOI: 10.1161/HYPERTENSIONAHA.115.05325.)

Key Words: blood pressure ■ carotid body tumor ■ chemoreceptor cells ■ glucose

Peripheral chemoreceptors play a role in reflex responses to chemical stimuli, including hypoxia, acidosis, and hypoglycemia. The carotid bodies—typically thought of as key peripheral chemoreceptors—may also have acute and chronic effects on blood pressure and an inverse relationship between peripheral chemosensitivity and baroreflex sensitivity has been shown previously.\(^1\)\(^2\) For example, transient blockade of peripheral chemoreceptors with hyperoxia temporarily increases baroreflex sensitivity,\(^3\) whereas activation of the peripheral chemoreceptors with hypoxia decreases baroreflex sensitivity.\(^4\) Consistent with the hypoxia data, our laboratory has shown hypoglycemia results in a reduction in spontaneous cardiac baroreflex sensitivity \((\text{scBRS})\) in healthy humans.\(^5\) In addition, the chemoreceptors seem to play an important role in resetting the baroreflex working range during hypoglycemia such that acute chemoreceptor desensitization results in a blunted rise in heart rate and reduction in blood pressure.\(^5\)

Bilateral carotid body resection in humans for removal of glomus tumors eliminates reflex responses \(\text{in changes in ventilation and blood pressure}\) to chemoreceptor stimulation with hypoxia.\(^6\)\(^8\) Given the growing interest in carotid body resection for the treatment of a variety of disorders\(^10\) and the potential widespread physiological effects of such procedures, we sought to examine cardiac baroreflex sensitivity during hypoglycemia in patients who have undergone bilateral carotid body resection. We hypothesized that carotid body–resected patients would exhibit an inability to maintain arterial blood pressure during hypoglycemia. We further hypothesized changes in baroreflex control of heart rate during hypoglycemia would be blunted in carotid body–resected patients compared with controls. Our hypotheses were based on our previous observations in normal subjects showing hypoglycemia results in a fall in blood pressure and attenuated heart rate response when the carotid chemoreceptors are desensitized with hypoxemia.

Methods

Approval

All experiments and procedures were approved by the Institutional Review Board at Mayo Clinic. Informed consent was obtained in writing from all subjects before study enrollment and testing. Studies conformed to the Declaration of Helsinki. Counterregulatory hormone responses to hypoglycemia in control subjects\(^5\)\(^11\) and carotid body–resected patients\(^12\) and pertinent methods were published previously.
Subjects
All subjects were aged 21 to 55 years, healthy, nonsmokers, non-pregnant/breast feeding, with body mass index 21 to 32 kg/m². All carotid body–resected patients received treatment at the Mayo Clinic in Rochester, MN. Each patient underwent separate surgeries for right and left removal of carotid body tumors (paraganglioma). During a screening visit, subjects completed a hypoxic response test to determine carotid body chemosensitivity.12 Subjects were instructed to avoid exercise, caffeine, medications (except birth control), and alcohol on the day before and day of the study.

Monitoring
A 20-gauge, 5-cm brachial artery catheter was placed under ultrasound guidance after local anesthesia for blood sampling and beat-to-beat blood pressure monitoring (TruWave Pressure Transducer; Edwards Lifesciences, Irvine, CA). Two intravenous catheters were placed in the arm opposite the brachial arterial catheter for infusions. Heart rate was monitored with a 5-lead ECG, respirations via a pneumobelt/capnography, and arterial oxygen saturation by a pulse oximeter (Cardiocap/5; Datex-Ohmeda Inc, Louisville, CO).

Hyperinsulinemic Hypoglycemic Clamp
Intravenous insulin (Novolin; Novo Nordisk Inc, Princeton, NJ) was infused at a constant rate of 2.0 mU/kg fat-free mass per minute from protocol time (T) 0 to T180 minutes and exogenous glucose (50% dextrose solution [Hospira, Inc, Lake Forest, IL]) was infused in amounts sufficient to maintain glucose concentrations at hypoglycemic levels (≈3.3 mmol/L).

Protocol
Subjects were admitted to the Clinical Research Unit of the Mayo Clinic at 17:00 hours on the evening before study. A standard 10 kcal/kg meal (55% carbohydrate, 30% fat, 15% protein) was eaten between 18:00 and 18:30 hours and the subject fasted thereafter until the end of the study. In the morning, the brachial arterial catheter and intravenous lines were placed. The insulin infusion was started at 09:00 hours. Arterial blood was drawn every 5 to 10 minutes at the bedside for measurement of plasma glucose using a glucose oxidase method (Analox Instruments USA Inc, Lunenberg, MA). Arterial blood was also drawn at specific time points (T-30, -20, -10, 0, 150, 160, 170, and 180 minutes) for measures of insulin (DxI automated immunoassay system; Beckman Instruments, Chaska, MN).

Spontaneous Cardiac Baroreflex Sensitivity
scBRS was assessed from 30-minute sections of data during euglycemic baseline (T-30–T0 [baseline]) and steady-state hypoglycemia (T150–T180 [clamp]) using methods published previously. Briefly, a computer software program (LabChart7; ADinstruments, Colorado Springs, CO) selected all sequences of ≥3 successive heart beats, in which there were concordant increases or decreases in systolic blood pressure (SBP) and R–R interval. A linear regression was applied to which there were concordant increases or decreases in SBP (y distribution curves. The operating points for the relationships were determined as the average heart rate and SBP from 5-minutes of data collected during selected time points. From the same 5-minute period, we also measured the coefficient of variation of SBP (% coefficient of variation; (SD/mean)×100) and tabulated the frequency of occurrence of each blood pressure in increments of 2 mm Hg with results presented as frequency distribution curves.

Data Analysis and Statistics
The number of subjects was determined a priori based on previous research from resected patients showing n=5 would provide >0.80 power to detect significant differences in baroreflex sensitivity. Where relevant, values are reported as an average from T-30 to T0 (baseline) and from T150 to T180 (clamp). Outcome variables were evaluated as a change from baseline (Δ=clamp−baseline). Subject characteristics, baseline measures, and change variables (Δ) were compared using a Student t test. Additional analyses were performed using a 2-way, repeated measures ANOVA, to examine the main effects of group (control and patients), time (baseline, clamp), and interactions between group and time on main outcome variables. Post hoc analyses were completed using the Bonferroni test. In all cases, distributional assumptions were assessed and appropriate transformations or nonparametric analyses (Mann–Whitney rank sum test) were used if necessary. When appropriate, Pearson product–moment correlations were used to determine the association between main outcome variables (eg, scBRS) and descriptive measurements (eg, hypoxic ventilatory response). All tests were 2-tailed with P<0.05 considered statistically significant and analysis was completed using SigmaPlot version 12.0 (Systat Software Inc; San Jose, CA). All values are reported as mean±SE.

Results
Five patients with bilateral carotid body resection and 10 healthy adults participated in this study. Groups were matched for weight, body composition, and cholesterol levels (Table 1).

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**Table 1. Subject Demographics**

<table>
<thead>
<tr>
<th>Subject Demographics</th>
<th>Control</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M/F</td>
<td>7/3</td>
<td>3/2</td>
</tr>
<tr>
<td>Age, y</td>
<td>25±1</td>
<td>40±5*</td>
</tr>
<tr>
<td>Height, cm</td>
<td>177±2</td>
<td>175±5</td>
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<tr>
<td>Weight, kg</td>
<td>75±3</td>
<td>80±7</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>25±2</td>
<td>27±3</td>
</tr>
<tr>
<td>Fat-free mass, kg</td>
<td>56±3</td>
<td>54±5</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>4.6±0.1</td>
<td>4.6±0.1</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>3.8±0.3</td>
<td>4.5±0.4</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>0.9±0.1</td>
<td>1.1±0.3</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
<td>1.4±0.2</td>
<td>1.5±0.2</td>
</tr>
<tr>
<td>LDL, mmol/L</td>
<td>2.0±0.2</td>
<td>2.5±0.3</td>
</tr>
<tr>
<td>Time from bilateral resection, y</td>
<td>…</td>
<td>5±2</td>
</tr>
</tbody>
</table>

F indicates female; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and M, male.

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Figure 1. Reflex responses to hypoxia. The hypoxic ventilatory response was significantly blunted in resected patients when compared with controls (P<0.01 vs control), with no significant difference in the heart rate response (P=0.24).
Carotid body–resected patients were significantly older than the control group ($P<0.01$). The hypoxic ventilatory response, a measure of carotid body chemosensitivity to hypoxia, was significantly blunted in resected patients when compared with controls ($P<0.01$; Figure 1). There was no difference in the heart rate response to hypoxia in carotid body–resected patients when compared with controls ($P=0.24$; Figure 1). Hypoxic ventilatory response was linearly related to both heart rate response to hypoxia ($r=0.69$, $P=0.04$) and the time from bilateral resection ($r=-0.84$, $P=0.08$). Given the potential for baroreceptor denervation during removal of glomus tumors, it is important to note scBRS was not impaired at baseline in resected patients ($ms/mm\text{Hg}$, $P=0.28$; $bpm/mm\text{Hg}$, $P=0.48$). In addition, blood pressure distribution (% coefficient of variation [CV] of SBPs) was not different between groups ($P=0.11$; Figure 2).

As designed, the hyperinsulinemic hypoglycemic clamp resulted in higher insulin concentrations (baseline to clamp values: control, 4±1−132±8 μU/mL; patient, 5±2−151±20 μU/mL) and lower glucose concentrations (control, 5.4±0.1–3.4±0.1 mmol/L; patient, 5.4±0.1–3.3±0.1 mmol/L) in both the groups (main effect of time, $P<0.01$) as compared with baseline. The glucose infusion rate required to maintain steady-state hypoglycemia was not different between control and resected groups (control, 28±4 μmol/kg per minute; patient, 38±11 μmol/kg per minute; $P=0.46$). More detailed discussion of hypoglycemia counterregulation is available in our previous publications.$^{11,12}$

Hypoglycemia resulted in a significant reduction in diastolic blood pressure in both the groups (main effect of time, $P<0.01$; Table 2). In control subjects, heart rate increased during hypoglycemia (interaction of group and time, $P<0.01$) and SBP and mean blood pressure were maintained at baseline levels (interaction of group and time, $P>0.05$; Figure 3). By contrast, hypoglycemia resulted in a significant reduction in SBP and mean blood pressure in carotid body–resected patients (interaction of group and time, $P<0.05$; Table 2). Despite lower blood pressures, increases in heart rate with hypoglycemia were blunted in carotid body–resected patients when compared with controls (interaction of group and time, $P<0.01$; Figure 3).

Consistent with this finding, scBRS was reduced from baseline during hypoglycemia (main effect of time, $P<0.01$) and was lower in carotid body–resected patients when compared with controls (main effect of group, $P<0.05$; Figure 3). In addition, the change in heart rate and SBP with hypoglycemia was related to scBRS (HR: $ms/mm\text{Hg}$, $r=0.46$, $P=0.08$; $bpm/mm\text{Hg}$, $r=-0.63$, $P=0.01$; SBP: $ms/mm\text{Hg}$, $r=0.61$, $P=0.02$; $bpm/mm\text{Hg}$, $r=-0.36$, $P=0.18$). Despite a reduction in scBRS with hypoglycemia, an increase in blood pressure distribution (% coefficient of variation of SBPs) with hypoglycemia was not observed (main effect of time, $P=0.46$; interaction of group and time, $P=0.52$; Figure 4).

**Discussion**

We demonstrate that intact carotid chemoreceptors are essential for increasing heart rate and maintaining arterial blood
pressure during hypoglycemia in humans. In this context, a rise in heart rate was not observed in carotid body–resected patients, despite ≈15 mm Hg reductions in arterial blood pressure during hypoglycemia (Table 2; Figure 3A and 3B). These observations highlight potential physiological consequences of carotid body resection in humans.

### Carotid Body Resection and Cardiac Baroreflex Function

During surgical removal of carotid body paragangliomas, branches of the carotid sinus nerves may be damaged and cause baroreflex failure. Baroreflex failure (sympathoexcitation, hypertension, and tachycardia) is often an early postsurgical response that resolves within months; however, both normalization of blood pressure and sustained hypertension have been observed in resected patients. Although overt baroreflex failure occurs in a minority of patients, baroreflex sensitivity may be ≈50% lower in some patients. In contrast to previous findings from other cohorts, we did not observe a significant impairment in baseline cardiac baroreflex sensitivity in the present group of resected patients.

Despite the relatively small number of patients studied and the significant age difference between groups, there is clear overlap in all indices of cardiac baroreflex function and blood pressure stability between patients and controls (Figure 2A and 2E). In addition, a post hoc sample size estimate revealed that 116 subjects would be necessary to provide 80% power to detect group differences—suggesting any group difference would be of limited physiological relevance. These findings support the concept that the carotid body–resected patients studied had relatively normal baseline cardiac baroreflex function. In contrast to scBRS, we observed an almost absent hypoxic ventilatory response with a nonsignificant blunting of the heart rate response to hypoxia in resected patients.

### Table 2. Changes in Hemodynamic Variables During Hypoglycemia

<table>
<thead>
<tr>
<th>Hemodynamic Variables</th>
<th>Baseline</th>
<th>Clamp</th>
<th>Δ</th>
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</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>59±2</td>
<td>75±4*</td>
<td>16±3</td>
</tr>
<tr>
<td>Patient</td>
<td>65±4†</td>
<td>72±6</td>
<td>7±2†</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>128±4</td>
<td>131±9</td>
<td>3±6</td>
</tr>
<tr>
<td>Patient</td>
<td>135±10</td>
<td>118±8*</td>
<td>-17±7†</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>65±2</td>
<td>57±3*</td>
<td>-8±2</td>
</tr>
<tr>
<td>Patient</td>
<td>62±6</td>
<td>50±3*</td>
<td>-12±4</td>
</tr>
<tr>
<td>Mean blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>86±3</td>
<td>82±4</td>
<td>-4±2</td>
</tr>
<tr>
<td>Patient</td>
<td>87±7</td>
<td>73±4*</td>
<td>-14±5†</td>
</tr>
</tbody>
</table>

*Effect of time: P<0.05 vs baseline.
†Effect of group: P<0.05 vs control.

### Figure 3. Changes in heart rate, blood pressure, and baroreflex sensitivity during hypoglycemia.

In control subjects, heart rate increased during hypoglycemia (A, †P<0.01 vs baseline) and blood pressure was maintained at baseline levels (B, P=0.05). Hypoglycemia-mediated reductions in blood pressure were observed in carotid body–resected patients (B, †P<0.05 vs baseline), although a rise in heart rate was not apparent (A, †P<0.05 vs control). scBRS was reduced from baseline during hypoglycemia (†P<0.01) and was lower in carotid body–resected patients when compared with controls (†P<0.05). Data are presented as group averages of the slope of the relationship between heart rate and systolic blood pressure (C, R–R interval [ms] and systolic blood pressure [mm Hg]; D, heart rate [bpm] and systolic blood pressure [mm Hg]).
These data are in agreement with findings from Niewinski et al, who have shown carotid body resection in patients with heart failure significantly blunts the ventilatory response, but not the heart rate response, to hypoxia. It is likely the response to hypoxia is mediated by multiple chemoreceptive sites; whereas the carotid bodies play a role in the ventilatory response to hypoxia, it seems the heart rate response may be mediated by another site (e.g., the aortic bodies or perhaps a site in the central nervous system).

Cardiac Baroreflex Control During Hypoglycemia

In response to a transient fall in blood pressure, the baroreceptors initiate reflex increases in heart rate to maintain blood pressure at optimal levels. However, baroreflex control of blood pressure may be altered by inhibition or activation of the carotid chemoreceptors. For example (1) transient blockade of peripheral chemoreceptors with hyperoxia temporarily increases baroreflex sensitivity in patients with heart failure, (2) unilateral carotid body resection in a human heart failure patient resulted in an improvement in baroreflex sensitivity, and (3) activation of the peripheral chemoreceptors with hypoxia decreases baroreflex sensitivity. In addition, previous studies have shown antecedent hypoglycemia to reduce baroreflex sensitivity and reset the baroreflex working range. Our laboratory has recently shown the baroreflex working range is reset to higher heart rates such that SBP is relatively maintained during hypoglycemia. By contrast, when the carotid chemoreceptors are acutely desensitized with systemic hyperoxia, there is a significant reduction in blood pressure and a blunted rise in heart rate compared with normoxic conditions. Given these changes were assessed in otherwise healthy adults, using acute (≈3 hours) hyperoxia to desensitize the carotid chemoreceptors, we sought to examine baroreflex sensitivity during hypoglycemia in patients after permanent bilateral carotid body resection. This has important clinical implications, given carotid body resection has emerged as a potential therapeutic target for the treatment of sympathoexcitatory conditions.

Surprisingly, both the groups (control and patients) exhibited a reduction in scBRS with hypoglycemia (Figure 3C and 3D). In healthy controls, this fall in scBRS was accompanied with a shift in the operating point to higher heart rates such that SBP was preserved (Table 2; Figure 3). However, carotid body–resected patients exhibited a large reduction in both SBP (−17±7 mm Hg) and mean (−14±5 mm Hg) blood pressure and a blunted rise in heart rate under hypoglycemic conditions (Table 2; Figure 3). These data demonstrate that intact carotid chemoreceptors are essential for increasing heart rate and maintaining arterial blood pressure within normal ranges during physiological stress in humans.
acute chemoreceptor desensitization with hypoglycemia improves baroreflex sensitivity.2,3

Hypoglycemia is achieved experimentally in humans through the use of a hyperinsulinemic clamp. Thus, it is important to acknowledge insulin may work at the level of the carotid body glomus cells to increase chemoreceptor-mediated afferent activity independent of hypoglycemia.4,5 In addition, insulin results in peripheral vasodilation, and in adults with autonomic failure, intravenous insulin infusion results in a reduction in blood pressure.6 However, given Young et al7 observed no effect of hyperinsulinemia alone on scBRS, any change in scBRS observed in this study is unlikely to be the result of hyperinsulinemia alone.

Spontaneous baroreflex sensitivity provides an estimate of the baroreflex sensitivity at the level of the operating point, thus it is possible that the observed reduction in baroreflex sensitivity with hypoglycemia is, rather than a reduction in scBRS, the result of a shift in the operating point. In addition, we examined the effect of hypoglycemia and carotid body resection on cardiac baroreflex sensitivity, however, the differential effect of hypoglycemia on SBP and diastolic blood pressure (Table 2) supports the idea of differing efferent pathways. Thus, it is possible activation of the carotid chemoreceptors with hypoglycemia increases sinus nerve afferent activity directed toward the nucleus tractus solitarius that differentially affects the vagus (heart rate and SBP) and rostral ventrolateral medulla (sympathetic activity, and diastolic blood pressure). The lack of corresponding increase in blood pressure variability (Figure 4) with reductions in scBRS (Figure 3) may support this point. Direct measures of sympathetic activity will be needed to address this issue.

Perspectives
Carotid body resection has recently been identified as a potential therapeutic strategy for diseases, such as heart failure and hypertension.8,9 However, concern exists about possible long-term effects of chronic denervation procedures. In this way, understanding the role of the carotid chemoreceptors in the integrated blood pressure responses to hypotensive stimuli will be a key before targeting these receptors for therapeutic interventions. Data from this study suggest that impaired blood pressure responses to physiological stressors may occur after carotid body denervation without the presence of overt baroreceptor failure. This observation raises the possibility that there may be unforeseen autonomic consequences of carotid body denervation, even in relatively healthy adults.

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Disclosures
None.

References
What Is New?
- We examined hypoglycemia-mediated changes in baroreflex control of heart rate in subjects with limited neural input from the carotid chemoreceptors as a result of bilateral surgical removal of these organs for carotid body glomus tumors. Despite relatively normal baroreflex function at baseline, we found the absence of carotid body chemoreceptors limits blood pressure regulation during hypoglycemia.

What Is Relevant?
- In addition to furthering our understanding of carotid chemoreflex and baroreflex interactions, these findings have therapeutic implications because carotid body resection has recently emerged as a potential strategy for the treatment of sympathoexcitatory conditions.

Summary
Hypoglycemia results in a reduction in cardiac baroreflex sensitivity and a shift in the baroreflex working range to higher heart rates; this effect is mediated, in part, by the carotid chemoreceptors.
Effect of Bilateral Carotid Body Resection on Cardiac Baroreflex Control of Blood Pressure During Hypoglycemia
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