Hypoglycemia-Induced Blood Pressure Elevation in Patients With Diabetes

Blood pressure elevation secondary to hypoglycemia has been demonstrated in human experimentation through the activation of the sympathoadrenal system. Though hypoglycemia is a fact of life for patients with both type 1 and type 2 diabetes mellitus, blood pressure (BP) variations after hypoglycemic events has not been clarified. Our aim was to determine the relationship between glucose level and BP swings in patients with diabetes under everyday conditions.

Methods. We performed 24-hour home monitoring of subcutaneous glucose level using a continuous glucose monitoring system (Medtronic, Minneapolis, Minnesota) and simultaneous ambulatory BP measurement (Diasys Integra II; NOVACOR, Rueil-Malmaison, France) in 22 patients with type 1 (n=4) or type 2 (n=18) diabetes (mean duration, 18 years). Of the 22 patients, 14 (64%; 10 with type 2 diabetes) were receiving long-term insulin therapy and 18 (82%) were taking hypotensive drugs. The Medtronic MiniMed continuous glucose monitoring system has been shown to be clinically accurate for the recording of hypoglycemic episodes in daily life conditions. Subcutaneous interstitial glucose values were recorded every 5 minutes, providing approximately 288 readings per day. Hypoglycemia was defined by a blood glucose value lower than 60 mg/dL (to convert to millimoles per liter, multiply by 0.0555).

Blood pressure was measured every 15 minutes during daytime (7 AM–11 PM) and 30 minutes during nighttime (11 PM–7 AM). The last BP and heart rate measurements before blood glucose level fell under 60 mg/dL were taken as reference values to assess the variability of cardiovascular parameters after the hypoglycemic episode and during the 1-hour period before, which was taken as the control period.

Statistical analyses were performed using SPSS software, version 14.0 for Windows (SPSS, Chicago, Illinois). The variables presented were summarized as means (SDs), medians, and extreme values. Categorical variables were described with frequencies and percentages. The Fisher exact test was used to compare proportions of baseline characteristics of the study population. The collected data were processed with nonparametric tests. Association between 2 variables was determined using the Spearman correlation coefficient. \( P < .05 \) was considered statistically significant. The study was approved by the ethics committee of Paris VII University, Paris, France, and patients gave their written informed consent.

Results. The general characteristics of the patient population are given in the Table. Fourteen hypoglycemic events (glucose levels, 40–59 mg/dL) were recorded in 12 patients (55%), 6 of whom were taking chronotrope/dromotrope (C/D)-negative agents (β-blockers [n=5] and diltiazem [n=1]). Eleven episodes occurred between 7 AM and 11 PM (daytime). No patient reported symptoms of hypoglycemia. Glucose and BP profiles of the 12 patients who had hypoglycemic recordings are shown in Figure 1. The median glucose value during hypoglycemia was 50 mg/dL (extreme values, 40–59 mg/dL), and the median duration of hypoglycemia was 25 minutes (extreme values, 10–120 minutes). Hypoglycemic events were followed 30 to 60 minutes later by a significant median 23% rise in systolic BP (SBP) (range, 3%–38%), from a mean (SD) of 125 (17) mm Hg to 154 (20) mm Hg (\( P = .003 \)); a nonsignificant 8% rise in diastolic BP (\( P = .07 \)); and no increase in heart rate (\( P = .30 \)). During the control period, the median percentage variability of SBP was 3% (from −6% to 20% [\( P = .15 \)] compared with the reference value). In 9 of these 12 patients (75%), the highest SBP recorded during the time a hypoglycemic event occurred (daytime or nighttime of the continuous BP recording) closely followed hypoglycemia. Individual SBP and heart rate values before and after hypoglycemic events are shown in Figure 2. The use of C/D-negative agents was associated with perfectly stable heart rate, whereas in the 6 patients free of C/D-negative agents, the heart rate tended to increase (Figure 2B) and was positively correlated with SBP elevation (\( P = .005 \)). No correlation was observed between the increase in SBP and the patient’s age, diabetes duration, renal function, and duration or severity of hypoglycemia. However, the ranges and duration of low glucose values were narrow.

Comment. The existence of a link between tight blood glucose control and BP elevation in patients with type 1 diabetes has been a matter of debate. Using 24-hour ambulatory BP measurement, Azar and Birbari found elevated nocturnal BP in 18 type 1 diabetic patients with a mean hemoglobin A\(_1c\) (HbA\(_1c\)) value of 8.1% compared with 18 type 1 diabetic patients with a mean HbA\(_1c\) value of 11.0%. The study results were attributed to a relative state of nocturnal hypoglycemia due to more intensive insulin therapy in the well-controlled diabetic group, with secondary increased catecholamine levels. Conversely, Poulsen et al found similar ambulatory BP measurement values among 128 type 1 diabetic patients stratified into quartiles according to mean HbA\(_1c\) values (from 7.0% to 9.7%) and concluded that tight glucose control is not associated with deleterious effect on BP in these conditions.
patients. However, none of these studies was designed to assess the direct relationship between hypoglycemia and hemodynamic changes, since the occurrence of hypoglycemic events was not documented at all.

Our results demonstrate a close temporal relationship between hypoglycemia and BP increase. Going further, it is highly probable that hypoglycemia-induced hypertension is amplified in patients experiencing frequent and severe hypoglycemia, as typically those receiving intensive insulin therapy, which may increase the risk of a broad spectrum of hypertension-related complications. Notably, it could have played a role in the disappointing cardiovascular results of intensive glucose control studies in diabetes, which raised great concern and remain poorly understood. A hallmark of these studies was a 2- to 3-fold increased risk of severe hypoglycemia, with the highest risk reported in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, in which the HbA1c target and HbA1c levels achieved were the lowest. It is noteworthy that this study showed an increased risk of cardiovascular and all-cause mortality. Because cardiovascular disease and all-cause mortality is closely linked to BP elevation, increased BP variability and recurrent post-hypoglycemic BP rises may partly explain these findings. More generally, through its impact on BP control, hypoglycemia may increase the rate of all diabetes complica-

### Table. Characteristics of 22 Patients With Type 1 or Type 2 Diabetes Mellitus

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Whole Population (N=22)</th>
<th>Patients With Hypoglycemic Events (n=12)</th>
<th>Patients Without Hypoglycemic Event (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, No. (%)</td>
<td>19 (86)</td>
<td>10 (83)</td>
<td>9 (90)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>60 (12)</td>
<td>60 (14)</td>
<td>60 (11)</td>
</tr>
<tr>
<td>Diabetes duration, mean (SD), y</td>
<td>18 (13)</td>
<td>17 (14)</td>
<td>18 (11)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>27.5 (3.4)</td>
<td>27.2 (3.6)</td>
<td>27.9 (3.3)</td>
</tr>
<tr>
<td>Glycosylated hemoglobin, mean (SD), %</td>
<td>7.3 (1.3)</td>
<td>7.1 (1.3)</td>
<td>7.6 (1.2)</td>
</tr>
<tr>
<td>Creatinine clearance, mean (SD), mL/min</td>
<td>69 (24)</td>
<td>67 (29)</td>
<td>71 (15)</td>
</tr>
<tr>
<td>Patients receiving long-term insulin, No. (%)</td>
<td>14 (64)</td>
<td>5 (42)</td>
<td>9 (90)</td>
</tr>
<tr>
<td>Patients taking hypotensive drugs, No. (%)</td>
<td>18 (82)</td>
<td>10 (83)</td>
<td>8 (80)</td>
</tr>
<tr>
<td>Patients taking C/D-negative agents, No. (%)</td>
<td>11 (50)</td>
<td>6 (50)</td>
<td>5 (50)</td>
</tr>
<tr>
<td>24-Hour glucose, mean (SD), mg/dL</td>
<td>150 (45)</td>
<td>126 (25)</td>
<td>179 (46)</td>
</tr>
<tr>
<td>24-Hour SBP, mean (SD), mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole 24-h period</td>
<td>133 (16)</td>
<td>141 (16)</td>
<td>124 (9)</td>
</tr>
<tr>
<td>Diurnal period, 7 AM to 11 PM</td>
<td>136 (17)</td>
<td>144 (17)</td>
<td>126 (10)</td>
</tr>
<tr>
<td>Nocturnal period, 11 PM to 7 AM</td>
<td>125 (16)</td>
<td>130 (16)</td>
<td>119 (15)</td>
</tr>
<tr>
<td>24-Hour heart rate, mean (SD), beats/min</td>
<td>75 (10)</td>
<td>75 (9)</td>
<td>74 (11)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); C/D, chronotrope/dromotrope; SBP, systolic blood pressure.

SI conversion factor: To convert glucose to millimoles per liter, multiply by 0.0555.

1 One patient had 3 hypoglycemic episodes during the study period: all values were averaged over the 3 episodes so that the study results are given per patient.

2 According to the Cockroft-Gault formula.

3 P= .03 vs patients with hypoglycemic events.

4 P= .006 vs patients with hypoglycemic events.

5 P= .01 vs patients with hypoglycemic events.

---

**Figure 1.** Concomitant values of mean glucose level and mean systolic blood pressure (SBP) on 24-hour continuous recordings in 12 diabetic patients with hypoglycemic episodes. One hypoglycemic event occurred in the morning; 7 between 4 PM and 8 PM (explaining the dramatic inverse movement of glucose and SBP curves at this period); 3 between 8 PM and 11 PM; and 3 between 11 PM and 7 AM (nighttime). The number of SBP data contributing to mean values was less during nighttime because blood pressure was recorded 2-fold less often than during daytime. To convert glucose to millimoles per liter, multiply by 0.0555.
Figure 2. Individual systolic blood pressure (A) and heart rate (B) values of the 12 patients with diabetes who showed hypoglycemic events (before [T0] and after [T1] the event). Full lines indicate the values from the 6 patients who were taking chronotrope/dromotrope-negative agents (β-blockers in 5 cases), whereas broken lines are dedicated to patients free of these drugs. One of the latter patients (full circles at broken line extremities) had only 2 glucose readings of 59 mg/dL (to convert to millimoles per liter, multiply by 0.0555) over a 10-minute period (ie, borderline normal values), and he was the only one who showed neither blood pressure nor heart rate modification between T0 and T1.

This hypothesis clearly deserves further study, since it may have important implications for the treatment and monitoring of diabetic patients in the future.

Sylvie Feldman-Billard, MD
Pascale Massin, MD, PhD
Taly Meas, MD
Pierre-Jean Guillausseau, MD
Emmanuel Héron, MD

Author Affiliations: Service de Médecine Interne, Centre Hospitalier National d’Ophthalmo"logie des Quinze-Vingts, Paris, France (Drs Feldman-Billard and Héron); and Service d’Ophthalmo"logie (Dr Massin) and Service de Médecine Interne B (Drs Meas and Guillausseau), Hôpital Lariboisière, Université Paris VII, Assistance Publique-Hôpitaux de Paris, Paris.

Correspondence: Dr Feldman-Billard, Service de Médecine Interne, Centre Hospitalier National d’Ophthalmo"logie des Quinze-Vingts, 28 rue de Charenton, 75571 Paris, CEDEX 12, France (s.feldman@quinze-vingts.fr).

Author Contributions: Dr Feldman-Billard had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis decision. Study concept and design: Feldman-Billard, Massin, and Meas. Acquisition of data: Massin and Guillausseau. Analysis and interpretation of data: Feldman-Billard and Héron. Drafting of the manuscript: Feldman-Billard, Meas, and Héron. Critical revision of the manuscript for important intellectual content: Massin and Guillausseau. Obtained funding: Massin. Study supervision: Feldman-Billard, Guillausseau, and Héron.

Financial Disclosure: Dr Feldman-Billard has received fees for lectures from Eli Lilly; Dr Massin has received fees for lectures and consultations from Eli Lilly and Takeda; and Dr Guillausseau has received fees for lectures and consultations from Astra-Zeneca, BMS, Eli Lilly, GlaxoSmithKline, Sanofi-Aventis, Servier, and Takeda.

Funding/Support: This study was supported by grants from Assistance Publique-Hôpitaux de Paris (CRC O2044) and Novo Nordisk (ALFEDIAM).

5. Azar ST, Barbati A. Nocturnal blood pressure elevation in patients with type 1 diabetes receiving intensive insulin therapy compared with that in patients receiving conventional insulin therapy. J Clin Endocrinol Metab. 1998;83(9):3190-3193.

HEALTH CARE REFORM

Coverage of FDA Medication Boxed Warnings in Commonly Used Drug Information Resources

A boxed (or “black box”) warning is the strongest medication-related safety warning that the Food and Drug Administration (FDA) can issue for a prescription drug.1 These warnings, which appear in the prescribing information, highlights of the prescribing information, and promotional materials for a given drug, are surrounded by a box that contains the word “WARNING” followed by a description of the safety risk.

The application of boxed warnings to commonly prescribed drugs in the past 5 years has captured the atten-