Relationship Between Hypoglycemic Episodes and Ventricular Arrhythmias in Patients With Type 2 Diabetes and Cardiovascular Diseases: Silent Hypoglycemias and Silent Arrhythmias

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OBJECTIVE

In patients with type 2 diabetes and cardiovascular diseases (CVDs), intensive treatment with insulin and/or sulfonylurea (SU) may be associated with excessive increased risk of hypoglycemic episodes. To evaluate the risk of critical arrhythmias related to glycemic variability, we carried out an observational study in type 2 diabetes patients with CVD.

RESEARCH DESIGN AND METHODS

Thirty patients with type 2 diabetes and documented CVD who had been treated with insulin and/or SU underwent 5 days of monitoring with a continuous glucose measurement system along with parallel electrocardiogram recording for monitoring of ventricular arrhythmias. Twelve age-matched patients with documented CVD who received treatment with metformin and/or dipeptidyl peptidase-4 inhibitor served as the control group. Patients were receiving stable treatment, and were instructed to notice symptoms of arrhythmias and hypoglycemia, respectively.

RESULTS

We observed a high incidence of asymptomatic severe episodes of hypoglycemia (<3.1 mmol/L) in patients receiving treatment with insulin and/or SU, whereas severe hypoglycemia did not develop in any of the control subjects. Patients with severe hypoglycemia (*n* = 12) had a higher number of severe ventricular arrhythmias (patients with versus without severe hypoglycemia, respectively: ventricular couplets 41.7 ± 81.8 vs. 5.5 ± 16.7; ventricular tachycardia 1.0 ± 1.9 vs. 0.1 ± 0.3). No direct correlation could be found among different variables of glucose profile, corrected QT interval, and ventricular arrhythmias.

CONCLUSIONS

Our results suggest that severe episodes of hypoglycemia are associated with an increased risk of severe ventricular arrhythmias.

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Patients with type 2 diabetes and cardiovascular diseases (CVDs) may represent a vulnerable high-risk group for hypoglycemic episodes (HEs) associated with arrhythmias and sudden death.

In patients with type 1 diabetes, sudden nocturnal death is described as "dead-in-bed" syndrome. A cause for this could be QTc prolongation leading to fatal ventricular arrhythmias due to long episodes of severe nocturnal hypoglycemia (1).

Diverse case reports about hypoglycemia and cardiac events are described in the literature (2,3), but it is still difficult to document these events in parallel. Moreover, many episodes with critical low glucose levels may be asymptomatic, and arrhythmias will be unrecognized during sleep.

Pathophysiological studies, partly with clamps, showed correlations between hypoglycemia and an increase of hormones like epinephrine and norepinephrine, which induce vasoconstriction, platelet aggregation, and thereby ischemia (4,5). Therefore, the question arose of whether strict glucose control with insulin and/or sulfonylurea, which is associated with increased risk of hypoglycemia and excessive glucose fluctuations, may have harmful effects on electric stability and myocardial blood flow.

In the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial, excessive mortality in the group receiving intensified glucose-lowering treatment has been discussed with respect to hypoglycemia being the cause for cardiovascular events (6). Severe, but not mild, hypoglycemia was associated with an odds ratio of 3.4 in a recently published retrospective observational study after adjustment for major risk factors and Charlson comorbidity index (7). A recently published retrospective register study in veterans reported a hazard ratio of 2.00 for cardiovascular events, and 1.76 for microvascular events for patients with HEs (8).

Little is known about the frequency of asymptomatic hypoglycemia, in particular nocturnal hypoglycemia; frequency of silent arrhythmias; and the relationship between these events in type 2 diabetes patients with CVD. Therefore, we used continuous glucose measurement and continuous electrocardiogram (ECG) monitoring in parallel for ~5 days in patients with type 2 diabetes, who had been treated with insulin and/or sulfonylurea, and documented CVD to investigate this in a cohort of frail patients.

RESEARCH DESIGN AND METHODS

Methods

Inclusion criteria were as follows: type 2 diabetes; age 50–80 years; proven CVD, including coronary heart disease, stroke, peripheral arterial disease, or cerebrovascular disease; and insulin and/or sulfonylurea treatment.

Exclusion criteria were as follows: type 1 diabetes; ECG changes like AV-Block II° and III°, or atrial fibrillation; implanted pacemaker or defibrillator; and treatment with antiarrhythmic drugs besides β-blockers and calcium channel blockers. Patients were excluded from the study if a blood sample, obtained at baseline, showed hyponatremia/hypernatremia, hypokalemia/hyperkalemia, or hypothyroidism/hyperthyroidism.

We recorded in parallel interstitial glucose (IG) concentrations with continuous glucose measurement system (CGMS) and long-term ECG for 5 days.

IG levels were measured every 5 min with CGMS Medtronic MiniMed Gold, and at day 2 patients ingested a standardized test meal. For ECG analysis, we used the Amedtec ECGpro system. IG levels between 3.1 and 3.9 mmol/L were defined as mild HEs, and IG levels <3.1 mmol/L IG were defined as severe episodes. Patients were instructed to notice all symptoms of hypoglycemia and arrhythmias with date and time in a predefined protocol during CGMS and ECG measurement.

Patient Characteristics

Thirty patients with type 2 diabetes and confirmed CVD, HbA_{1c} levels <9% (75 mmol/mol), and age 56–80 years, who had been treated with insulin and/or sulfonylurea, were considered.

Seventeen patients (57%) were treated with insulin, 4 patients (13%) were treated with sulfonylurea, and 9 patients (30%) were treated with a combination of insulin and sulfonylurea (comedications: anti-hypertensives 90%, β-blockers 70%, statins 93%). The following cardiovascular comorbidities were diagnosed: coronary heart disease 19 patients; combination of coronary heart disease and stroke or peripheral arterial disease 4 patients; cerebrovascular disease 4 patients; stroke 2 patients; and peripheral arterial disease 1 patients. Twelve age-matched patients with type 2 diabetes and confirmed CVD served as the control group. These patients were treated with anti-hyperglycemic agents that do not increase the risk of hypoglycemia: five patients received metformin, and seven patients received metformin in combination with a dipeptidyl peptidase-4 inhibitor. Eight patients (66%) used a β-blocker, and all of them received treatment with statins. The following cardiovascular comorbidities were diagnosed: coronary heart disease, 8 patients; combination of coronary heart disease and stroke or peripheral artery disease, 1; cerebrovascular disease, 2; and peripheral artery disease, 1.

The baseline characteristics of both groups are shown in Table 1.

Target Parameters

We calculated the following parameters with CGMS: average IG and SD; mean amplitude of glucose excursions (MAGE); area under the curve (AUC); minimum and maximum IG; frequency and time of HE. We calculated the following parameters with ECG: heart rate (in beats per minute [bpm]); QTc time; ventricular extrasystoles (VESs); couplets; triplets; and ventricular tachycardias (VTs). Heart rate variability was assessed as the SD of normal RR intervals (SDNNs).

RESULTS

As shown in Table 1, both groups were well-balanced for HbA_{1c}, blood pressure, parameters of lipid metabolism, and renal function.

Average IG as well as maximum IG, SD of IG values, MAGE, or the 24 h IG AUC were not different between the group at risk and the control group (Table 1);

Table 1—Baseline characteristics and parameters of glycemic control during 5 days of CGMS recording

Characteristics	Group	Mean	SD	*P* value	Range
Age (years)	1	67.6	6.4	0.540	56–80
	2	66.2	7.0		51–77
HbA_{1c} (%)	1	7.3	0.8	0.349	5.9–8.9
	2	7.6	0.7		6.6–9.0
HbA_{1c} (mmol/mol)	1	56	6.1	0.349	41–74
	2	60	5.5		51–75
Systolic BP (mmHg)	1	146.2	20.7	0.508	105–183
	2	142.0	10.1		125–155
Diastolic BP (mmHg)	1	78.8	9.2	0.528	61–98
	2	80.6	4.6		73–90
Sodium (mmol/L)	1	138.1	2.9	0.684	132.4–144
	2	137.7	3.2		132.5–143.2
Potassium (mmol/L)	1	4.42	0.36	0.727	3.6–4.9
	2	4.38	0.39		3.77–5.06
Cholesterol (mmol/L)	1	4.7	0.9	0.940	3.2–7.0
	2	4.7	1.3		2.7–6.1
HDL cholesterol (mmol/L)	1	1.2	0.3	0.180	0.7–1.8
	2	1.4	0.4		0.7–2.1
LDL cholesterol (mmol/L)	1	2.6	0.7	0.942	1.0–4.0
	2	2.5	0.9		1.3–3.6
Triglycerides (mmol/L)	1	2.4	1.7	0.052	0.4–7.9
	2	1.4	0.3		0.6–1.7
Creatinine (μmol/L)	1	82.3	21.3	0.280	68–124
	2	76.4	14.0		49–98
Mean IG	1	8.20	1.67	0.422	5.6–11.4
	2	8.63	1.15		5.9–10.3
Maximal IG (mmol/L)	1	15.7	3.3	0.578	9.5–22.2
	2	15.1	2.2		11.7–17.9
Minimal IG (mmol/L)	1	3.28	0.9	0.000	2.2–6.0
	2	5.01	1.0		3.7–6.7
SD of IG (mmol/L)	1	2.33	0.78	0.148	1.3–4.3
	2	1.97	0.55		1.2–3.0
AUC_D2 (mmol/L-1 h)	1	2,368	613	0.129	1,630–3,869
	2	2,670	438		1,714–3,479
MAGE (mmol/L)	1	4.9	1.5	0.649	2.78–9.42
	2	4.5	1.7		2.71–6.55
HEs per patient with IG <3.1 mmol/L	1	1.0	1.6	0.049	0–6
	2	0	0		0
HEs per patient with IG <3.9 mmol/L	1	2.6	3.1	0.010	0–12
	2	0.2	0.4		0–1
Time spent with IG <3.1 mmol/L (min)	1	39.5	70.5	0.008	0–240
	2	0	0		0
Time spent with IG <3.9 mmol/L (min)	1	156	255	0.047	0–996
	2	2.9	7.5		0–25
Distribution of HEs*					
Daytime (6:00 A.M.–10:00 P.M.): 11					
Nocturnal (10:00 P.M.–6:00 A.M.): 26					

Group 1, high-risk group (29 men, 1 woman); group 2, control group (9 men, 3 women). AUC_D2, AUC for glucose at recording day 2. χ^2 test for sex: $P = 0.063$. *<3.1 mmol/L for group 1.

however, the minimum IG was significantly lower in the group at risk for hypoglycemia (3.28 ± 0.9 vs. 5.01 ± 1.0 mmol/L, $P < 0.01$).

Over 5 days, the average number of HEs with an IG <3.1 mmol/L was 1.0 ± 1.6 per patient in the group at risk. We did not detect any severe HEs in the control group (Table 1). Furthermore, we found a higher frequency of mild HEs in patients at risk compared with the control group (2.6 ± 3.1 vs. 0.2 ± 0.4 HEs, $P < 0.05$). During the whole recording time, patients in the group at risk spent 39.5 ± 70.5 min with an IG level <3.1 mmol/L, and 156 ± 255 min with an IG level <3.9 mmol/L (Table 1). However, only 14 mild symptomatic hypoglycemias and 1 serious hypoglycemia were noticed by the patients. Silent HEs occurred more often at night (26 episodes at night vs. 11 during the daytime).

In the group at risk, 28 patients had VESs, but 11 control subjects also had VESs (Table 2). We observed, however, multiple ventricular arrhythmias (couplets 17 patients [56.7%]; triplets 10 patients [33.3%]; VTs 5 patients [16.7%]) in the high-risk group (Table 2). The longest VT continued for about 9 beats. We found a maximum of 258 couplets per patient, 32 triplets per patient, and 6 VTs per patient. However, only one patient noticed cardiac arrhythmias. No VT was observed among control subjects, and triplets were distinctly rarer among controls. SDNN as a marker of cardiac autonomic neuropathy was not significantly different between patients in the high-risk group versus subjects in the control group (Table 2). Furthermore, we did not find a significant correlation between SDNNs and ventricular arrhythmias.

We divided the whole study population into patients in whom severe HEs developed ($n = 12$) and patients in whom severe HEs did not develop ($n = 30$), independent from their glucose-lowering medication (Table 3). Again, we found a significantly higher frequency of severe cardiac arrhythmias such as couplets or VTs in patients with severe HEs.

Furthermore, we analyzed the relationship between markers of glucose fluctuations and ventricular arrhythmias in the high-risk group. The SD of IG levels was not related to VESs or more severe arrhythmias. For MAGE, we calculated the following tertiles: <4.02 mmol/L, 4.02–5.61 mmol/L, and >5.61 mmol/L. The duration of severe HEs (IG < 3.1 mmol/L) was classified into 0, 1–35, and >35 min. We found a significantly higher incidence of VESs in patients with a MAGE >5.61 mmol/L and severe HEs of >35 min ($P = 0.008$)

Table 2—ECG parameters during 5 days of parallel recording

Parameters	Group	Mean	SD	*P* value	Range	Comment
Mean heart rate (bpm)	1	69.4	8.6	0.096	55–89	
	2	78.0	15.8		64–96	
Minimal heart rate (bpm)	1	53.1	8.9	0.603	43–78	
	2	54.5	3.9		46–60	
Maximal heart rate (bpm)	1	110.5	17.7	0.293	79–159	
	2	117.6	23.9		72–154	
Mean QTc (ms)	1	376.9	48.7	0.531	300–475	
	2	388.0	50.2		307–445	
SDNNs (ms)	1	121.2	36.2	0.448	55–225	
	2	112.6	22		84–184	
SVESs per patient (*n*)	1	633	1,345	0.458	6–6,938	
	2	322	764		0–2,723	
VESs per patient (*n*)	1	3,607	7,977	0.027	1–35,328	28 patients in group 1
	2	144	217		0–732	11 patients in group 2
Couplets per patient (*n*)	1	20.5	53.3	0.054	0–258	17 patients (56.7%) in group 1
	2	0.9	1.2		0–4	6 patients (50%) in group 2
Triplets per patient (*n*)	1	2.2	6.3	0.080	0–32	10 patients (33.3%) in group 1
	2	0.1	0.3		0–1	1 patient (8.3%) in group 2
VTs per patient (*n*)	1	0.5	1.3	0.05	0–5	5 patients (16.7%) in group 1
	2	0	0		0	None in group 2

Group 1, high-risk group; group 2, control group; SVES, supra-VES.

(Supplementary Table 1). More severe ventricular arrhythmias were, however, not different between tertiles of MAGE (data not shown). Correlation analysis did not show a direct relationship between parameters of glycemic variability, quality of diabetes control, and risk of severe ventricular arrhythmias in this heterogeneous population. Case reports are represented in Supplementary Figs. 1 and 2.

CONCLUSIONS

Our investigations of parallel recording of CGMS and ECG reveal a high incidence of both asymptomatic episodes of critically low IG levels and silent severe ventricular arrhythmias in CVD patients with type 2 diabetes who were treated with insulin substitution therapy and/or sulfonylurea. Although only 1 serious HE and 14 mild symptomatic HEs were reported from 30 participants, we found a high incidence of asymptomatic episodes with IG levels $<$3.1 mmol/L (one HE per patient per 5 days). Twice as many HEs were recognized at night as during the daytime. This points to the fact that nocturnal HEs are under-reported but may be associated with serious cardiovascular complications. Even more critical, we detected a high incidence of asymptomatic serious ventricular arrhythmias in our patients, but only one patient reported arrhythmias. Ten patients (33.3%) had triplets, and 5 patients (16.7%) had VTs. These silent ventricular arrhythmias also occurred more at night than at daytime. In the ACCORD and ADVANCE studies, severe hypoglycemia did not show a direct relationship to cardiovascular events and mortality (6,9). Thus, the question was whether hypoglycemia labels a vulnerable group of patients, rather than the cause of death. Some investigators even suggest that mild hypoglycemia has no harmful effect on cardiovascular outcome (ischemic conditioning). ECG recording in the dead-in-bed syndrome in patients with type 1 diabetes without CVD revealed an increase in QTc time and rhythm disturbances only for long-lasting HEs of $>$30 to 150 min (1). Accordingly, we found a significantly higher number of VTs in patients with HEs $<$3.1 mmol/L (Table 3). Of notice, the first data in patients with heart failure and CGMS recording have shown that rapid glycemic fluctuations calculated as MAGE are a significant risk factor for arrhythmias and all-cause mortality if MAGE exceeds 5 mmol/L (10). In our high-risk group who had been treated with insulin and/or sulfonylurea, we found significantly more VESs in

Table 3—Relationship between severe HEs and cardiac arrhythmia during 5 days of parallel recording

Outcomes	HE	Mean	SD	*P* value
VESs per patient (*n*)	Yes	3,377	7,219	0.688
	No	2,371	6,416	
Couplets per patient (*n*)	Yes	41.7	81.8	0.024
	No	5.5	16.7	
Triplets per patient (*n*)	Yes	2.36	4.3	0.597
	No	1.33	5.8	
VTs per patient (*n*)	Yes	1.0	1.9	0.017
	No	0.1	0.3	

HE "Yes," *n* = 12; HE "No," *n* = 30.

patients with MAGE >5.61, representing the highest tertile of MAGE (Supplementary Table 1). For this high range of fluctuations, Monnier et al. (11) could show increased oxidative stress. Oxidative stress is likely to predispose patients to atrial fibrillation, a frequent finding in patients with type 2 diabetes (12). High MAGE was, however, not associated with a significantly increased number of triplets and VTs in our patients with CVD but without symptoms of severe heart failure. Mechanistic studies of hyperinsulinemic hypoglycemia in healthy subjects have shown a prolongation of QTc time and the production of proarrhythmogenic catecholamines. Thus, sympathetic activation by rapid fluctuations and critically low glucose levels may be an important link in provoking severe arrhythmias (13). However, we did not find a correlation between QTc and HEs in our study population. Another important mechanism in the pathogenesis of critical arrhythmias not considered in our study is the association of HEs and cardiac ischemia. As described by Desouza et al. (14), cardiac ischemia is particularly common in patients with high fluctuations (MAGE) in blood glucose who are receiving treatment with insulin. This may explain why in our patients with pre-existing CVD a high MAGE during longer periods of critically low glucose levels was associated with a higher rate of VESs.

In conclusion, patients with type 2 diabetes and CVD who receive treatment with insulin and/or sulfonylurea exhibit a high incidence of both asymptomatic HEs and silent severe arrhythmias, particularly at bedtime. This has to be considered in a patient-centered treatment decision. Prospective trials with parallel recording of CGMS and ECG are urgently needed to evaluate the predictors of harmful cardiovascular events of intensive glucose control.

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