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Reduced capacity of heart rate regulation in response to mild hypoglycemia induced by glibenclamide and physical exercise in type 2 diabetes

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ARTICLE INFO

Article history:
Received 1 June 2012
Accepted 4 December 2012

Keywords:
Hypoglycemia
Type 2 diabetes
Autonomic regulation
Heart rate variability
Glibenclamide

ABSTRACT

Objective. Decreased heart rate variability (HRV) is associated with enhanced mortality due to abnormal cardiac rhythm. While hypoglycemic events are increasingly common in the treatment of type 2 diabetes, HRV is part of the counter-regulation against low blood glucose levels. We hypothesized that HRV was impaired in mild hypoglycemia in diabetic individuals.

Materials/Methods. Hyperinsulinemic–hypoglycemic clamps were performed in twelve type 2 diabetic patients without cardiovascular disease and in non-diabetic subjects matched for age, sex, and weight. In an additional study, hypoglycemic events, induced by either a single morning dose of glibenclamide or physical exercise, were recorded for the subsequent 24 h. Blood glucose concentrations and electrocardiograms were continuously monitored. Serum hormone levels, hypoglycemic symptoms, and forearm blood flow were measured at defined time points.

Results. Occurrence of a symptomatic hypoglycemic episode (mean blood glucose 3.1 ± 0.4 mmol/l) attenuated most of the time and frequency domain measurements in both healthy and diabetic individuals. The magnitude of reduction of HRV parameters was significantly lower in diabetic compared to healthy subjects. Glibenclamide taken in the morning enhanced the daily number of mild hypoglycemic events compared with placebo or moderate exercise. Concordantly, 24-h mean HRV measurements were decreased.

Conclusion. HRV response to hypoglycemia is impaired in type 2 diabetic subjects resulting in a higher than expected risk for sudden arrhythmia following mild hypoglycemic episodes.

Abbreviations: HRV, heart rate variability; DAN, diabetic autonomic neuropathy; CAN, cardiovascular autonomic neuropathy; OAD, antidiabetic drug.

Eudract-CT No. 2008-003222-42.

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0026-0495/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.metabol.2012.12.003

1. Introduction

Compared to type 1 diabetes the risk of symptomatic hypoglycemia in type 2 diabetic patients is low, but increases with targeting intensive glycemic control [1]. Any hypoglycemic event is considered mild when the patient reacts without third-party assistance; whereas it is referred to as severe, if assistance is required for recovery. In recent clinical trials, prevalence of severe hypoglycemia was reported to depend on the mode of anti-diabetic therapy and on the presence of vascular co-morbidities [2,3]. However, little is known about the frequency of mild hypoglycemia because symptoms are often self-reported by the patient without confirmation of blood glucose measurement, and if blood glucose levels are documented they are frequently within the normal range. Repeated hypoglycemic events could compromise both the patient's self-care routine and the communication between patient and health care provider [4]. Thresholds for symptom recognition were diminished with the effect that especially older patients were unaware of low blood glucose concentrations [5].

Acute fluctuations of blood glucose levels were observed in diabetic patients exercising after a meal [6]. Such glucose changes had a powerful impact on heart rate variability (HRV) and induced signs of cardiac ischemia [7,8]. Elevation of epinephrine and norepinephrine release, enhancement of sympathetic neural activity [9], and decrease in cardiac vagal outflow [10–12] characterize the physiological regulation of low blood glucose levels. Reduction of HRV was associated with sudden cardiac death in patients with coronary heart disease [13–15], and was used to confirm autonomic neuropathy in diabetes patients [16,17].

On the basis of known associations between HRV, blood glucose, and cardiac mortality the present study investigated the association of mild hypoglycemic episodes in type 2 diabetic patients with specific patterns of HRV compared to non-diabetic persons. Only well-controlled patients without a history of cardiovascular disease or autonomic neuropathy were included in the study. Under these conditions changes in HRV during drug- or exercise-induced hypoglycemia were investigated.

2. Methods

2.1. *Type 2 diabetic patients*

Patients, either on an anti-diabetic diet or taking metformin, and non-diabetic subjects were admitted to pre-study visits for acquisition of informed consent and screening measurements. The maximal rate of oxygen consumption (VO_{2max}) was determined by indirect calorimetry (Deltatrac II, Datex, Freiburg, Germany) using an incremental protocol of 12.5 W/min performed on an electromagnetically braked cycle ergometer until the participant was unable to maintain a pedal cadence of 60 rpm. A 12-channel ECG was simultaneously recorded to exclude signs of cardiac ischemia. Patients were instructed to self-monitor their blood glucose regularly, maintain diet and medication, and avoid alcohol 24 h before admission.

All patients participated in a local diabetes care program with regular medical check-ups. Three of them had mild albuminuria, but none showed a history of diabetic autonomic neuropathy, myocardial infarction, stroke, or peripheral arterial disease. Mean duration of diabetes was 3.6±0.4 years, and glycated hemoglobin was within an acceptable range (6.5±0.2%, (Table 1). Non-diabetic subjects undergoing hypoglycemic clamp were matched pairwise by age, sex and weight to the diabetes patients. At the screening visit none of the participants had pathological electrocardiograms (ECG), history of cardiovascular disease, or were taking medication with known effects on heart rate, such as beta-blockers or calcium antagonists. Individuals diagnosed with retinopathy or reduced creatinine clearance were not included.

2.2. *Hypoglycemia induced by hyperinsulinemic clamp*

The study protocols conformed to good clinical practice guidelines and were carried out in accordance with the Declaration of Helsinki with approval by the University of Giessen ethics committee.

Subjects were admitted to the University of Giessen Clinical Research Unit between 6:00 and 7:00 pm in the evening before the clamp and fasted overnight. Blood glucose

Table 1 – Demographic and medical characteristics of type 2 diabetic patients.

Patient	Age (years)	BMI (kg/m^2)	Years with diabetes	Sex F/M	Therapy	HbA1c (%)	Diabetes-related complications	Triglycerides (mg/dl)
1	59	28.7	3	F	OAD	6.1	–	175
2	67	27.3	5	F	OAD	6.1	Albuminuria	201
3	75	22.1	2	M	OAD	6.7	–	64
4	57	28.0	2	M	OAD	6.4	–	168
5	40	39.5	3	M	Diet	6.5	–	137
6	66	22.1	4	M	Diet	6.2	–	182
7	70	32.1	3	M	OAD	7.1	Albuminuria	166
8	71	27.7	5	F	OAD	6.0	–	137
9	62	26.4	4	M	OAD	5.9	Albuminuria	112
10	61	25.9	5	F	OAD	7.1	–	98
11	61	26.1	4	F	Diet	6.5	–	167
12	53	28.4	3	F	Diet	6.2	–	132
Mean±SEM	56±3	28.1±1.6	3.6±0.4	5/6		6.5±0.2	–	144±15