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Impact of type 2 diabetes on cardiac autonomic responses to sympathetic stimuli in patients with coronary artery disease

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ABSTRACT

Type 2 diabetes (T2D) has shown limited impact on cardiac autonomic function in patients with cardiac disease at rest. The effect of T2D on autonomic responses to sympathetic stimuli, such as passive tilt and static exercise, is not well known in patients with coronary artery disease (CAD). Heart rate, arterial pressure, and their variability along with baroreflex sensitivity (BRS) were analyzed at supine rest and during passive head-up tilt (TILT) and static handgrip exercise (HG) in CAD patients with (T2D+, n = 68, 61 ± 6 years, 14 women) and without T2D (T2D−, n = 68, 62 ± 6 years, 17 women). The effect of T2D at rest and in responses to TILT and HG was examined. In T2D+, the normalized low-frequency (0.04–0.15 Hz) power of R–R intervals was higher at rest (44 ± 17 vs. 38 ± 17 nu, p = 0.015) and its response to TILT and HG was lower than that in T2D− (8 ± 21 vs. 2 ± 17 nu, p = 0.041 and 3 ± 18 vs. −4 ± 15 nu, p = 0.019, respectively). Vagally mediated heart rate variability indices and BRS were not different between T2D+ and T2D−. We concluded that T2D has a specific impact on low-frequency oscillation of R–R interval among patients with angiographically documented CAD. This may indicate increased basal sympathetic modulation of sinoatrial node and lower sympathetic responsiveness to sympathetic activation by baroreceptor unloading and exercise pressor response. Limited effects of T2D on vagally mediated heart rate variability and baroreflex were observed in the patients with CAD.

1. Introduction

Diabetes impairs cardiovascular autonomic regulation in patients without evidence of cardiac disease (Masaoka et al., 1985; Pagani et al., 1988a; Frattola et al., 1997; Tank et al., 2001; Gulli et al., 2005; Schroeder et al., 2005; Yun et al., 2010). Typically, this has been observed as decreased heart rate (HR) variability and baroreflex sensitivity (BRS) at rest that mostly indicates depressed vagal modulation of sinoatrial node. Despite the deleterious effects of type 2 diabetes (T2D) on cardiac mortality in patients with cardiac disease (Haffner et al., 1998; Junttila et al., 2010), there are only few studies describing cardiac autonomic function in cardiac patients with T2D. Surprisingly, no significant decrements in vagally mediated HR variability and BRS have been observed in T2D patients with coronary artery disease (CAD) or heart failure compared to those without T2D (Burger and Aronson, 2001; Wykretowicz et al., 2005; Kiviniemi et al., 2010b). Potential reason for these unexpected findings may be that they have been limited to resting or ambulatory conditions. For instance, lesser vagal activation has been observed in cardiac patients with T2D during acute post-exercise conditions involving autonomic challenge (Neves et al., 2011; Karjalainen et al., 2012).

Passive head-up tilt has been a widely used test to detect abnormal autonomic regulation induced by diabetes (Pagani et al., 1988b; Gulli et al., 2005; Yun et al., 2010). Normal autonomic response to such baroreceptor unloading involves decreased vagally mediated HR variability and prominent low-frequency (LF, 0.04–<0.15 Hz) oscillation of R–R interval (RRi) describing orthostatic sympathetic excitation (Montano et al., 1994; Pagani et al., 1997; Furlan et al., 2000; Kiviniemi et al., 2010a). Interestingly, decreased response in LF oscillations of RRi to passive tilt has been reported specifically in patients with diabetes (Pagani et al., 1988b; Gulli et al., 2005; Yun et al., 2010), mostly without discriminating the type or insulin-dependency of diabetes, however. Handgrip exercise is another autonomic challenge that has been used to assess autonomic responsiveness to sympathetic stimuli in patients with diabetes (Ewing et al., 1985; Franklin et al., 2008; Hagglund et al., 2012). Sympathetic excitation and vagal withdrawal during exercise occur via mechanisms different from passive tilt and include central baroreflex resetting and metaboreflex activation (Rowell and O'Leary, 1990). Therefore, it provides substantial information on autonomic function in diabetes.

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It is not known how T2D affects autonomic responses to passive tilt and handgrip exercise in patients with CAD. First, it is important to address whether T2D induces impairments in autonomic function that are additive to those associated with CAD. Secondly, whereas resting measurements have revealed limited effects of T2D on autonomic function in patients with cardiac disease, such assessments during autonomic challenge may prove to be more sensitive. Therefore, the primary purpose of the present study was to test the hypothesis that T2D impairs cardiac autonomic function, particularly in responses of LF oscillatory patterns to sympathetic stimuli, in patients with angiographically documented CAD.

2. Methods

2.1. Subjects and study protocol

The present study is part of the ARTEMIS study (Innovation to Reduce Cardiovascular Complications of Diabetes at the Intersection) in the Division of Cardiology at Oulu University Hospital (Oulu, Finland) and the Department of Exercise and Medical Physiology at Verve (Oulu, Finland). The ARTEMIS study is registered at ClinicalTrials.gov, Record 1539/31/06. The study was performed according to the Declaration of Helsinki, the local research ethics committee of the Northern Ostrobothnia Hospital District approved the protocol, and all the subjects gave their written informed consent.

All the patients were diagnosed as having CAD, which had been documented previously by coronary angiography. Patients with CAD and T2D (T2D+ group, n = 80, 18 women, duration of T2D: 74 ± 84 months) and CAD patients without T2D (T2D− group, n = 80, 20 women) were recruited from the ARTEMIS database, observing the following exclusion criteria: advanced age > 70 years, BMI > 40 kg/m^2, NYHA class III or IV, left ventricular ejection fraction < 40%, scheduled cardiac revascularization therapy, heart failure, unstable angina pectoris, severe peripheral atherosclerosis, type 1 diabetes, pre-diabetes, or inability to perform an exercise stress test, e.g. due to musculoskeletal problems. Type 2 diabetes was verified according to the current criteria (WHO, 1999). Patients who had a fasting capillary plasma glucose level ≥7.0 mmol·L^{-1} or 2 h plasma glucose during OGTT ≥ 12.2 mmol·L^{-1} who were on antihyperglycemic medication based on a prior diagnosis of T2D were included in the T2D+ group. Patients with pre-diabetes, i.e. impaired fasting glucose (two-hour plasma glucose < 8.9 mmol·L^{-1} and fasting plasma glucose ≥ 6.1 but ≤6.9 mmol·L^{-1}) or impaired glucose tolerance (two-hour plasma glucose ≥ 8.9 but ≤12.1 mmol·L^{-1} and fasting plasma glucose < 7.0 mmol·L^{-1}) were excluded. Coronary artery disease and its severity were assessed by measurement of the SYNTAX score (n = 130) in coronary angiography (Sianos et al., 2005), and left ventricular mass index (LVMI) and systolic (ejection fraction, LVEF) and diastolic function (ratio of early transmitral flow velocity to early diastolic mitral annulus velocity, E/E′) were measured with two-dimensional tissue Doppler echocardiography (Vivid 7, GE Healthcare, Wauwatosa, WI, USA). Urine and fasting blood samples were obtained for analysis of renal function, inflammation markers, blood lipids, insulin, plasma glucose, and glycated hemoglobin (Oulu University Hospital, Oulu, Finland).

The patients were invited to further laboratory measurements in the Department of Exercise and Medical Physiology at Verve (Oulu, Finland). The subjects were not allowed to eat or drink coffee for 3 h before the tests. Strenuous physical activity and alcohol consumption were prohibited on the day of the test and the preceding day. Anthropometric data (height, weight, waist and hip circumference) and maximal voluntary handgrip force (best of three attempts) (Jamar Hand Dynamometer, Sammons Preston, Inc., IL, USA) were measured. Subsequent protocol included 5-min supine baseline, 5-min passive tilt (TILT, 80°), 10-min recovery, 5-min supine baseline and 5-min static handgrip at 20% of maximal handgrip force (HG). The patients lay down on a tilt table with arm supports adjusted at heart level and a seat on which the patients sat, avoiding foot contact on the surface during the passive tilt. Standard lead-II ECG (Cardiolife, Nihon Kohden, Japan), expiration flow (Spirometer, ADInstruments, Australia), and finger arterial pressure (Nexfin, BMEYE Medical Systems, the Netherlands) were continuously recorded during the protocol using a PowerLab data acquisition system (PowerLab/8SP, ADInstruments, Australia) with a sampling frequency of 1000 Hz. Arterial pressure was also measured by automated sphygmomanometer (Tango, SunTech, Raleigh, NC, USA), which was used for re-calibration of the finger arterial pressure signal (Epstein et al., 1991). The patients were allowed to breathe spontaneously throughout the protocol.

After autonomic testing, the patients performed an incremental symptom-limited maximal exercise test on a bicycle ergometer (Monark Ergomedic 839 E, Monark Exercise AB, Vansbro, Sweden) for assessment of peak oxygen uptake and maximal exercise capacity. The test was started at 30 W and the work rate was increased by 15 W in men and 10 W in women every minute until voluntary exhaustion or ST segment depression >0.2 mV on a 15-lead ECG (GE Healthcare, CAM-14, Freiburg, Germany). Ventilation and gas exchange (M909 Ergospirometer, Medikro, Kuopio, Finland) were monitored continuously during the test. The highest 1-min mean value of oxygen consumption was taken to express peak oxygen uptake. Exercise capacity was calculated in metabolic equivalents (METs) from the mean workload during the last minute of the test. Relative exercise capacity was expressed as a percentage of the predicted exercise capacity, which was calculated using the following formula: $EC_{pred} = 18 - (0.15 \cdot age)$ for men and $14.7 - (0.13 \cdot age)$ for women (Kim et al., 2007).

2.2. Data analysis

R–R interval (RRi) and beat-to-beat systolic arterial pressure (SAP) values were extracted from the continuous ECG and arterial pressure recordings at the 5-min baseline recording and during the two last minutes of TILT and HG as discrete event series that were then interpolated at 2 Hz (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). In order to have time-synchronous signals, the respiratory signal was down-sampled at 2 Hz, as well. Very-low-frequency components (<0.04 Hz) of the RRi and SAP oscillations were removed using the Savitzky–Golay method (Orfanidis, 1996). The respiratory component was extracted using a least-mean-square adaptive filter described previously in detail (Tiinanen et al., 2008; Kiviniemi et al., 2010b). This method enables accurate measurement of respiratory sinus arrhythmia (RSA) and low-frequency (0.04–<0.15 Hz) oscillation in RRi and SAP which is not confounded by slow breathing. Power spectral analyses of RRi and SAP variability were performed using a fast Fourier transform (Welch method) where segments of 128 samples overlapped in 50% steps throughout the analyzed period. The power spectrum densities of the LF oscillations in RRi and SAP were calculated as absolute (ms^2, mm Hg^2) and normalized units ($nu = 100 \cdot Power \cdot Power_{0.04–0.40\ Hz}$ (without filtering)$^{-1}$) (Kiviniemi et al., 2010b). LF oscillation of RRi includes both vagal and sympathetic effects on sinoatrial node (Akselrod et al., 1981). Normalized power LF component of RRi oscillations and the absolute power of LF oscillations in SAP have been used to estimate cardiovascular sympathetic modulation (Malliani et al., 1991; Pagani et al., 1997). RSA (ms^2) was calculated from the power subtracted by adaptive filtering at 0.04–0.40 Hz (RSA = $Power_{0.04–0.40\ Hz}$ (without filtering) − $Power_{0.04–0.40\ Hz}$ (after filtering)) and was used to evaluate cardiac vagal modulation (Akselrod et al., 1985). To establish the resonant frequency of the LF component, median frequencies of RRi and SAP oscillations at LF were calculated as the frequency that divides the LF band in two segments having equal power (Stulen and DeLuca, 1981). Baroreflex sensitivity (BRS) was analyzed from the LF band by using the alpha method (Pagani et al., 1988a). Mean breathing frequency was also calculated for each data sequence.