# Glycemic Variability Is Associated With Reduced Cardiac Autonomic Modulation in Women With Type 2 Diabetes

DOI: 10.2337/dc14-0654

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## OBJECTIVE

**To investigate the sex differences in cardiac autonomic modulation in patients with newly diagnosed type 2 diabetes and to determine whether cardiac autonomic modulation is associated with glycemic variability.**

## RESEARCH DESIGN AND METHODS

**We investigated a cohort consisting of 48 men and 39 women with non-insulin-treated type 2 diabetes and a known duration of diabetes <5 years. All patients were equipped with a continuous glucose monitoring sensor for 3 days, and the mean amplitude of glycemic excursions (MAGE) was calculated to obtain individual glycemic variability. Cardiac autonomic modulation was quantified by analysis of heart rate variability (HRV) in time and frequency domains and during cardiovascular reflex tests (response to standing [RS], deep breathing [expiration–inspiration], and Valsalva maneuver).**

## RESULTS

**Sex differences in age- and heart rate–adjusted HRV measures were observed in both active and passive tests. Low frequency (LF; $P = 0.036$), LF/high frequency (HF; $P < 0.001$), and RS ($P = 0.006$) were higher in men, whereas expiration–inspiration ($P < 0.001$), but not HF, was higher in women. In women, reduced cardiac autonomic modulation as assessed by the standard deviation of normal-to-normal intervals ($P = 0.001$), the root mean square of successive differences ($P = 0.018$), LF ($P < 0.001$), HF ($P = 0.005$), total power ($P = 0.008$), RS ratio ($P = 0.027$), and expiration-to-inspiration ratio ($P = 0.006$) was significantly associated with increased glycemic variability as assessed by MAGE. This was not the case in men. The association in women persisted in a multivariate regression analysis controlling for weight, mean heart rate, blood pressure (systolic), and triglycerides.**

## CONCLUSIONS

**In patients with newly diagnosed and well-controlled type 2 diabetes, increased glycemic variability was associated with reduced cardiac autonomic modulation in women but not in men.**

Evidence points toward a cardioprotective effect of sex hormones (estrogen and progesterone) in premenopausal women, one possibly mediated through improved cardiac autonomic balance both centrally and peripherally by suppression of sympathetic tone and elevation of parasympathetic tone (1,2). The presence of diabetes has been shown to reduce the sex difference and minimize cardioprotection in

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Received 13 March 2014 and accepted 8 December 2014.

Clinical trial reg. no. NCT00674271, clinicaltrials.gov.

women (3), possibly by suppressing cardiac parasympathetic tone (4). In diabetes, hyperglycemia apparently contributes relatively more to increased cardiovascular risk in women compared with men (5,6). A recent large, population-based, retrospective cohort study of more than 70,000 individuals supports a sex difference in all-cause and cardiovascular mortality in individuals with diabetes, implying a greater risk of mortality among women than men with diabetes (7). However, this increased risk of mortality and hospitalizations in women with diabetes is not fully understood (7). In both men and women with diabetes chronic hyperglycemia predicts all-cause mortality and is involved in the development of autonomic neuropathy (8,9). Autonomic neuropathy is a severe complication of diabetes and is associated with higher cardiovascular mortality (10). A recent study reported that not only hyperglycemia but also glycemic variability (GV), assessed by postprandial glucose, were stronger predictors of cardiovascular events in women than in men (11). Large GV increases circulating concentrations of inflammatory cytokines more than continuous hyperglycemia (12), and it is related to oxidative stress in patients with diabetes (13). In line with this, autonomic dysfunction, which develops early in diabetes (14), may occur alongside alterations in various inflammatory cytokines, including interleukin-6 (15). Accumulating data suggest a link between the small and rapid glycemic excursions that are reflected only in GV and autonomic dysfunction (16,17). GV affects sympathovagal balance in type 2 diabetic patients with optimal metabolic control and without overt autonomic neuropathy (18).

The aim of this study was to investigate whether there is a sex difference in cardiac autonomic modulation in newly diagnosed, non-insulin-treated patients with type 2 diabetes and whether cardiac autonomic modulation is associated with GV in men and women.

## RESEARCH DESIGN AND METHODS

Patients with newly diagnosed type 2 diabetes (48 men and 39 women) were consecutively recruited from the outpatient clinics at Aarhus University Hospital, Aarhus, Denmark. The cohort is part of an ongoing study of type 2 diabetes complications (19–21). In brief, inclusion criteria were age >18 years, diagnosis of type 2 diabetes according to World Health Organization criteria, known duration of diabetes <5 years, no insulin treatment, and no cardiac autonomic neuropathy diagnosis. Exclusion criteria were acute or chronic infectious disease, end-stage renal failure, pregnancy or lactation, cancer, and contraindications to MRI (claustrophobia, magnetic material in the body, and body weight >120 kg). MRI data are presented elsewhere (19). The study protocol was approved by the local ethical committee, and the study was conducted according to the principles of the Helsinki Declaration II. All patients gave their written informed consent.

### Assessment of Glycemic Variability

For 3 days, all patients were equipped with a continuous glucose monitoring (CGM) sensor (CGMS iPro Continuous Glucose Recorder; Medtronic MiniMed). At Aarhus University Hospital, Denmark, the CGM sensor was inserted in the morning of day 0 and removed on day 3. Patients were instructed to maintain their usual diet and treatment and were instructed not to change their meal patterns during the period of CGM. The patients also were instructed to perform self-monitored blood glucose measurements, using a OneTouch Ultra 2 blood glucose monitor (Lifescan, Milpitas, CA), before breakfast, lunch, and dinner and before going to bed. The CGM and self-monitored blood glucose data collection software were synchronized upon insertion of the CGM sensor. Upon return of the equipment, data were downloaded to a computer for analysis of the glucose profile.

On days 2 and 3 of the CGM, the mean amplitude of glycemic excursions (MAGE) was calculated to assess individual GV. MAGE was defined as the average of absolute values of differences between adjacent peaks and nadirs for all differences greater than 1 SD (22). MAGE is sensitive to large excursions in blood glucose and has previously been proposed as a component to assess glycemic control, along with $HbA_{1c}$, postprandial glucose, and fasting plasma glucose.

### Assessment of Cardiac Autonomic Modulation

A detailed description of autonomic measures has been reported previously (16). Heart rate variability (HRV) in time and frequency domains and during conventional cardiovascular reflex tests was measured by laboratory technicians using Vagus (Medicus Engineering, Denmark) (23–25). This device automatically records an electrocardiographic (ECG) signal, with a sampling frequency of 1,000 Hz, from which heart rate and HRV are deduced and shown on a display. All data, including the ECG measurements and the actual exhale pressure during the Valsalva maneuver (VM), are automatically stored on a memory card in the device and evaluated manually by a central technician. All laboratory tests were performed between 9:00 A.M. and 1:00 P.M. in a quiet and isolated examination room, according to recommendations (26). Smoking, food, and liquids containing caffeine were prohibited 2 h before laboratory testing.

### Passive HRV Tests

The following time-domain HRV matrices were used: SD of normal-to-normal intervals (SDNN) and root mean square of successive differences (RMSSD). The HRV parameter SDNN is a measure of combined sympathetic and parasympathetic activity (27), whereas RMSSD reflects only parasympathetic activity (28). In the frequency domain we used the low-frequency (LF; 0.04–0.15 Hz) and high-frequency (HF; 0.15–0.4 Hz) components, as well as the total power (TP; ≤0.4 Hz). The LF component is influenced by sympathetic, parasympathetic, and baroreflex sensitivity. The HF band from 0.15–0.4 Hz is influenced by parasympathetic activity and normal breathing rhythm, and it mainly contributes to power with a center frequency around 0.3 Hz (29). The TP is a measure of and correlates to SDNN in the time domain.

### Active HRV Tests

Three cardiovascular reflex tests were performed using a standard protocol following recommendations (26,30): *1*) The response to standing (RS) ratio is the ratio of the maximum and minimum heart rate during and shortly after standing from a supine position. *2*) The expiration-to-inspiration (EI) ratio is the mean ratio of the maximum and minimum heart rate during a deep-breathing respiratory cycle. *3*) The VM ratio is the ratio of the maximum and minimum heart rate during and immediately after a VM.

Clinical data were collected before CGM measurements and included medical

history, lifestyle, blood pressure, ECG, and fasting blood samples, including plasma glucose, $HbA_{1c}$, lipids, and lipid concentrations. Measurements of HRV during passive tests (5 min of supine resting) and during active cardiovascular reflex tests (RS, deep breathing, and the VM) were performed in all patients.

### Statistical Analysis

Patient characteristics and results are presented as mean (SD) or median (25th, 75th percentiles), as appropriate. Transformation with natural logarithms was performed to adjust for skewness and to obtain a normal distribution. Data were inspected using Q-Q plots. Adjustment for the effect of age and heart rate on HRV matrices were performed with multilinear regression analysis within each sex. To assess sex differences in the effect of glycemic variability on HRV, women and men were divided according to MAGE quartile (Q1–4); Q4 was the group with the highest GV. The Jonckheere trend test was used to test for linear trends in HRV parameters in relation to MAGE quartile for both sexes. ANCOVA statistics were used first to assess the impact of the interaction of sex and GV on HRV. Thereafter covariates were added to adjust for variables known to influence HRV. To describe possible associations between MAGE and measures of HRV in the total population, multiple linear regression analysis with MAGE as the dependent variable was used.

## RESULTS

The characteristics of the study population according to sex are presented in Table 1. No major sex differences were seen, although weight and blood pressure were higher in men than in women. There were no sex differences in measures of GV. As shown in Table 2, age- and heart rate–adjusted measures of HRV showed a significantly higher sympathetic tone in men assessed by LF power ($P = 0.036$); furthermore, the LF-to-HF ratio ($P < 0.001$) exhibited a significant shift toward LF among men. Age- and heart rate–adjusted RS was significantly higher in men ($P = 0.006$), and deep breathing was higher in women ($P < 0.001$).

**Table 1—Baseline characteristics of the study population**

| | Sex | | |
|---|---|---|---|
| Baseline data | Men | Women | *P* value |
| Patients, *N* (%) | 48 (55) | 39 (45) | |
| Age (years) | 62 (9) | 60 (10) | NS |
| $HbA_{1c}$ (mmol/mol) | 46.4 (3) | 49.0 (3) | NS |
| $HbA_{1c}$ (%) | 6.4 (0.6) | 6.6 (0.7) | NS |
| Weight (kg) | 93.0 (15) | 80.3 (14) | 0.0001 |
| BMI ($kg/m^2$) | 29.6 (4) | 29.7 (5) | NS |
| Current smokers (%) | 22.0 | 20.0 | NS |
| Blood pressure (mmHg) | | | |
| Systolic | 129 (11) | 123 (13) | 0.05 |
| Diastolic | 81 (9) | 77 (8) | 0.02 |
| Pulse pressure (mmHg) | 45 (15) | 45 (13) | NS |
| Heart rate (bpm) | 65 (10) | 68 (9) | NS |
| Total cholesterol (mmol/L) | 4.3 (0.7) | 4.5 (0.8) | NS |
| LDL cholesterol (mmol/L) | 2.2 (0.6) | 2.4 (0.7) | NS |
| HDL cholesterol (mmol/L) | 1.3 (0.3) | 1.4 (0.3) | NS |
| Triglycerides (mmol/L) | 1.6 (0.8) | 1.6 (0.7) | NS |
| Glycemic variability | | | |
| Mean (mg/dL) | 126 (18) | 123 (20) | NS |
| SD | 24 (10) | 26 (12) | NS |
| MAGE (mg/dL) | 64 (36) | 65 (38) | NS |

Continuous measures are shown as mean (SD). NS, not significant.

### Grouping MAGE into Quartiles

As shown in Table 3, MAGE values were divided into quartiles (Q1 <40; 40 < Q2 < 54; 54 < Q3 < 81; Q4 >81 mg/dL). The difference between GV in Q1 compared with Q4 is illustrated by two cases of each sex (Fig. 1). In women, a consistent reduction in mean HRV was related to increased MAGE/GV. This observation was confirmed by the Jonckheere trend test: Among women, SDNN ($P = 0.001$), RMSSD ($P = 0.018$), LF power ($P < 0.001$), HF power ($P = 0.005$), TP ($P = 0.008$), RS ratio ($P = 0.027$), and EI ratio ($P = 0.006$)

**Table 2—HRV measures adjusted for age and heart rate**

| | Values by sex | | | Values by sex, adjusted for age and heart rate | | |
|---|---|---|---|---|---|---|
| HRV | Men | Women | *P* value | Men | Women | *P* value |
| Passive* | | | | | | |
| SDNN (ms) | 34 (27; 49) | 33 (22, 48) | NS | 35 (29, 44) | 30 (24, 43) | NS |
| RMSSD (ms) | 22 (12; 33) | 21 (14, 30) | NS | 22 (16, 30) | 19 (13, 31) | NS |
| LF power ($ms^2$) | 95 (35; 202) | 80 (26, 222) | NS | 93 (69, 156) | 68 (39, 136) | 0.036 |
| HF power ($ms^2$) | 57 (18; 96) | 60 (16, 153) | NS | 51 (28, 95) | 44 (19, 132) | NS |
| LF-to-HF ratio | 1.7 (1.0; 4.2) | 1.7 (0.69, 3.0) | NS | 1.9 (1.6, 2.7) | 1.5 (1.1, 2.0) | <0.001 |
| TP ($ms^2$) | 401 (151; 657) | 330 (151, 657) | NS | 392 (262, 603) | 276 (172, 537) | 0.053 |
| Active† | | | | | | |
| RS (ratio) | 1.27 (0.20) | 1.22 (0.15) | NS | 1.27 (0.09) | 1.22 (0.08) | 0.006 |
| EI (ratio) | 1.20 (0.12) | 1.24 (0.13) | NS | 1.20 (0.06) | 1.24 (0.04) | <0.001 |
| VM (ratio) | 1.57 (0.26) | 1.63 (0.37) | NS | 1.57 (0.11) | 1.63 (0.18) | NS |

Continuous measures are shown as mean (SD) or median (25th; 75th percentile). Sex differences were tested by a parametric two-sample *t* test. *Natural log transformed for analysis. The following passive HRV parameters were used: passive tests; SDNN, RMSSD, LF power, HF power, TP, and LF-to-HF ratio. †The following active tests were used: response to standing (RS), deep breathing (EI), and Valsalva maneuver (VM). NS, not significant.

**Table 3—Passive and active HRV test measures in women and men according to MAGE quartiles**

| | MAGE quartile subgroups (mg/dL) | | | | | |
|---|---|---|---|---|---|---|
| | < 40 > | < 54 > | < 81 > | | Regression* | |
| Tests | Q1 | Q2 | Q3 | Q4 | β | *P* value |
| Patients (*n*) | | | | | | |
| Women | 9 | 13 | 6 | 11 | | |
| Men | 13 | 7 | 17 | 11 | | |
| SDNN (ms) | | | | | | |
| Women† | 43 (38, 60) | 33 (23, 50) | 26 (21, 38) | 22 (14, 40) | −0.18 | >0.01 |
| Men | 39 (27, 46) | 36 (20, 46) | 34 (24, 51) | 33 (21, 49) | | 0.73 |
| RMSSD (ms) | | | | | | |
| Women† | 30 (21, 47) | 19 (12, 29) | 14 (9, 24) | 17 (9, 30) | −0.19 | 0.03 |
| Men | 22 (21, 32) | 24 (15, 29) | 22 (10, 35) | 18 (7, 34) | | 0.84 |
| LF power ($ms^2$) | | | | | | |
| Women† | 137 (80, 335) | 113 (38, 332) | 64 (24, 126) | 20 (9, 59) | −1.01 | >0.01 |
| Men | 99 (33, 196) | 43 (29, 130) | 149 (55, 238) | 93 (24, 294) | | 0.35 |
| HF power ($ms^2$) | | | | | | |
| Women† | 123 (71, 396) | 49 (15, 161) | 29 (13, 74) | 29 (6, 132) | −1.02 | >0.01 |
| Men | 73 (49, 89) | 59 (32, 100) | 50 (10, 76) | 36 (7, 157) | | 0.48 |
| TP ($ms^2$) | | | | | | |
| Women† | 625 (389, 809) | 383 (162, 994) | 230 (153, 443) | 152 (62, 305) | 0.98 | >0.01 |
| Men | 421 (239, 634) | 472 (181, 520) | 366 (213, 711) | 300 (172, 860) | | 0.50 |
| RS ratio | | | | | | |
| Women† | 1.29 (0.16) | 1.22 (0.16) | 1.18 (0.10) | 1.15 (0.13) | | 0.30 |
| Men | 1.25 (0.15) | 1.34 (0.37) | 1.25 (0.15) | 1.25 (0.15) | | 0.61 |
| EI ratio | | | | | | |
| Women† | 1.32 (0.14) | 1.24 (0.11) | 1.24 (0.11) | 1.15 (0.09) | −0.0017 | 0.02 |
| Men | 1.16 (0.07) | 1.21 (0.20) | 1.18 (0.09) | 1.23 (0.12) | | 0.44 |
| VM ratio | | | | | | |
| Women | 1.79 (0.36) | 1.57 (0.34) | 1.50 (0.28) | 1.62 (0.44) | | 0.68 |
| Men | 1.60 (0.28) | 1.59 (0.35) | 1.58 (24) | 1.49 (0.19) | | 0.86 |

Data are mean (SD) or median (25th percentile [quartile 1], 75$^{th}$ percentile [quartile 2]). *Linear regression with adjustment for weight, blood pressure (systolic), heart rate, and triglycerides, presented as adjusted effect (β) estimates for MAGE and adjusted *P* values. †Significant linear trend ($P < 0.05$).

were all significantly correlated to MAGE quartiles. Among men, none of the HRV parameters were significantly trend-related to MAGE quartiles: SDNN ($P = 0.427$), RMSSD ($P = 0.196$), LF power ($P = 0.554$), HF power ($P = 0.089$), TP ($P = 0.49$), RS ratio ($P = 0.948$), EI ratio ($P = 0.244$), and VM ratio ($P = 0.454$).

When ANCOVA statistics were applied to data, interaction between sex and MAGE quartiles were significant predictors of LF power ($P = 0.035$), TP ($P < 0.001$), and EI ratio ($P = 0.024$). This relationship remained significant for LF power ($P = 0.018$), TP ($P = 0.0011$), and EI ratio ($P = 0.014$) when the following covariates were added to the model: $HbA_{1c}$, age, BMI, systolic blood pressure, and mean heart rate. Adjusting for medications with a potential beneficial effect on the cardiovascular system (ACE inhibitors and β-blockers) did not alter the association. The association between MAGE quartiles and measure of autonomic function LF power and EI is illustrated in Fig. 2.

### Without Grouping MAGE into Quartiles

When using MAGE without grouping to predict measures of autonomic function in a multiple linear regression controlling for weight, mean heart rate, blood pressure (systolic), and triglycerides (Table 1), MAGE remained a significant predictor. In women SDNN ($\beta = -0.18$; $P > 0.01$), RMSSD ($\beta = -0.19$; $P = 0.03$), LF power ($\beta = -1.01$; $P > 0.01$), HF power ($\beta = -1.02$; $P > 0.01$), and EI ratio ($\beta = -0.0017$; $P = 0.02$) were significant. VM and RS were not significant. In men, no significant findings were observed.

## CONCLUSIONS

The main finding of this study is that GV is significantly associated with cardiac autonomic modulation in women but not in men. This occurred despite no observed sex differences in overall regulation of $HbA_{1c}$, GV, cholesterol levels, and smoking habits. Cardiac autonomic modulation was measured noninvasively with HRV in the resting state and during active tests, which is a well-established diagnostic method to assess cardiac autonomic neuropathy in patients with diabetes (16). Cardiac autonomic neuropathy is a severe complication of diabetes and is associated with impaired left ventricular function, impaired dilations of coronary resistance vessels, unawareness of hypoglycemia, exercise intolerance, increased intraoperative cardiovascular risk, increased arterial pulse pressure, and a higher prevalence of reduced circadian variation in blood pressure (31). Furthermore, cardiac autonomic neuropathy has been associated with an increased risk of compromised cerebral blood flow (32,33), hypertension (34), silent myocardial ischemia (35), and higher cardiovascular mortality (10).

The benchmark target in glycemic control is achieving and keeping $HbA_{1c}$ at or

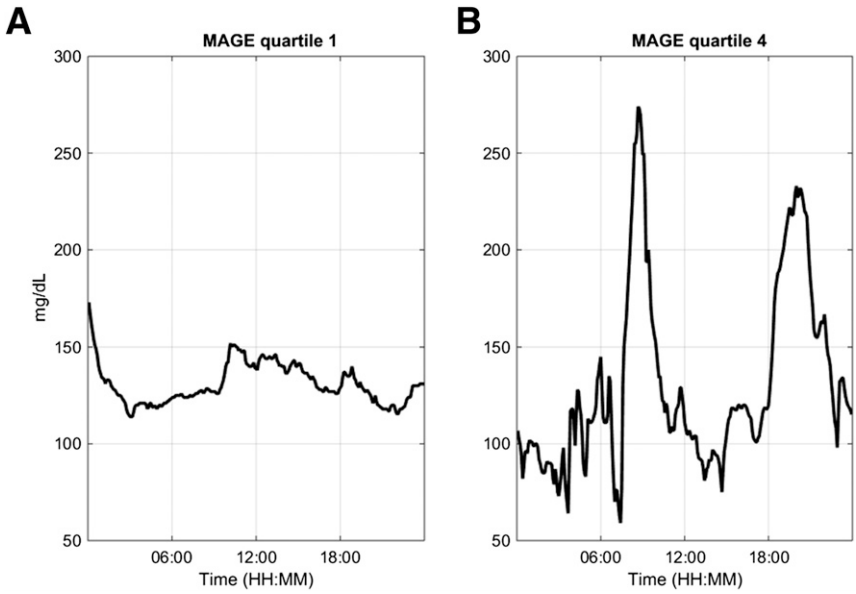


**Figure 1**—The graphs show 24-h glycemic profiles from CGM. *A*: Low glycemic variability, MAGE quartile 1 (<40 mg/dL), in a woman (age 74; $HbA_{1c}$ 6.7% [50 mmol/mol]). *B*: Pronounced glucose fluctuations, MAGE quartile 4 (>81 mg/dL), in a woman (age 61; $HbA_{1c}$ 6.9% [52 mmol/mol]). HH, hours; MM, minutes.

below 7.0% (53 mmol/mol). However, reaching this target with intensive glycemic control has been related to autonomic neuropathy and sudden death (36). Our result adds to the growing body of evidence demonstrating that $HbA_{1c}$ alone does not reflect all important aspects of glycemic disruption, especially in patients with autonomic dysfunction.

It is well known that increased resting heart rate is associated with increased risk of all-cause mortality (30,36–38). In this study, however, we used both active and passive HRV tests, which provide early and more detailed information of the imbalance in the autonomic nervous system (39). Furthermore, heart rate alone cannot be used as a reliable estimator of autonomic modulation because it is subject to other control mechanisms in addition to the autonomic nervous system (40). Therefore both heart rate and age need to be considered when autonomic modulation is indirectly estimated by HRV. Age- and heart rate–adjusted HRV measures indicated that men had more pronounced sympathetic modulation, reflected in higher LF power and LF-to-HF ratio, compared with women, which is in line with other studies of healthy counterparts (4). The LF component is influenced by sympathetic, parasympathetic, and baroreflex sensitivity, however, and other studies have shown that LF power calculated from short-term supine measurement is predominantly influenced by parasympathetic control (41). Therefore the LF component should be interpreted as a measure of sympathetic modulation with some reservation. Several studies have shown that an overall low HRV is a predictor of the development of heart diseases (27,41,42). Our results show that overall HRV is lower in women compared with men.

Furthermore, our data showed a higher RS ratio in men than in women, supporting a possible difference in postural cardiac autonomic modulation between men and women (43). The RS ratio is the result of a transient decrease in blood pressure and an increase in heart rate following translocation of blood due to active standing from a supine position. In healthy subjects the heart rate and blood pressure reach normal homeostatic levels after approximately 30 s of standing (44). Healthy women have demonstrated lower sympathetic responsiveness in the supine position and greater parasympathetic responsiveness in the upright position, resulting in a lower orthostatic tolerance compared with men (43). The decrease in systolic blood pressure during standing has been used as a measure of sympathetic dysfunction; however, the change in blood pressure develops late in diabetic neuropathy compared with the results of heart rate–based tests used in this study (30).

Finally, there was no consistency in tests of parasympathetic activity. The test to measure EI ratio showed higher vagal modulation in women compared with men, whereas there was no difference in HF power. Several studies have shown healthy women to have higher

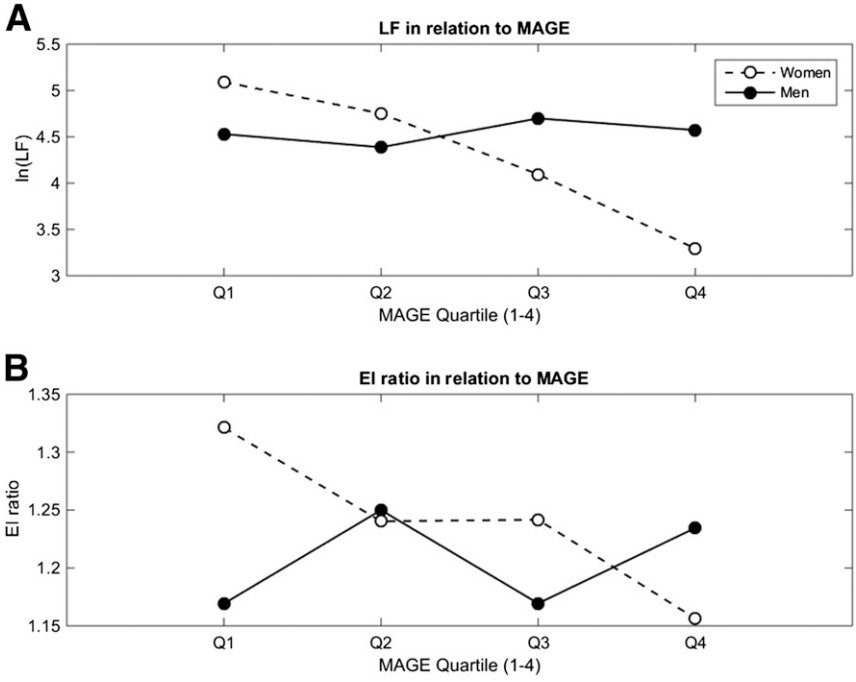


**Figure 2**—*A*: Mean LF in women and men, divided according to MAGE quartile. *B*: Mean EI ratio from the active deep breathing test in women and men, divided according to MAGE quartile. ln(LF), natural logarithm.

parasympathetic activity (higher HF power) than men (4,45). One reason for this difference between EI and HF power may be that the passive HRV test provides earlier additional information of both sympathetic and parasympathetic modulation than the active tests (16). The reduction in cardiac parasympathetic tone (HF power) in women with newly diagnosed type 2 diabetes may therefore be an early sign of an attenuation of the usual gap between the sexes.

To our knowledge, this is the first study to show that in women, but not men, with newly diagnosed type 2 diabetes, increased GV is associated with reduced cardiac autonomic modulation despite reduced LF power. In our data adjusting for mean heart rate, weight, blood pressure, triglycerides, and medications with a potential beneficial effect on the cardiovascular system (ACE inhibitors and β-blockers) did not alter the association between GV and autonomic modulation. The current study was designed as an observational study, and whether GV is a cause or consequence of decreased autonomic modulation remains to be elucidated. Nevertheless, studies have shown that glycemic disorders and decreased autonomic modulation are both associated with increased concentrations of inflammatory markers (46,47). As recently demonstrated, there is only a weak correlation between variables of GV and $HbA_{1c}$, implying that measurement of $HbA_{1c}$ alone does not reflect all important aspects of glycemic disorders (16). In the literature, GV has been associated with micro- and macrovascular complications (18), and GV increases circulating cytokines more than stable elevated glucose concentrations (12). In spite of these associations, the major challenges regarding GV estimation and evaluation is the fact that there is no consensus on data acquisition, data analysis, and therapeutic target. Furthermore, intervention studies are needed to demonstrate that minimizing GV reduces overall risk.

According to a recent study (7), cardiovascular diseases have a greater impact on women than on men with diabetes, especially when diabetes is diagnosed at a later stage. Our observational study shows that diabetes attenuates the sex difference in cardiac parasympathetic tone and supports different management strategies that may be considered for men and women at the time of diagnosis. Given the observational nature of this study, however, our results need to be confirmed in a prospective study.

In conclusion, in patients with newly diagnosed and well-controlled type 2 diabetes we found that increased glycemic variability was associated with reduced cardiac autonomic modulation in women but not in men.

**Acknowledgments.** The authors thank laboratory technicians Merete Møller and Lisa Buus, from the Medical Research Laboratory at the Department for Endocrinology and Internal Medicine, Aarhus University Hospital, for excellent technical assistance.

**Duality of Interest.** J.F. holds stock in Medicus Engineering. No other potential conflicts of interest relevant to this article were reported.

**Author Contributions.** J.F. generated the study hypothesis, developed the study design, acquired, analyzed, and interpreted data, and drafted and revised the manuscript. S.L.C. developed the study hypothesis, analyzed data, and critically revised the manuscript. P.H. and E.L. designed the study, acquired and interpreted data, and critically revised the manuscript. P.L.P. and J.S.C. designed the study, interpreted data, and critically revised the manuscript. L.T. analyzed and interpreted data, supervised the study, and critically revised the manuscript. T.K.H. designed the study, interpreted data, provided administrative support, and critically revised the manuscript. J.F. is the guarantor of this work and, as such, 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.

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