

# Impact of Glycemic and Blood Pressure Variability on Surrogate Measures of Cardiovascular Outcomes in Type 2 Diabetic Patients

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**OBJECTIVE**—The effect of glycemic variability (GV) on cardiovascular risk has not been fully clarified in type 2 diabetes. We evaluated the effect of GV, blood pressure (BP), and oxidative stress on intima-media thickness (IMT), left ventricular mass index (LVMI), flow-mediated dilation (FMD), and sympathovagal balance (low frequency [LF]/high frequency [HF] ratio) in 26 type 2 diabetic patients (diabetes duration  $4.41 \pm 4.81$  years;  $HbA_{1c}$   $6.70 \pm 1.25\%$ ) receiving diet and/or metformin treatment, with no hypotensive treatment or complications.

**RESEARCH DESIGN AND METHODS**—Continuous glucose monitoring (CGM) data were used to calculate mean amplitude of glycemic excursion (MAGE), continuous overall net glycemic action (CONGA)-2, mean blood glucose (MBG), mean postprandial glucose excursion (MPPGE), and incremental area under the curve (IAUC). Blood pressure (BP), circadian rhythm, and urinary 15-F<sub>2t</sub>-isoprostane (8-iso-prostaglandin F<sub>2α</sub> [PGF<sub>2α</sub>]) were also evaluated. Subjects were divided into dipper (D) and nondipper (ND) groups according to  $\Delta$ BP.

**RESULTS**—IMT and LVMI were increased in ND versus D ( $0.77 \pm 0.08$  vs.  $0.68 \pm 0.13$  [ $P = 0.04$ ] and  $67 \pm 14$  vs.  $55 \pm 11$  [ $P = 0.03$ ], respectively). MBG, MAGE, and IAUC were significantly associated with LF/HF ratio at night ( $r = 0.50$ ,  $P = 0.01$ ;  $r = 0.40$ ,  $P = 0.04$ ;  $r = 0.41$ ,  $P = 0.04$ , respectively), MPPGE was negatively associated with FMD ( $r = -0.45$ ,  $P = 0.02$ ), and CONGA-2 was positively associated with LVMI ( $r = 0.55$ ,  $P = 0.006$ ). The  $\Delta$ systolic BP was negatively associated with IMT ( $r = -0.43$ ,  $P = 0.03$ ) and with LVMI ( $r = -0.52$ ,  $P = 0.01$ ). Urinary 8-iso-PGF<sub>2α</sub> was positively associated with LVMI ( $r = 0.68$ ,  $P < 0.001$ ).

**CONCLUSIONS**—An impaired GV and BP variability is associated with endothelial and cardiovascular damage in short-term diabetic patients with optimal metabolic control. Oxidative stress is the only independent predictor of increased LV mass and correlates with glucose and BP variability.

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The role of hyperglycemia in the pathogenesis of micro- and macrovascular complications is well known (1). However, glycemic variability (GV) may be important in the development of chronic diabetes complications, beyond the average blood glucose (BG) concentration (2). This issue has not been fully

clarified, because no gold standard measure of GV is currently available, and  $HbA_{1c}$ , which is an undisputable index of overall glycemic control, only partially depicts glycemic excursions, in particular, postprandial spikes.

A recent systematic review of the effect of GV on the development of diabetes

complications suggested a correlation in type 2 diabetes but not in type 1 (3). The San Luigi Gonzaga Diabetes Study supports the theory of a predictive role of glucose spikes on the development of cardiovascular events, showing that BG levels after lunch better predict the occurrence of cardiovascular events than fasting BG and confirming previous observations that postprandial hyperglycemia—but not fasting BG—is an independent risk factor for cardiovascular disease (4).

It is still unclear whether postprandial glucose excursions, rather than chronic hyperglycemia, are responsible for the activation of oxidative stress pathways and contribute to the development of cardiovascular disease (5,6). Although the influence of a sustained increase in blood pressure (BP) on cardiovascular disease is well known, less data are available on the role of altered circadian rhythm of BP. The aim of our study was to investigate the relative role of overall glycemic load, GV, abnormal BP circadian rhythm, and oxidative stress activation on organ damage in short-term, well controlled type 2 diabetic patients without overt complications.

## RESEARCH DESIGN AND METHODS

The study recruited 26 consecutive type 2 diabetic subjects (11 men, 15 women) from the Department of Endocrinology and Diabetes, S. Giovanni Calibita Fatebenefratelli Hospital of Rome, who were being treated with diet and/or metformin. Informed consent was obtained from all participants. Exclusion criteria were diabetic autonomic neuropathy, micro- or macroalbuminuria, proliferative retinopathy, history of cardiovascular events, hypotensive treatment, or neoplastic, immunologic, or other diseases that were able to modify glucose metabolism. All study investigations were performed in accordance with the principles of the Declaration of Helsinki, and the protocol was approved by the hospital ethics committee.

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### Study design

On the first day, all patients underwent a general medical examination, and anthropometric parameters and cardiovascular autonomic neuropathy from Ewing tests were evaluated. Blood and urine samples were obtained for the determination of the albumin excretion rate (AER) and levels of cholesterol, triglycerides, and HbA<sub>1c</sub>. After an overnight fast, all subjects simultaneously underwent 24-h continuous glucose monitoring (CGM) with the CGM Minimed System (CGMS; Medtronic, Northridge, CA), ambulatory BP monitoring (ABPM; TM2430, Intermed, Milan; Italy), and electrocardiogram monitoring (Aria Holter System, Del Mar Reynolds Medical, Hertford, U.K., and Irvine, CA). The application of the subcutaneous sensor for the CGMS was performed approximately 2 h before starting BP and electrocardiogram (ECG) monitoring to calibrate the instrument. The FreeStyle Lite (Abbott Laboratories, Abbott Park, IL) BG-monitoring system was used to calibrate the CGMS. ComStation, which allowed us to download monitor data of glycemia into specified files while data processing was performed using CGMS 3.0C Solutions Software (Minimed, Medtronic). ABPM was monitored by the noninvasive oscillometric technique (TM2430, Intermed), validated by the British Hypertension Society (7).

A spectral analysis of Holter tapes (Impresario 2.8, Del Mar Reynolds Medical) was obtained from the ECG monitoring system. Frequency domain measures of heart rate variability were analyzed in accordance with European Society of Cardiology/North American Society of Pacing and Electrophysiology recommendations (8). Each patient collected a 24-h urine sample until analysis for 15-F<sub>2t</sub>-isoprostane (or 8-iso-prostaglandin F<sub>2α</sub> [PGF<sub>2α</sub>]) and creatinine. On the second day, measurements of carotid intima-media thickness (IMT), left ventricular mass, and endothelial function, studied with flow-mediated dilation (FMD), were performed.

### Assessment of GV indexes

The intraday GV indexes were mean amplitude of glycemic excursions (MAGE), defined as the average of all blood glucose excursions of more than 1 SD of the 24-h mean blood glucose value (9), and continuous overall net glycemic action (CONGA-2), defined as the SD of the differences between the current observation and the previous 2-h observation (10).

To assess postprandial glucose excursions from the CGM data, the mean postprandial glucose excursions (MPPGEs) of lunch and dinner and the average were calculated as the arithmetic mean of the differences between the postprandial peak glucose values and the corresponding preprandial glucose values for lunch and dinner. The incremental area under the curve (IAUC) after lunch and dinner and the average were also calculated.

The overall glycemic load was evaluated by HbA<sub>1c</sub> and by mean BG value (MBG), calculated as the arithmetic mean of 24-h glucose values from the CGM data.

### Assessment of blood pressure indexes

The percentage change from day to night ( $\Delta$ ) for systolic BP (SBP) and diastolic BP (DBP) was defined as  $\{[(\text{mean value during the day} - \text{mean value at night}) \times 100] / \text{mean value during the day}\}$ . A  $\Delta$ BP of less than 10% indicated a nondipper (ND) BP profile (11).

### Assessment of sympathovagal balance

Fourier transformation was used to transform fluctuations in RR interval widths into a frequency waveform that depicted periodic oscillations in sympathetic and parasympathetic function. The frequency domain variables, including total power (0.01–0.40 Hz), high-frequency (HF; 0.15–0.40 Hz), low-frequency (LF; 0.04–0.15 Hz) power, and the HF/LF ratio of day, night, and 24 h, were calculated, which served as a reliable index of the sympathovagal balance.

### Assessment of endothelial function and cardiovascular surrogates

Carotid IMT was obtained by B-mode ultrasound examination (MyLab30, Esaote, Italy). For each subject, the maximal carotid IMT was imaged for the near and far wall of each common carotid artery, according to the protocol for measuring carotid IMT used in the Asymptomatic Carotid Artery Plaque Study (ACAPS) (12).

Echocardiographic examination was performed with a Vivid 7 system (GE Healthcare, Milwaukee, WI). Left ventricular mass (LVM) by 2-dimensional imaging was studied and normalized to body surface area as the LVM index (LVMI). Recordings were digitally stored and evaluated off-line (EchoPac station) according to the guidelines of the American Society of Echocardiography (13).

Endothelial function was evaluated using the FMD of the brachial artery according to guidelines of the International Brachial Artery Reactivity Task Force (14).

All examinations were performed by using an ultrasound system (ACUSON Sequoia C512 System; Siemens, Erlangen, Germany) with a broadband 8–14-MHz transducer. In our laboratory, the coefficient of variation for FMD repeated measurements is 15%. Because of circadian variations of peripheral vascular tone, the FMD investigation was performed on all patients between 8:00 A.M. and 9:00 A.M. in a quiet, temperature-controlled room (22–24°C). All subjects were studied after an overnight fast. Arterial diameter was determined as the internal dimension of the vessel wall from the anterior-to-posterior interface between the lumen and the intima. The mean diameter was calculated from three measurements of arterial diameter performed at end-diastole with the R wave on a continuously recorded ECG. The response of the vessel diameter to reactive hyperemia was expressed as a percentage change relative to the diameter before cuff inflation.

### Laboratory measurements

Measurements of 8-iso-PGF<sub>2α</sub> and creatinine were accomplished using an enzyme-linked immunosorbent assay (ELISA) method (Cayman Chemical Co, Ann Arbor, MI) without extraction in the urine sample before immunoenzymatic assay. The normal reference unit used in this study was 1.02–1.3 ng/mg creatinine. The mean value  $\pm$  SD of 8-iso-PGF<sub>2α</sub> in our control group of normal healthy individuals was 1.18  $\pm$  0.50 ng/mg creatinine.

HbA<sub>1c</sub> was analyzed by high-performance liquid chromatography (VARIANT 2; Bio-Rad Laboratories, Munich, Germany), with intra- and interassay coefficients of variation of 0.46 to 0.77 and 0.69–0.91%, respectively. Total cholesterol, HDL cholesterol, and triglycerides were determined by the Cobas enzymatic colorimetric test (Roche Diagnostic, Indianapolis, IN). AER was determined by the Tina-quant immunoturbidimetric assay (Cobas; Roche Diagnostic). Urine samples were collected simultaneously with CGM, ABPM, and ECG monitoring and stored at  $-20^{\circ}\text{C}$  until analysis.

### Statistical analysis

Descriptive statistics were reported as the mean and SD for normally distributed continuous variables or median with a

25th–75th interquartile range (IQR) for skewed distribution. Normality of distribution was tested by calculating skew and kurtosis values. Continuous variables were compared by the Student *t* test for independent samples, and skewed distributions were compared using the Mann–Whitney *U* test. Univariate analysis was done by using linear regression and by determining the Pearson correlation coefficient (*r*). Multivariate regression analysis was used to assess independent predictors of cardiovascular diabetes complications, and adjustment for age was done. Correlation analysis was performed to investigate the relationship between 8-iso-PGF<sub>2α</sub> and glycemic and BP control parameters. A test result with *P* < 0.05 was considered statistically significant. For statistical analysis, Stata/SE 11.0 software (StataCorp LP, College Station, TX) was used.

**RESULTS**—Clinical and laboratory characteristics of the study population are reported in Table 1. Other values included FMD, 15 ± 7%; IMT, 0.7 ± 0.1 mm; LF/HF day, 2.8 ± 1.9; LF/HF night, 2.2 ± 1.9; and LVMI, 61.3 ± 13.8 g/m<sup>2</sup>.

The ΔSBP (%) was used to divide all subjects into two groups: dipper (D, 17.5 ± 4.3%) and ND (5.9 ± 2.4%). No differences were found between the two groups in general characteristics and in 24-h mean SBP and DBP. The ND and D groups were significantly different in IMT (0.77 ± 0.08 vs. 0.68 ± 0.13 mm,

*P* = 0.04) and LVMI (67 ± 14 vs. 55 ± 11 g/m<sup>2</sup>, *P* = 0.03).

### Univariate analysis

The association of all GV indexes with cardiovascular parameters was tested by univariate regression analysis. A significant association with LF/HF night was found for MBG (*r* = 0.50, *P* = 0.01), 24-h MAGE (*r* = 0.40, *P* = 0.04), and dinner IAUC (*r* = 0.41, *P* = 0.04). MPPGE lunch was negatively associated with FMD (*r* = −0.45, *P* = 0.02). CONGA-2 was positively associated with LVMI (*r* = 0.55, *P* = 0.006). However, no association was observed between HbA<sub>1c</sub> or MBG (*r* = −0.01, *P* = 0.94) and LVMI (*r* = 0.37, *P* = 0.06). ΔSBP and ΔDBP were negatively associated with IMT (*r* = −0.43, *P* = 0.03; *r* = −0.51, *P* = 0.009, respectively), and ΔSBP was negatively associated with LVMI (*r* = −0.52, *P* = 0.01). Finally, a positive association was found between 8-iso-PGF<sub>2α</sub> and LVMI (*r* = 0.68, *P* < 0.001).

### Multivariate analysis

Because our data showed a significant effect of GV and BP variability indexes and oxidative stress on LVM, the independent effects of age, CONGA-2, ΔSBP, and 8-iso-PGF<sub>2α</sub> on LVMI were assessed by multivariate analysis. The only independent predictor of increased LVMI was 8-iso-PGF<sub>2α</sub> (Table 2).

### Relationship between 8-iso-PGF<sub>2α</sub> and glycemic and BP indexes

We found a positive correlation between 8-iso-PGF<sub>2α</sub> and CONGA-2 (*r* = 0.57, *P* = 0.003), MPPGE lunch (*r* = 0.52, *P* = 0.008), and average IAUC (*r* = 0.46, *P* = 0.02), as well as a negative correlation with ΔSBP (*r* = −0.46, *P* = 0.02) and ΔDBP (*r* = −0.43, *P* = 0.03).

**CONCLUSIONS**—The main finding of this study is the effect of GV, abnormal circadian BP rhythm, and oxidative stress activation on LVMI. An increased LVMI has already been shown in ND patients

with essential hypertension (15) and in type 2 diabetic patients with autonomic neuropathy (16). We now demonstrate that the effects of an ND pattern on cardiac mass are already detectable in patients with normal mean BP values and with an LVMI within the normal range. Few and inconsistent data are available on the role of glycemic control on LVMI (17), although several studies have shown that deteriorating glucose tolerance is associated with increased LVM. The pathophysiologic mechanisms underlying this association are still controversial (18).

It is noteworthy that only GV was associated with LVMI in our study, and no association was observed between HbA<sub>1c</sub> and LVMI, in agreement with other reports (19).

To our knowledge, this is the first report of a correlation between GV and organ damage in well controlled, uncomplicated type 2 diabetic patients. We demonstrate that GV evaluated as CONGA-2—but not overall glycemic load—has a deleterious effect on LVMI in well controlled type 2 diabetic patients. The observation that only CONGA-2, among all parameters of GV, was significantly associated with increased LVMI is possibly attributed to the metabolic characteristics of our patients. CONGA-2 is known to detect small glycemic swings, occurring over short intervals (20), thus appropriately describing the glycemic fluctuations of patients in optimal metabolic balance, without “peaks and valleys” related to hypoglycemic treatment, because all of our patients were being treated with diet or by diet and metformin. Thus, our data suggest that such rapid and small glycemic excursions seem to be involved in the development of early cardiovascular damage in type 2 diabetic patients with short-term disease and optimal glycemic control.

The pathophysiologic mechanism responsible for this association could be represented by the activation of the oxidative stress pathway. In agreement with this hypothesis, we found a positive association between LVMI and 8-iso-PGF<sub>2α</sub>, a

**Table 1—General characteristics of all subjects**

Variable	Mean ± SD
Age (years)	59.2 ± 10.6
Diabetes duration (years)	4.4 ± 4.8
BMI (kg/m <sup>2</sup> )	26.9 ± 3.6
AER (mg/g creatinine)	7.1 ± 7.6
Cholesterol	
Total (mmol/L)	5.2 ± 0.9
HDL (mmol/L)	1.3 ± 0.3
Triglycerides (mmol/L)	1.4 ± 0.5
8-iso-PGF <sub>2α</sub> (ng/mg creatinine)	1.8 ± 0.8
FBG (mmol/L)	7.1 ± 1.6
HbA <sub>1c</sub> (%)	6.7 ± 1.3
MBG (mmol/L)	7.2 ± 1.6
MAGE (mmol/mol)	3.2 ± 1.7
CONGA-2 (mmol/mol)	1.8 ± 0.6
MPPGE (mmol/mol)	1.5 ± 2.1
Avg IAUC (mmol/L/h)	483 ± 111
ΔSBP (%)	11.7 ± 6.8
ΔDBP (%)	12.8 ± 7.8

**Table 2—Multivariate analysis of independent effects on LVMI**

Variable	Coefficient	95% CI	<i>r</i>	<i>P</i>
Age	0.22	−0.20 to 0.64	0.17	0.286
CONGA-2	0.24	−0.14 to 0.63	0.18	0.199
ΔSBP	0.41	−1.14 to 0.31	−0.19	0.250
8-iso-PGF <sub>2α</sub>	6.83	0.69–12.96	0.42	0.031

*R*<sup>2</sup> = 0.573.

reliable marker of oxidative stress. Moreover, multivariate analysis showed that 8-iso-PGF<sub>2α</sub> appeared to be the only independent predictor of increased LVMI. We also observed a significant correlation between 8-iso-PGF<sub>2α</sub> and GV as well as abnormal circadian BP rhythm. Therefore, an increased activation of oxidative stress might represent the common pathogenetic mechanism, linking GV and abnormal circadian BP rhythm with an increased LVMI.

Our study confirms an association between the ND profile of BP and increased IMT, whereas no association was observed between IMT and GV or overall glycemic load. The apparent contradiction between our data and one report of a correlation between postprandial hyperglycemia and IMT (21) may be explained by the suboptimal metabolic control of the studied population, which does not allow the role of GV to be discriminated from that of hyperglycemia per se. In contrast, our patients were in optimal metabolic control and our results are consistent with the report by Karrei et al. (22), who did not find a correlation in type 2 diabetic patients with fair glycemic control between carotid IMT and glucose fluctuations measured by serum 1,5-anhydroglucitol.

We also found a negative correlation between postprandial hyperglycemia and endothelial function, in agreement with Shige et al. (23), thereby establishing postprandial hyperglycemia as a determinant of reduced flow-mediated vasodilation in type 2 diabetes. These effects of postprandial hyperglycemia on endothelial function are probably linked to oxidative stress activation, as suggested by the positive significant correlation between postprandial hyperglycemia, measured as MPPGE and IAUC, and urinary isoprostanes. However, no correlation was found with overall glucose load, different from what was observed by Monnier et al. (5); again, this discrepancy was attributed to the almost normal blood glucose values of our patients.

Finally, 24-h GV, postprandial hyperglycemia, and MBG significantly affect LF/HF night. Although a relative prevalence of sympathetic over parasympathetic activity has been reported in insulin-resistant states, even in the absence of diabetes (24), no data are available on the possible effect of GV on sympathetic activity. We now demonstrate that GV chronically affects sympathovagal balance in well controlled diabetic patients without overt autonomic neuropathy. We also confirm the influence

of postprandial hyperglycemia on sympathovagal activation, as described previously (25). However, the significant association between MBG and LF/HF, in the presence of almost normal average blood glucose levels, underlines the role of overall glycemic load, even in the absence of sustained hyperglycemia, on autonomic balance.

In conclusion, we demonstrate that an impaired GV and BP variability is associated with endothelial dysfunction and increased cardiac mass in diabetic patients with short-term disease and optimal metabolic control. The activation of oxidative stress is associated with increased LVM and variability of glucose levels and BP. Intervention studies are needed to investigate the benefits of the correction of glucose fluctuations on cardiovascular parameters, and to address the issue of treatment choices, in diabetic patients.

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A.D.F. and F.P. researched the data, contributed to the discussion, and wrote the manuscript. P.D.S. reviewed and edited the manuscript. I.G. and I.M. researched the data, contributed to the discussion, and wrote the manuscript. P.M. researched the data and contributed to the discussion. P.P., F.S., C.P., and F.F. researched the data. G.F. contributed to the discussion. S.F. researched the data, contributed to the discussion, wrote the manuscript, and reviewed and edited the manuscript.

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