Autonomic, Cardiovascular and Respiratory Responses to Hyperglycemic Stimulus in Healthy Subjects

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Abstract

In ten healthy subjects we assessed the effects of hyperglycemia, provoked by the ingestion of 75 g of glucose on: R-R intervals (RR), systolic pressure (SP), diastolic pressure (DP), respiratory frequency (RF) and tidal volume (V_T) 5-min time series; the time course of their low-frequency (LF_{RR}, LF_{SP}, LF_{DP}), high-frequency (HF_{RR}, HF_{DP}, HF_{Res}) powers and their central frequencies ($cfLF_{DP}$, $cfHF_{RR}$, $cfHF_{DP}$), computed by a time-frequency distribution; baroreflex (BRS) and respiratory sinus arrhythmia sensitivities (RSAS), obtained by alpha index and their coherences (cBRS and cRSAS) by cross time-frequency analysis. In relation to control, in hyperglycemia (peak of 143±12 mg/100 ml, $p<0.001$)1-min epoch mean values of: LF_{RR}, LF_{DP}, HF_{RR}, HF_{Res}, BRS, cBRS, RR, DP and V_T decreased ($p<0.03$); $cfLF_{DP}$, $cfHF_{RR}$, RSAS, cRSAS and RF increased ($p<0.04$); and LF_{SP} and SP were similar. Our findings outline an integrative dynamic response to hyperglycemia characterized by: vagal activity inhibition associated to RR shortening; sympathetic outflow inhibition associated to reduced DP, which, via baroreflex with reduced sensitivity and input-output coupling degree, reinforces the vagal reduction; and respiratory activity modification associated to V_T decrease, RF increase and improved respiratory modulation of cardiovascular function.

1. Introduction

Although hyperglycemia is a common condition presented postprandially in healthy subjects and chronically sustained in diabetic patients, its autonomic, cardiovascular and respiratory (ACR) effects are not clearly understood [1,2], partially because they have been poorly studied and the reported findings in healthy subjects are equivocal. For instance, studies evaluating spectral measures of cardiovascular variability (CVV), have reported that sympathetic activity increases [1] or remains unchanged [2], and that vagal activity either increases [3], does not change [1,2] or decreases [4]. In diabetic patients, the postprandial fluctuations of hyperglycemia evoke depression of sympathetic and vagal activities, additionally influenced by the presence or lack of autonomic neuropathy [5]. To provide some insight into this issue, by using a robust methodology that comprises the analysis of time series of cardiovascular-respiratory variables and of time-frequency measures of vagal and sympathetic activities and autonomic control, we sought to characterize an integrative response to hyperglycemia in healthy individuals. Thus, our aim was to assess the effects of hyperglycemia on heart rate (HR), arterial pressure (AP), tidal volume (V_T) and respiratory frequency (RF), the power and central frequencies of spectral measures of HRV and AP variability, baroreflex (BRS) and respiratory sinus arrhythmia sensitivities (RSAS). Correlations among indexes were examined.

2. Methodology

2.1. Subjects

Ten euglycemic, normotensive and sedentary subjects, 7 men and 3 women, were studied. Their mean age, height and weight were 22.6±2.0 years, 165±7 cm and 64±6 kg respectively. Their written informed consent was requested to participate.

2.2. Protocol

Volunteers visited the laboratory twice. The first time, their health status and anthropometric variables were evaluated, and on the second visit the experimental stage was carried out. After an overnight fast, subjects drank 75 gr of glucose. A blood sample of 35 μl was collected from a fingertip every 10 minutes for the following 180 min to measure blood glucose level by enzymatic method (Boehringer). In supine position, 5-min signal recordings were obtained before glucose ingestion (control), 40 min after, during the hyperglycemic peak, and when glucose returned to baseline (recovery), around 180 min later.

2.3. Signal recording and acquisition

ECG was detected at the CM5 bipolar lead using a

 ISSN: 2325-887X DOI: 10.22489/CinC.2018.026

bioelectric amplifier (Biopac Systems). Noninvasive AP was measured by Finapres (Ohmeda). Respiration (Res) was detected by a pneumograph (Nihon Kohden). All recorded signals were digitized at a sampling rate of 1 kHz via an acquisition system (Biopac Systems).

2.4. Data processing

Maxima and minima of ECG, AP and Res signals were detected to generate time series of R-R intervals (RR), systolic pressure (SP), diastolic pressure (DP), V_T and RF. All series were cubic-spline interpolated, detrended and resampled at 4 Hz. Time-frequency spectra of the series were estimated with the smoothed pseudo-Wigner-Ville distribution and integrated in the standard frequency bands of HRV analysis to compute their instantaneous low frequency powers (LF_{RR}, LF_{SP} and LF_{DP}), high frequency powers (HF_{RR}, HF_{DP} and HF_{Res}) and their central frequencies ($cfLF_{DP}$, $cfHF_{RR}$ and $cfHF_{DP}$). Instantaneous BRS and RSAS were computed by alpha index, using LF_{RR}/LF_{SP} and HF_{RR}/HF_{Res} respectively, and their coherences (cBRS and cRSAS) were estimated by cross time-frequency analysis. Measures dynamics were expressed as change from their mean baseline, segmented into 1-min epochs for statistical analysis and ensemble-averaged for visualization.

2.5. Statistical analysis

Data of the measures were expressed as mean±SD. Differences between baseline, hyperglycemia and recovery values were tested by ANOVA for repeated measures. Post-hoc pairwise comparisons were performed by the Tukey test. Using the 1-min epochs means, linear regressions and correlations between the indexes were computed for each subject. Statistical significance was accepted at p<0.05.

3. Results

In relation to glycemia control level (82±10 mg/100 ml), around 40 min after glucose ingestion a hyperglycemic peak of 143±12 mg/100 ml (p<0.001) was reached. Glycemia returned to baseline after 120 min.

Relative to control (Fig. 1A and C), time-frequency spectra of RR and DP series during hyperglycemia showed reductions of HF_{RR} and LF_{RR} powers (with two overshoots) with increase of $cfHF_{RR}$ (Fig. 1B), and LF_{DP} reduction (with an overshoot) and $cfLF_{DP}$ increment (Fig. 1D). Instantaneous powers and central frequencies presented strikingly large fluctuations during baseline and hyperglycemia.

In relation to baseline, in hyperglycemia 1-min epoch mean values of instantaneous response patterns of the three types of measures behaved as follows:

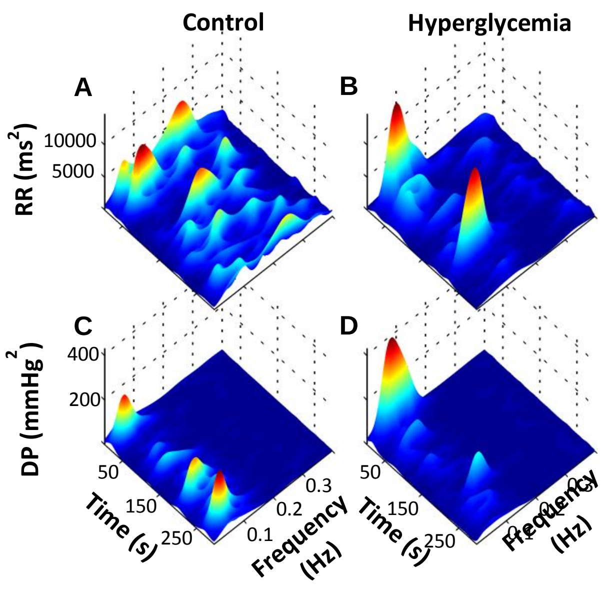

Fig. 1. Representative time-frequency distributions of RR and DP series during control (A and C) and hyperglycemia (B and D) respectively.

• *Cardiovascular and respiratory function:* RR (Fig. 2A), DP (except one epoch mean, Fig. 2B), and V_T (Fig. 2C), were smaller (p<0.04); RF (Fig. 2D) was larger (p<0.03); and SP was similar. In recovery, RF was greater (p<0.04) and V_T was smaller (p<0.02) than their control.

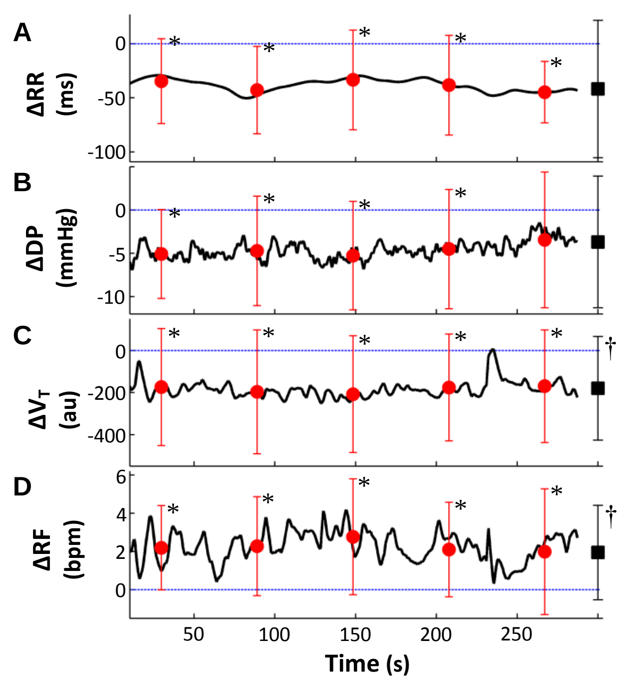

Fig. 2. Ensemble averages and 1-min epoch means±SD of the dynamics of cardiovascular respiratory variables: A)RR, B)DP, C)V_T and D)RF. ■=mean recovery. *p<0.04 hyperglycemia vs. control. † p<0.04 recovery vs. control.

- *Autonomic activity:* LF_{RR} (Fig. 3A), LF_{DP} (except two epoch means, one was greater and the other similar, Fig. 3C), $\ln HF_{RR}$ (Fig. 3D), HF_{Res} (Fig. 3E) and HF_{DP} were smaller ($p<0.04$); $cfLF_{DP}$ (except one epoch mean, Fig. 3F), $cfHF_{DP}$ (Fig. 3G) and $cfHF_{RR}$ were larger ($p<0.04$); and LF_{SP} was similar (Fig. 3B). In recovery, HF_{Res} was less than its baseline ($p<0.01$).

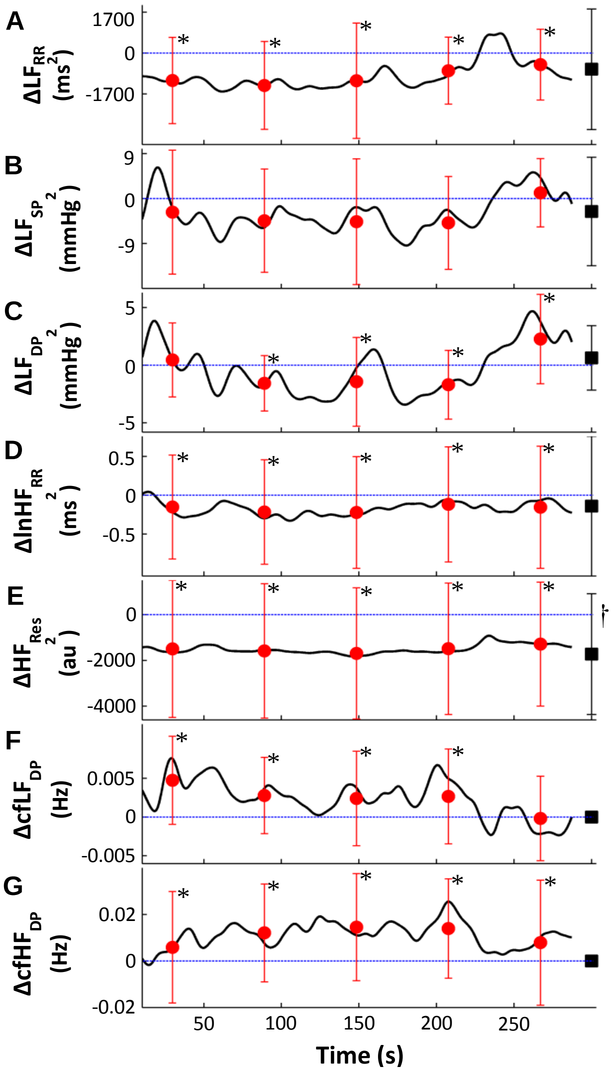

Fig. 3. Ensemble averages and 1-min epoch means±SD of the dynamics of spectral autonomic activity measures: A) LF_{RR}, B) LF_{SP}, C) LF_{DP}, D) $\ln HF_{RR}$, E) HF_{Res}, F) $cfLF_{DP}$ and G) $cfHF_{DP}$. ■=mean recovery. *$p<0.04$ hyperglycemia vs. control. † $p<0.01$ recovery vs. control

- *Autonomic control mechanisms:* BRS (Fig. 4A) and cBRS (except two epoch means, Fig. 4B) were smaller ($p<0.04$); RSAS (Fig. 4C) and cRSAS (except one epoch mean, Fig. 4D) were greater ($p<0.02$). Control mean value of cBRS was 0.77±0.09 and that of cRSAS was 0.92±0.05. In recovery, cRSAS was greater than its value in control ($p<0.02$).

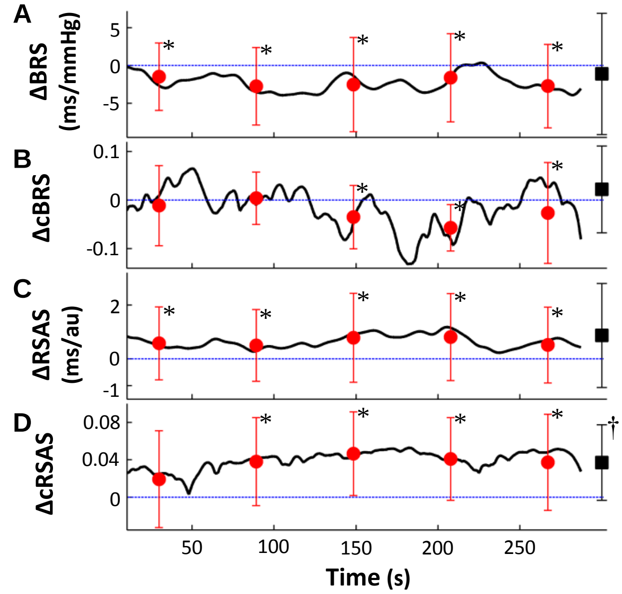

Fig. 4. Ensemble averages and 1-min epoch means±SD of the dynamics of autonomic control estimators: A)BRS, B)cBRS, C)RSAS, D)cRSAS. ■=mean recovery. *$p<0.04$ hyperglycemia vs. control. † $p<0.02$ recovery vs. control

$cfLF_{DP}$-LF_{DP} relation was inverse (Fig. 5A) and $cfHF_{DP}$-RF (Fig. 5B), BRS-cBRS (Fig. 5C) and RSAS-cRSAS (Fig. 5D) relations were direct. $cfHF_{RR}$-RF correlation was 0.65±0.12; HF_{RR}-V_T and HF_{DP}-V_T correlations were 0.36±0.24 and 0.28±0.33 respectively. All correlations were significant ($p<0.004$).

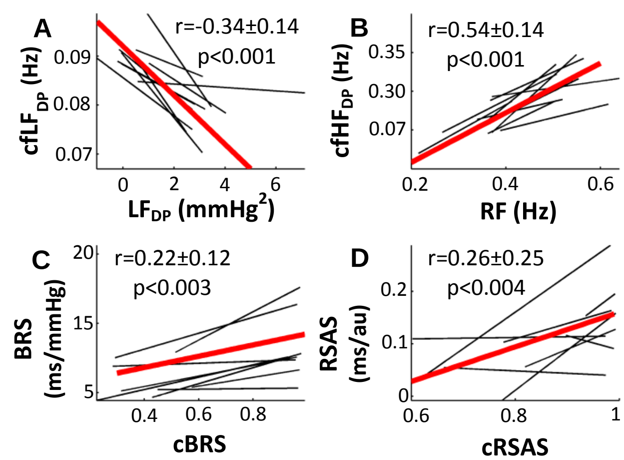

Fig. 5. Individual (thin black lines) and mean (thick red lines) regressions and correlations for: A)$cfLF_{DP}$-LF_{DP}, B) $cfHF_{DP}$-RF, C)BRS-cBRS, D)RSAS-cRSAS relations.

4. Discussion

Our robust analysis methodology revealed an integrative functional picture of the ACR response of healthy subjects to hyperglycemia, supported by our main findings in three types of estimators: *Cardiovascular-respiratory function,* reduction of DP, RR and V_T and increase of RF; *sympathetic and vagal activities,* reductions of LF_{RR}, LF_{DP}, $lnHF_{RR}$, HF_{DP} and HF_{Res}, and increases of $cfLF_{DP}$, $cfHF_{RR}$ and $cfHF_{DP}$; *autonomic control mechanisms,* decrease of BRS and cBRS and increase of RSAS and cRSAS. Additionally, some degree of covariation is found in $cfLF_{DP}$-LF_{DP}, BRS-cBRS, RSAS-cRSAS, HF_{RR}-V_T, HF_{DP}-V_T, $cfHF_{RR}$-RF and $cfHF_{DP}$-RF.

Our methodological approach, based on the use of time series and a time-frequency distribution, a valuable tool for non-stationary signal spectral analysis that avoids the need for stationarity testing, shows that the time course of ACR function measures in hyperglycemia are highly fluctuating, especially the sympathetic ones. To achieve a robust estimation of sympathetic activity we employed three of its most common spectral measures, LF_{RR}, LF_{SP} and LF_{DP}, of which LF_{SP} (Fig. 3B) fails to mark the effect of hyperglycemia. Additionally, LF_{DP} presents weak yet significant negative correlation with $cfLF_{DP}$ (Fig. 5A), which suggests that the responses of its power and central frequency to sympathetic activity changes are inversely proportional. Significant correlations of BRS-cBRS (Fig. 5C) and RSAS-cRSAS (Fig. 5D) relations suggest some functional interdependency between the sensitivity of each control system and its coherence, which we consider indicates their degree of input-output coupling. The weak correlations found for the RF-$cfHF_{RR}$, RF-$cfHF_{DP}$ (Fig. 5B), V_T-HF_{RR} and V_T-HF_{DP} relations, add supporting evidence that the respiratory variables are relevant functional correlates of the spectral components of CVV in the high frequency band, RF for central frequencies and V_T for powers.

Previous studies on the ACR response of healthy subjects to hyperglycemia have in common that: hyperglycemia has been provoked by either glucose [2,3] or meal ingestion [4,6]; to assess its effects, spectral measures of CVV have been used more frequently than microneurography, always assuming stationary signals, which implies the use of ad hoc spectral analysis techniques [1-4,6]; and have attributed the autonomic effects to insulin [1,6]. The following effects of hyperglycemia on ACR measures have been reported: HR increment [1,3,4,7] or no change [2]; AP increase [1,6], no change [2] or decrease [3]; sympathetic activity increase [1,3,6,8] or no change [2]; vagal activity increase [3], decrease [4] or no change [1,2]; and BRS decrease [1,3,7]. Therefore, the reported ACR effects of hyperglycemia are equivocal; however, most authors consider the sympathoexcitatory pressor effect to be the most relevant one [1,6,8], notion that contrasts with the dynamic and integrative mechanism supported by our findings, consisting in: vagal activity inhibition (Fig. 3D) associated to RR shortening (Fig. 2A); sympathetic activity inhibition (Fig. 3A, C and F) associated to DP reduction (Fig. 2B), which, by baroreflex with reduced sensitivity (Fig. 4A) and input-output coupling degree (Fig. 4B), somewhat contributes to vagal withdrawal; and respiratory activity modification leading to reduced V_T (Fig. 2C) and increased RF (Fig. 2D), with greater RSAS (Fig. 4C) and degree of respiratory-cardiovascular coupling (Fig. 4D). The sporadic sympathetic bursts (Fig. 3C) transiently recover DP level (Fig. 2B). With the return of glycemia to its control level, the studied measures recover their control values, except for the respiratory variables: RF remains elevated (Fig. 2C) and V_T persists reduced (Fig. 2D).

In conclusion, our robust methodology based on the analysis of time series, and their time-frequency spectra, and strengthened by the finding of some covariation between LF_{DP} and $cfLF_{DP}$ and between the sensitivities and their coherences, documents an integrative dynamic response to hyperglycemia characterized by: depressed vagal, sympathetic (with some activation bursts), BRS, DP and V_T levels, and increased HR and RF with a higher degree of coupling of respiratory modulation of CVV.

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