FOLIA MEDICA CRACOVIENSIA
Vol. LXII, 3, 2022: 111–122
PL ISSN 0015-5616
DOI: 10.24425/fmc.2022.142374

Effect of acute hyperglycemia on baroreflex sensitivity in healthy young adults

Navkiran Ranjan, Kiran Prakash, Anita S. Malhotra

Department of Physiology, Government Medical College and Hospital, Chandigarh, India

Corresponding author: Dr. Kiran Prakash, Ass. Prof.
Department of Physiology, Government Medical College and Hospital, Sector 32, Chandigarh, India
Phone: +91 872 785 584; E-mail: kiranprakash009@gmail.com

Abstract: Background: Autonomic dysfunction, impaired baroreflex sensitivity (BRS), and deranged circulatory homeostasis have been observed in chronic hyperglycemia and found to be associated with increased cardiovascular morbidity and mortality. However, the acute effects of hyperglycemia in healthy subjects have been rarely studied. The present study explores the effect of acute hyperglycemia on conventional and unconventional parameters of BRS in healthy young adults.
Methods: For the estimation of BRS beat-to-beat blood pressure (BP) and electrocardiogram were recorded in forty-two young, healthy subjects during fasting and at 1hr of the oral glucose load. Analysis of BRS was carried out by sequence and spectral method. Number of UP-, DOWN- and ALL-sequences between ramps of BP and RR-interval were calculated as an unconventional measure of BRS along with the other conventional parameters.
Results: We observed significant alteration of unconventional parameters of autonomic functions [the number of sequences of UP- ($p = 0.0039$) and ALL-sequences ($p = 0.0233$) of systolic BP and RR interval; and, UP- ($p = 0.0380$), DOWN- ($p = 0.0417$) and ALL-sequences ($p = 0.0313$) of mean BP and RR-interval] during acute hyperglycemia as compared to the fasting state. However, no significant changes were observed in any of the conventional parameters of BRS during acute hyperglycemia as compared to the fasting state.
Conclusions: Present study concludes that the unconventional parameters of BRS — the number of sequences between the ramp of BP and RR-interval — change significantly during acute hyperglycemia. However, the conventional parameters do not show significant changes during acute hyperglycemia. We may hypothesize that the relatively constant BRS is maintained at the expense of increased oscillations in the ramp of BP and RR-interval.

Keywords: spectral, sequence, beat-to-beat blood pressure, electrocardiogram.

Submitted: 17-Jan-2022; **Accepted in the final form:** 25-Aug-2022; **Published:** 15-Sep-2022.

Introduction

Altered homeostasis of glucose metabolism and systemic blood pressure (BP) are established risk factors for the various cardiovascular diseases [1, 2] and are primary pathologies behind life style diseases [3–6]. Similarly, altered baroreflex functions and deranged circulatory homeostasis are associated with abnormal functions of the autonomic nervous system and increased risk of cardiovascular morbidity and mortality [7–9]. Impaired baroreflex functions and baroreflex sensitivity (BRS) have been reported in many diseases such as diabetes mellitus [10, 11], metabolic syndrome [12, 13] etc.

The arterial baroreceptor reflex system maintains the relatively constant systemic arterial BP [14]. Measurement of BRS is carried out by quantifying the change in heart rate in response to the changes in the systemic arterial BP. This change in the systemic arterial BP can be induced by specific manoeuvres, vasoactive drugs or it can be the spontaneous one [15, 16]. BRS measures are sensitive and reliable parameters for the assessment of autonomic control of the cardiovascular system[16, 17]. Reduced BRS has been reported to be an independent risk factor for cardiovascular morbidity and mortality [17, 18]. Impaired function of the autonomic nervous system and altered BRS has been reported even in early or uncomplicated diabetes mellitus [11, 19]. The deleterious effects of hyperglycemia on the cardiovascular system and its mechanisms are well explained in the literature [20–22]. Hyperglycemia increases intracellular oxidative stress and induces vascular damage via polyol pathway activation and formation of advanced glycation end products. Several other polymorphous pathways also increase oxidative stress on the peripheral nervous system because of hyperglycemia [23]. These eventually cause cardiovascular and other complications in diabetes mellitus [24].

Although the long-term effect of sustained hyperglycemia on cardiovascular autonomic functions is well documented, the effect of transient hyperglycemia on baroreflex sensitivity is rarely studied [25]. Therefore, the present study was designed and conducted to explore the effect of transient hyperglycemia on different parameters of BRS. This study also explored the association of other unconventional parameters of BRS, along with the conventional ones, with hyperglycemia.

Materials and Methods

Subjects

Forty-two young, healthy subjects [19.0 (18.0–20.0) years] were recruited for the study. Written informed consent was obtained from all the subjects. All the recordings and measurements were carried out in the Autonomic Function Laboratory, Department of Physiology at Government Medical College and Hospital, Chandigarh, India.

The institute's research and ethics committee [IEC/2018/77] approvals were obtained to conduct this study, and it has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Healthy subjects were identified and recruited based on the detailed clinical history and physical examination. Subjects with any acute or chronic diseases were excluded from the study. Subjects were asked to report at 8:30 a.m. after an overnight fast. Demographic details and clinical history were recorded. For producing hyperglycemic state, subjects were instructed to take 75 gm of glucose with water, orally. The blood sample was obtained for the blood sugar estimation, both during the fasting and at the end of one hour of the oral glucose load. Beat-to-beat BP and lead II electrocardiogram (ECG) were recorded for the assessment of BRS, both during the fasting state and at the one hour of the oral glucose load. These recordings were carried out in a temperature-controlled room. All the recordings of the female subjects were carried out within the week of the start of their menstrual cycle to minimize the effect of ovarian hormones on the recorded parameters.

Data Acquisition

Subjects were instructed to refrain from tea or caffeinated beverages for at least 12 h before the recordings. Beat-to-beat BP was recorded by the 'volume clamp method' of Penaz, from the right middle finger, using the computer-based digital data acquisition system Finometer (Finometer® model 2; Finapres Medical Systems, Amsterdam, the Netherlands). Signal acquisition was carried out using the software Beatscope Easy® (Finapres Medical Systems). The sampling rate for acquiring the BP signals was 200 Hz. Lead II ECG was obtained using LabChart Pro 7® software (AD Instruments, Australia). Sampling frequency for ECG acquisition was kept at 1 kHz, with digital bandpass filter between 0.5 Hz and 35 Hz. Recorded data were saved with appropriate annotations for further offline analysis.

Analysis of Baroreflex Sensitivity

Signals of beat-to-beat BP and ECG were analyzed by LabChart Pro 7 software. BRS was analyzed by sequence and spectral methods by Nevrocard software. Analysis of BRS by sequence method was based on the identification of the sequences of three or more consecutive beats characterized by a progressive change in BP (rise or fall) and RR interval (lengthening or shortening). Criteria used for identifying sequences were (1) RR variation greater than 5 ms, (2) BP changes greater than 0.5 mmHg, (3) sequences of 3 beats or longer, and (4) sequences correlation coefficient greater than 0.85. The average slope of regression lines identified by the above criteria gives the estimate of BRS by sequence method. BRS by sequence method has been carried out

for UP-sequences, DOWN-sequences, and ALL-sequences of systolic BP, diastolic BP and mean BP during fasting and hyperglycemic state of the subjects. These data were also analyzed for the changes in the number of UP-, DOWN- and ALL-sequences identified during 5 min baseline recordings of beat-to-beat BP (systolic, diastolic and mean) and RRI, and were statistically compared during fasting and hyperglycemic state.

For the determination of BRS by spectral method, simultaneously recorded beat-to-beat BP and RRI signals were analyzed by Fast Fourier transformation. The coherence between power spectral densities of RR interval and BP in low frequency (LF, 0.04–0.15 Hz) and high frequency (HF, 0.15–0.40 Hz) band were computed. The baroreflex gain was calculated by dividing the amplitude of RR oscillations by the amplitude of corresponding oscillations in the systolic, mean and diastolic BP, in the 'Low' and 'High' frequency bands. These were referred as α-LF and α-HF in their respective frequency bands. Both α-LF and α-HF are expressed as ms/mmHg. LF/HF ratio has been calculated by dividing the power in the low and high-frequency zone of the frequency distribution spectrum of systolic, mean, or diastolic BP.

Statistical Analysis

Descriptive statistics were used to summarize all the variables. All parameters were tested for the distribution of data using standard normality tests (D'Agostino-Pearson omnibus normality test, Kolmogorov-Smirnov test and Shapiro-Wilk test). Data with normal distribution are expressed as mean ± SD; data with non-parametric distribution are expressed as median with interquartile range. To compare the mean or the median of different parameters during fasting and hyperglycemic state, paired t-test or Wilcoxon matched paired test, depending upon the distribution of data, were carried out. The level of statistical significance was set at $p < 0.05$. Statistical analyses were carried out using GraphPad Prism version 5.01 for Windows (GraphPad Software, Inc., USA).

Results

The study was conducted on forty-two young, healthy subjects (15 male and 27 female). The demographic and anthropometric characteristics of the subjects are listed in Table 1.

Hyperglycemia has significantly affected cardiovascular parameters (Table 2). To evaluate the effect of hyperglycemia on different BRS parameters assessed by sequence and spectral method, group mean or median values, during fasting and hyperglycemic states, were compared. No significant effect of hyperglycemia was observed on the BRS assessed by sequence method. On analyzing the impact of hyperglycemia on BRS

Table 1. Demographic and anthropometric characteristics of the subjects.

Parameter	Value
Age (years)	19 (18–20)
Male (%)	35.7
Weight (Kg)	63.79 ± 13.89
Height (cm)	166 ± 7.27
Body Mass Index (Kg/m2)	23.04 ± 4.14

Normally distributed data are expressed as mean ± SD, and non-parametric data are expressed as median (inter-quartile range).

Table 2. Comparison of parameters during fasting and hyperglycemic state.

Parameter	**Fasting**	**1 Hr of Glucose Load**	**P value**
Blood glucose	86.33 ± 8.34	126.8 ± 29.29	<0.0001
Systolic blood Pressure	118 (113–120.5)	115.1 ± 7.99	<0.0001
Mean Blood Pressure	88.53 ± 7.31	86.23 ± 7.18	<0.0001
Diastolic Blood Pressure	73.81 ± 7.58	71.81 ± 7.38	<0.0001
Heart Rate	72.36 ± 10.24	75.64 ± 8.5	0.0003

Normally distributed data are expressed as mean ± SD, and non-parametric data are expressed as median (inter-quartile range).

assessed by spectral method, no significant changes were observed in α-LF or α-HF. However, a significant decrease in LF/HF ratio was observed (Table 3).

Novel findings were observed while evaluating the effect of hyperglycemia on the number of sequences of progressive changes in systolic or mean BP and RRI. It was observed that there was significant increase in the number of UP- [8.238 ± 6.32 vs 10.5 (5–18.25); p = 0.0039] and ALL-sequences [14.5 (5.75–20) vs 15 (8.5–31.25); p = 0.0233] of systolic BP and RRI; and, UP- [8.095 ± 5.29 vs 10.17 ± 6.4; p = 0.0380], DOWN- [7.5 ± 5.8 vs 8.5 (4–13.25); p = 0.0417] and ALL-sequences [15.6 ± 10.05 vs 16.5 (11.75–27.25); p = 0.0313] of mean BP and RRI (Fig. 1). No significant changes were observed in the number of DOWN-sequences of systolic BP and RRI [5 (2–10.01) vs 5 (2–12.5), p = 0.2638], and number of UP-, DOWN- and ALL-sequences of diastolic BP and RRI [9.81 ± 7.37 vs 11.4 ± 7.17, p = 0.1872; 8.93 ± 6.7 vs 8.5 (03–16.01), p = 0.2445; 8.74 ± 12.97 vs 20.9 ± 13.39, p = 0.2535, respectively] during fasting and hyperglycemic states.

Correlation analyses were carried out to explore any potential correlation between heart rate and different BRS parameters. Significant correlations were observed between heart rate during fasting and hyperglycemic state and sequential BRS assessed by UP-,

Table 3. Effect of Hyperglycemia on BRS parameters determined by sequence and spectral method.

Parameter	Fasting	1 Hr of Glucose Load	P value
Sequential BRS accessed by UP sequences of BP and RR interval			
SBP	25.34 (17.27–41.06)	25.42 (16.81–34.18)	NS
MBP	43 ± 26.37	44.84 ± 21.05	NS
DBP	43.96 (30.21–54.88)	47.51 ± 12.61	NS
Sequential BRS accessed by DOWN sequences of BP and RR interval			
SBP	25.59 (16.29–33.3)	23.12 ± 12.47	NS
MBP	37.84 ± 21.69	41.43 ± 16.92	NS
DBP	36.86 (24.08–45.05)	37.56 (28.65–45.37)	NS
Sequential BRS accessed by ALL sequences of BP and RR interval			
SBP	27.02 (20.21–38.63)	26.85 ± 14.2	NS
MBP	42.06 ± 20.37	44.57 ± 15.23	NS
DBP	42.22 (31.39–52.53)	45.46 ± 17.94	NS
αLF of spectral BRS			
SBP	6.65 ± 3.76	6.345 (4.81–8.35)	NS
MBP	7.015 (5.34–9.95)	7.41 (5.57–10.08)	NS
DBP	7.72 (6.05–11.6)	8.305 (5.97–11.39)	NS
αHF of spectral BRS			
SBP	12.18 ± 6.65	8.945 (7.23–13.27)	NS
MBP	24.05 ± 12.81	22.69 ± 10.25	NS
DBP	18.29 ± 5.32	18.03 (13.64–23.78)	NS
LF/HF ratio			
SBP	2.42 (0.78–6.64)	1.5 (0.85–3.48)	0.0453
MBP	11.38 (4.2–28.32)	8.825 (3.39–14.48)	0.0164
DBP	3.335 (1.17–5.97)	4.721 ± 3.36	NS

Normally distributed data are expressed as mean ± SD, and non-parametric data are expressed as median (inter-quartile range). BRS, Baroreflex sensitivity; BP, Blood pressure; SBP, Systolic blood pressure; MBP, Mean blood pressure; DBP, Diastolic blood pressure; NS, Not significant

DOWN- and ALL-sequences of BP and RR interval (Fig. 2a). No significant correlations were observed between the number of sequences of UP-, DOWN- and ALL-sequences of systolic, mean, and diastolic BP, and RR interval. On correlation analyses between heart rate during fasting and hyperglycemic state and spectral BRS parameters, significant correlations were observed with αHF of spectral BRS of systolic, mean and diastolic BP and RR interval, αLF of spectral BRS of diastolic BP and RR interval, and, LF/HF ratio of spectral BRS of systolic and mean BP and RR interval (Fig. 2b).

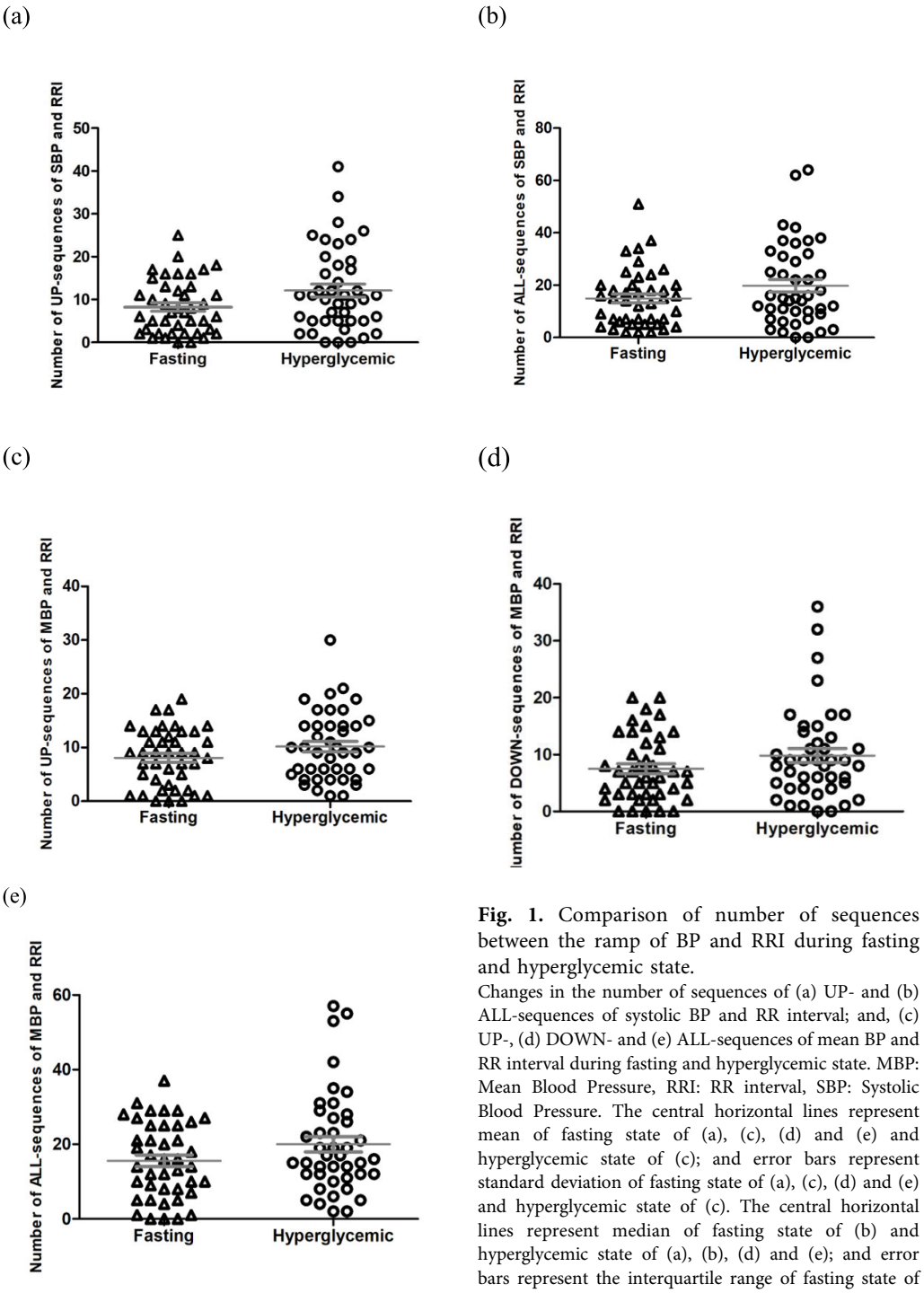
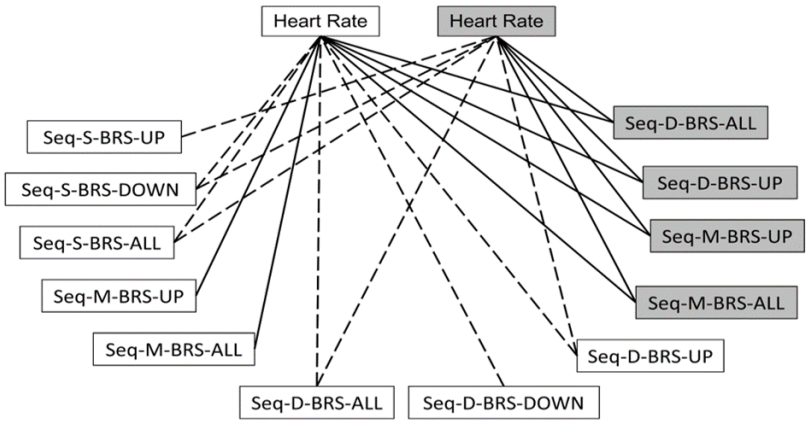


Fig. 1. Comparison of number of sequences between the ramp of BP and RRI during fasting and hyperglycemic state.

Changes in the number of sequences of (a) UP- and (b) ALL-sequences of systolic BP and RR interval; and, (c) UP-, (d) DOWN- and (e) ALL-sequences of mean BP and RR interval during fasting and hyperglycemic state. MBP: Mean Blood Pressure, RRI: RR interval, SBP: Systolic Blood Pressure. The central horizontal lines represent mean of fasting state of (a), (c), (d) and (e) and hyperglycemic state of (c); and error bars represent standard deviation of fasting state of (a), (c), (d) and (e) and hyperglycemic state of (c). The central horizontal lines represent median of fasting state of (b) and hyperglycemic state of (a), (b), (d) and (e); and error bars represent the interquartile range of fasting state of (b) and hyperglycemic state of (a), (b), (d) and (e).

(a)



(b)

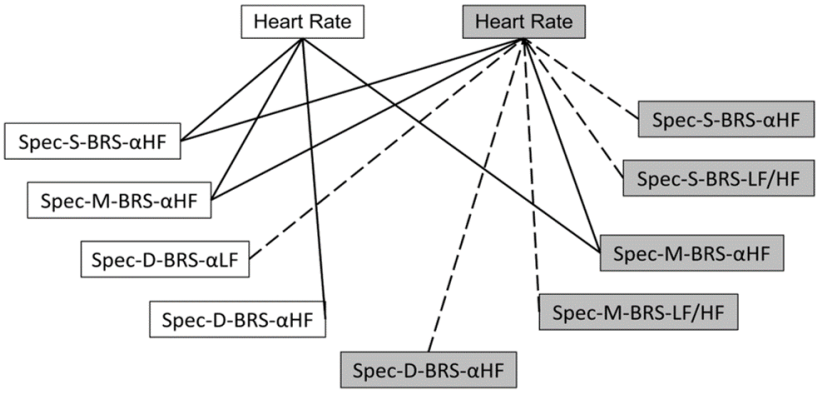


Fig. 2. Correlation web between different BRS-parameters and heart rate during fasting and hyperglycemic state.

Correlation web showing significant correlations among heart rate during fasting and hyperglycemic state and different BRS parameters assessed by sequence (a) and spectral (b) method. All the correlations are negative correlations. Solid lines indicate Pearson correlation; broken lines indicate Spearman correlation. Parameters in clear boxes indicate fasting status and parameters in grey boxes indicate hyperglycemic status. Seq-S-BRS-UP, Seq-S-BRS-DOWN, Seq-S-BRS-ALL: Baroreflex sensitivity assessed by UP-, DOWN- and ALL- sequences of systolic blood pressure and RR interval, respectively; Seq-M-BRS-UP, Seq-M-BRS-ALL: Baroreflex sensitivity assessed by UP-and ALL- sequences of mean blood pressure and RR interval, respectively; Seq-D-BRS-UP, Seq-D-BRS-DOWN, Seq-D-BRS-ALL: Baroreflex sensitivity assessed by UP-, DOWN- and ALL- sequences of diastolic blood pressure and RR interval, respectively. Spec-S-BRS-αHF, Spec-M-BRS-αHF, Spec-D-BRS-αHF: Baroreflex sensitivity assessed by αHF from spectral analysis of RR oscillations and systolic, mean and diastolic blood pressure oscillations, respectively; Spec-D-BRS-αLF: Baroreflex sensitivity assessed by αLF from spectral analysis of RR oscillations and diastolic blood pressure oscillations; Spec-S-BRS-LF/HF, Spec-M-BRS-LF/HF: Baroreflex sensitivity assessed by LF/HF from spectral analysis of RR oscillations and systolic and mean blood pressure oscillations, respectively.

Discussion

The present study evaluated the effect of acute hyperglycemia on BRS, assessed by sequence and spectral methods, in young, healthy subjects. The novel findings of this study are the significant effect of hyperglycemia on the number of UP-, DOWN- and ALL-sequences of mean BP and RRI, and, UP- and ALL-sequences of systolic BP and RRI. However, the study didn't find any significant effect of hyperglycemia on most of the conventional BRS parameters. By these findings, it can be hypothesized that different body and homeostatic mechanisms tend to keep the BRS unaffected by hyperglycemia, at the expense of increase or decrease in the number of sequential changes in BP and RR interval.

Impaired BRS indicates the impaired function of the autonomic nervous system, and has been reported in subjects with newly diagnosed diabetes mellitus or even those with impaired glucose tolerance [11–13]. Impaired BRS is associated with adverse cardiovascular outcomes in patients with diabetes mellitus and hypertension [26]. However, rarely has any study been carried out in healthy subjects to evaluate the acute effect of hyperglycemia in healthy subjects. The study by Holwerda *et al.* [25] reported impaired spontaneous BRS in healthy subjects during acute hyperglycemia. The present study didn't find any significant changes in most of the BRS parameters, except for the LF/HF ratio. The impaired BRS maybe because of the effect of glucose on the vagal afferent nerve terminals and nucleus tractus solitarius [27–29], which forms important parts of the baroreflex loop.

A novel finding in the present study was the significant changes in the number of increasing and decreasing sequences of BP and RR interval, during hyperglycemia. This finding further supports that basic alterations in cardiovascular rhythms aims to maintain the relatively constant vital cardiovascular parameters such as BP [30, 31], and probably the BRS. Although, to the best of our search, we didn't find any study reporting the number of increasing and decreasing sequences of BP and RRI, during the sequential analysis of BRS, and its alterations in different physiological and pathological conditions.

The present study observed significant correlations between heart rate during fasting and acute hyperglycemic state and various spontaneous BRS parameters, assessed by sequence and spectral methods. These findings indicate the mutual and synchronized functioning of central and peripheral cardiovascular sensors, centres and effectors [31, 32] to optimize the BRS. However, further studies are required to decipher the detailed mechanisms behind it.

A few limitations should be considered while interpreting the results of the present study. Insulin levels per se can affect the BRS, in addition to hyperglycemia. In the present study, insulin levels have not been assessed. Further, insulin sensitivity or resistance can have an influence on BRS. In addition, more female subjects are re-

cruited than male subjects in the present study. Therefore, the results and interpretation may be viewed in this context. Further studies with sufficient numbers of male and female subjects and in wide age ranges are required to validate the findings of the present study.

In conclusion, the present study addressed the effect of acute hyperglycemia on BRS in young, healthy subjects. Most of the BRS parameters remain unaffected during acute hyperglycemia. However, the number of UP-, DOWN- and ALL-sequences of BP and RR interval by sequential analysis of BRS, show significant changes during the acute hyperglycemic state compared to the fasting state. Therefore, the present study suggests that the number of sequences between the ramps of BP and RR interval affected significantly during acute hyperglycemia than the other conventional spontaneous BRS parameters per se in young, healthy subjects. We may hypothesize that the relatively constant BRS is maintained at the expense increased oscillations in the ramp of BP and RRI.

Funding

The author(s) received no financial support for the research, authorship and/or publication of this article.

Acknowledgements

None declared.

Conflict of interest

None declared.

Abbreviations

BP — blood pressure
BRS — baroreflex sensitivity
ECG — electrocardiogram
HF — high-frequency band
LF — low-frequency band

References

1. *Goldberger J.J., Arora R., Buckley U., Shivkumar K.*: Autonomic Nervous System Dysfunction: JACC Focus Seminar. J Am Coll Cardiol. 2019 Mar 19; 73 (10): 1189–1206.
2. *Chiasson J.-L., Josse R.G., Gomis R., et al.*: Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. JAMA. 2003; 290 (4): 486–494. doi: 10.1001/jama.290.4.486.

3. *Lamounier-Zepter V., Ehrhart-Bornstein M., Bornstein S.R.*: Insulin resistance in hypertension and cardiovascular disease. Best Pract Res Clin Endocrinol Metab. 2006; 20 (3): 355–367. doi: 10.1016/j.beem.2006.07.002.
4. *Flynn C., Bakris G.L.*: Role of ambulatory blood pressure monitoring in hypertension and diabetes. Curr Hypertens Rep. 2013; 15 (3): 137–142. doi: 10.1007/s11906-013-0352-5.
5. *Ansarimoghaddam A., Adineh H.A., Zareban I., Iranpour S., HosseinZadeh A., Kh F.*: Prevalence of metabolic syndrome in Middle-East countries: Meta-analysis of cross-sectional studies. Diabetes Metab Syndr. 2018; 12 (2): 195–201. doi: 10.1016/j.dsx.2017.11.004.
6. *Adnan E., Rahman I.A., Faridin H.P.*: Relationship between insulin resistance, metabolic syndrome components and serum uric acid. Diabetes Metab Syndr. 2019; 13 (3): 2158–2162. doi: 10.1016/j.dsx.2019.04.001.
7. *Kishi T.*: Disruption of Central Antioxidant Property of Nuclear Factor Erythroid 2-Related Factor 2 Worsens Circulatory Homeostasis with Baroreflex Dysfunction in Heart Failure. Int J Mol Sci. 2018; 19 (3). doi: 10.3390/ijms1903064.
8. *La Rovere M.T., Pi na G.D.*: Beneficial effects of physical activity on baroreflex control in the elderly. Ann Noninvasive Electrocardiol Off J Int Soc Holter Noninvasive Electrocardiol Inc. 2014; 19 (4): 303–310. doi: 10.1111/anec.12170.
9. *Monahan K.D.*: Effect of aging on baroreflex function in humans. Am J Physiol Regul Integr Comp Physiol. 2007; 293 (1): R3–R12. doi: 10.1152/ajpregu.00031.2007.
10. *Kück J.-L., Bönhof G.J., Strom A., et al.*: Impairment in Baroreflex Sensitivity in Recent-Onset Type 2 Diabetes Without Progression Over 5 Years. Diabetes. Published online February 21, 2020. doi: 10.2337/db19-0990.
11. *Wu J.-S., Lu F.-H., Yang Y.-C., et al.*: Impaired baroreflex sensitivity in subjects with impaired glucose tolerance, but not isolated impaired fasting glucose. Acta Diabetol. 2014; 51 (4): 535–541. doi: 10.1007/s00592-013-0548-9.
12. *Straznicky N.E., Lambert G.W., Masuo K., et al.*: Blunted sympathetic neural response to oral glucose in obese subjects with the insulin-resistant metabolic syndrome. Am J Clin Nutr. 2009; 89 (1): 27–36. doi: 10.3945/ajcn.2008.26299.
13. *Straznicky N.E., Grima M.T., Sari C.I., et al.*: Neuroadrenergic dysfunction along the diabetes continuum: a comparative study in obese metabolic syndrome subjects. Diabetes. 2012; 61 (10): 2506–2516. doi: 10.2337/db12-0138.
14. *Rabinovitch A., Friedman M., Braunstein D., Biton Y., Aviram I.*: The Baroreflex Mechanism Revisited. Bull Math Biol. 2015; 77 (8): 1521–1538. doi: 10.1007/s11538-015-0094-4.
15. *Pinna G.D., Maestri R., Capomolla S., et al.*: Applicability and clinical relevance of the transfer function method in the assessment of baroreflex sensitivity in heart failure patients. J Am Coll Cardiol. 2005; 46 (7): 1314–1321. doi: 10.1016/j.jacc.2005.06.062.
16. *La Rovere M.T., Pinna G.D., Raczak G.*: Baroreflex sensitivity: measurement and clinical implications. Ann Noninvasive Electrocardiol Off J Int Soc Holter Noninvasive Electrocardiol Inc. 2008; 13 (2): 191–207. doi: 10.1111/j.1542-474X.2008.00219.x.
17. *La Rovere M.T., Pinna G.D., Maestri R., Sleight P.*: Clinical value of baroreflex sensitivity. Neth Heart J. 2013; 21 (2): 61–63. doi: 10.1007/s12471-012-0349-8.
18. *Johansson M., Gao S.A., Friberg P., et al.*: Baroreflex effectiveness index and baroreflex sensitivity predict all-cause mortality and sudden death in hypertensive patients with chronic renal failure. J Hypertens. 2007; 25 (1): 163–168. doi: 10.1097/01.hjh.0000254377.18983.eb.
19. *Ziegler D., Voss A., Rathmann W., et al.*: Increased prevalence of cardiac autonomic dysfunction at different degrees of glucose intolerance in the general population: the KORA S4 survey. Diabetologia. 2015; 58 (5): 1118–1128. doi: 10.1007/s00125-015-3534-7.
20. *Katakami N.*: Mechanism of Development of Atherosclerosis and Cardiovascular Disease in Diabetes Mellitus. J Atheroscler Thromb. 2018; 25 (1): 27–39. doi: 10.5551/jat.RV17014.
21. *Fiorentino T.V., Prioletta A., Zuo P., Folli F.*: Hyperglycemia-induced oxidative stress and its role in diabetes mellitus related cardiovascular diseases. Curr Pharm Des. 2013; 19 (32): 5695–5703. doi: 10.2174/1381612811319320005.

22. *Bathula R., Hughes A.D., Panerai R., et al.*: Indian Asians have poorer cardiovascular autonomic function than Europeans: this is due to greater hyperglycaemia and may contribute to their greater risk of heart disease. Diabetologia. 2010; 53 (10): 2120–2128. doi: 10.1007/s00125-010-1818-5.
23. *Madonna R., De Caterina R.*: Cellular and molecular mechanisms of vascular injury in diabetes — part I: pathways of vascular disease in diabetes. Vascul Pharmacol. 2011; 54 (3–6): 68–74. doi: 10.1016/j.vph.2011.03.005.
24. *Sakamoto M., Matsutani D., Kayama Y.*: Clinical Implications of Baroreflex Sensitivity in Type 2 Diabetes. Int Heart J. 2019; 60 (2): 241–246. doi: 10.1536/ihj.18-455.
25. *Holwerda S.W., Reynolds L.J., Restaino R.M., et al.*: The influence of reduced insulin sensitivity via short-term reductions in physical activity on cardiac baroreflex sensitivity during acute hyperglycemia. J Appl Physiol Bethesda Md 1985. 2015; 119 (12): 1383–1392. doi: 10.1152/japplphysiol.00584.2015.
26. *Gerritsen J., Dekker J.M., TenVoorde B.J., et al.*: Impaired Autonomic Function Is Associated With Increased Mortality, Especially in Subjects With Diabetes, Hypertension, or a History of Cardiovascular Disease: The Hoorn Study. Diabetes Care. 2001; 24 (10): 1793–1798. doi: 10.2337/diacare.24.10.1793.
27. *López-Gambero A.J., Martínez F., Salazar K., Cifuentes M., Nualart F.*: Brain Glucose-Sensing Mechanism and Energy Homeostasis. Mol Neurobiol. 2019; 56 (2): 769–796. doi: 10.1007/s12035-018-1099-4.
28. *Wan S., Browning K.N.*: Glucose increases synaptic transmission from vagal afferent central nerve terminals via modulation of 5-HT3 receptors. Am J Physiol — Gastrointest Liver Physiol. 2008; 295 (5): G1050–G1057. doi: 10.1152/ajpgi.90288.2008.
29. *Dallaporta M., Himmi T., Perrin J., Orsini J.C.*: Solitary tract nucleus sensitivity to moderate changes in glucose level. Neuroreport. 1999; 10 (12): 2657–2660. doi: 10.1097/00001756-199908200-00040.
30. *Elstad M., O'Callaghan E.L., Smith A.J., Ben-Tal A., Ramchandra R.*: Cardiorespiratory interactions in humans and animals: rhythms for life. Am J Physiol Heart Circ Physiol. 2018; 315 (1): H6–H17. doi: 10.1152/ajpheart.00701.2017.
31. *Dick T.E., Hsieh Y.-H., Dhingra R.R., et al.*: Cardiorespiratory coupling: common rhythms in cardiac, sympathetic, and respiratory activities. Prog Brain Res. 2014; 209: 191–205. doi: 10.1016/B978-0-444-63274-6.00010-2.
32. *Grossman P., Taylor E.W.*: Toward understanding respiratory sinus arrhythmia: relations to cardiac vagal tone, evolution and biobehavioral functions. Biol Psychol. 2007; 74 (2): 263–285. doi: 10.1016/j.biopsycho.2005.11.014.