Brief Report

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Possible relationship between the heart rates and serum amyloid A in a hyperglycemic population

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Summary **Hyperglycemia predicts cardiovascular disease (CVD)-related outcomes. The resting heart rates (HRs) and serum amyloid A (SAA), an inflammatory marker, are respectively factors associated with CVD-related outcomes; however, little is known regarding the associations between these two factors. This study aimed to investigate the correlation between the HRs and SAA levels under hyperglycemic conditions. This study included 298 subjects (males, 44%; mean age, 61.1 years) without a history of CVD and/or hypertensive levels. Clinical data, including general laboratory measurements, HRs and SAA, were measured. The analyses were performed after dividing all of the subjects into two groups based on the blood glucose level (< or ≥ 6.1 mmol/L). There was a higher SAA level in the hyperglycemic group (n = 143; median [interquartile range] 6.1 [4.1-10.6] μg/mL) than in the counterpart group (n = 155; 6.0 [3.5-8.5] μg/mL; $p < 0.01$). There was a trend toward increased HRs in the hyperglycemic group (mean [standard deviation] 65.3 [11.2] bpm) compared to the counterpart group (63.2 [9.4] bpm; $p = 0.08$). In the hyperglycemic group, there was a significant positive correlation between the HRs and SAA levels (multiple variables-adjusted analysis: β = 0.21, $p = 0.02$), while no correlation was found in the counterpart group (β = 0.06, $p = 0.50$). In summary, a positive correlation between the HRs and SAA levels can present under hyperglycemic conditions. These findings may provide relevant insights into the CVD-related pathologies associated with hyperglycemia. Further studies are warranted.**

Keywords: Amyloid A protein, diabetes mellitus, glucose intolerance, heart rhythm, inflammation.

1. Introduction

Hyperglycemia (even when the plasma glucose concentration is at a prediabetic level) predicts cardiovascular disease (CVD)-related outcomes (*1,2*). An increase in the resting heart rates (HRs) also predicts CVD-related outcomes (*3*), while abnormal HRs are often seen in hyperglycemic subjects (*4-6*). Recently, low-grade chronic inflammation has been reported to be a crucial player under hyperglycemic conditions (*7-9*). Therefore, knowledge about the association between the heart rhythmicity and chronic inflammation would be helpful for understanding and managing the pathologies associated with hyperglycemia.

Serum amyloid A (SAA) is induced by various proinflammatory cytokines (*e.g.*, interleukin 6) and is clinically used as an inflammatory marker of CVD (*10*). The SAA level is sometimes increased in hyperglycemic subjects (*11,12*). Several prior studies have indicated a positive correlation between the HRs and C-reactive protein (CRP), another inflammatory marker (*13,14*). However, these studies did not focus on hyperglycemia, and there has been an observation that SAA is closer to CVD-related pathologies than other markers, such as CRP (*15-17*). Therefore, this study aimed to investigate the association between the HRs and SAA levels under conditions of hyperglycemia.

2. Materials and Methods

A total of 298 subjects who visited our University Hospital were enrolled in this study. The subjects

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Table 1. The characteristics of the subjects according to the blood glucose levels (< *vs.* ≥ 6.1 mmol/L)

Items	All subjects (*n* = 298)	Subjects < 6.1 mmol/L (*n* = 155)	Subjects ≥ 6.1 mmol/L (*n* = 143)	*p*-value
Age, years old	61.1 ± 10.8	60.4 ± 9.8	62.0 ± 11.8	0.21
Males/females, *n*	131/167	55/100	76/67	< 0.01*
Current smokers, *n* (%)	42 (14.1%)	18 (11.6%)	24 (16.8%)	0.20
Body mass index, kg/m^2	24.0 ± 3.5	23.9 ± 3.2	24.1 ± 3.7	0.74
Heart rates, bpm	64.2 ± 10.4	63.2 ± 9.4	65.3 ± 11.2	0.08
Systolic BP, mmHg	122.5 ± 9.3	123.8 ± 8.9	121.1 ± 9.4	0.01*
Diastolic BP, mmHg	75.3 ± 7.8	76.3 ± 8.0	74.3 ± 7.4	0.03*
Total cholesterol, mmol/L	5.3 ± 0.9	5.3 ± 0.9	5.1 ± 0.9	0.06
Triglyceride, mmol/L	1.2 (0.9-1.7)	1.2 (0.9-1.7)	1.2 (0.9-1.6)	0.88
HDL-cholesterol, mmol/L	1.5 ± 0.5	1.5 ± 0.4	1.5 ± 0.5	0.54
Glucose, mmol/L	6.0 (5.3-7.7)	5.3 (4.9-5.7)	7.7 (6.7-9.6)	< 0.01*
Serum amyloid A, μg/mL	6.1 (3.8-9.3)	6.0 (3.5-8.5)	6.1 (4.1-10.6)	< 0.01*

BP: blood pressure, HDL: high-density lipoprotein. The data are shown as the means ± standard deviations, medians (interquartile ranges) or subject numbers (%). *p*-values: $p < 0.05$ was set as the significance level in the comparison between the subjects with glucose levels of < and ≥ 6.1 mmol/L (*t*-tests).

included those without acute infectious diseases and severe liver or kidney diseases (these are possible diseases that are associated with unstable glucose levels (*18*)). The excluded subjects were those with a history of CVD events and those who showed a hypertensive level of systolic/diastolic blood pressure (SBP/DBP) of ≥ 140/90 mmHg (*19*), because these subjects could receive drugs affecting their HRs. Current smokers were defined as those who reported a current smoking habit.

The institutional ethics committee approved this study, and informed consent was obtained from all subjects. The body mass index (BMI) was determined while the subjects were wearing light clothes without shoes. Physiological variables, such as the HRs and SBP/DBP in the subject's right arm, were measured after a five-minute rest at room temperature. After blood was sampled while fasting, the concentrations of serum lipids (total cholesterol [TC], triglyceride [TG], high-density lipoprotein cholesterol [HDL-C]) and plasma glucose were enzymatically measured. The SAA concentrations were measured by an ELISA format.

The differences between the groups were examined using t-tests and Chi-square tests. Correlations between the HRs and SAA levels were examined using Pearson's correlation tests and multiple regression analyses adjusted for confounding variables (we entered the SBP only into the adjusted models due to the collinearity of the SBP and DBP). Because of their skewed distribution, the TG, glucose and SAA levels were log-transformed in all analyses. A subgroup analysis was performed after dividing all of the subjects into two groups based on their blood glucose level (< and ≥ 6.1 mmol/L), because this glucose level reflects impaired glucose tolerance (*20,21*) A p-value of < 0.05 was considered to be statistically significant.

3. Results and Discussion

The clinical data of all subjects to be included in the study are shown in Table 1. The data regarding the age, current smoking status, BMI, HRs and lipid concentrations did not show any relative differences between the subject groups divided according to their glucose levels (Table 1). Compared with the subjects with a glucose level of < 6.1 mmol/L, those with a glucose level of ≥ 6.1 mmol/L included more males, and exhibited a lower SBP/DBP, as well as higher glucose and SAA levels.

In all of the subjects, the correlation between the HRs and SAA levels was significant but weak ($r = 0.14$, $p = 0.02$). When the data were adjusted for confounding factors (age, gender, smoking, BMI, SBP, lipids and glucose), the adjustment did not largely affect the correlation between the HRs and SAA levels ($\beta = 0.15$, $p = 0.02$). The subgroup analyses were performed using similar analyses, and found a significant and greater correlation between the HRs and SAA levels ($r = 0.18$, $p = 0.03$; $\beta = 0.21$, $p = 0.02$) in the subjects with the blood glucose level of ≥ 6.1 mmol/L, while there was a nonsignificant correlation between the HRs and SAA levels ($r = 0.04$, $p = 0.67$; $\beta = 0.06$, $p = 0.50$) in the subjects with the glucose level of < 6.1 mmol/L.

Thus, the present study noted a significantly positive correlation between the HR and SAA levels in the hyperglycemic population. There has been no study on the association between the HRs and SAA with special reference to hyperglycemia, although these factors are known to have value for predicting the outcomes related to CVD, such as ischemic heart disease and acute coronary syndrome (*1-3*,*15-17*). Therefore, the present study findings can offer relevant information for the CVD-related pathologies associated with hyperglycemia.

There are two possible explanations for the present study results. First, increased HRs are often seen in hyperglycemic subjects (this trend was also observed in the present study), who may have impaired autonomic nervous system function, such as activated sympathetic and decreased parasympathetic modulation of the heart (*4-6*). The sympathetic activation itself promotes the secretion of pro-inflammatory cytokines, leading to increased inflammation (*4,6*). Another idea can also be considered. Hyperglycemia is an inflammatory condition

(*7-9*), and in fact, the present study demonstrated a higher SAA level in the hyperglycemic population than in the counterpart population, in line with the prior studies (*11,12*). This inflammatory condition creates sympathetic activation, leading to increased HRs (*4,6*).

The present study is associated with some limitations. First, the study design was cross-sectional; accordingly, the causality of the results could not completely be determined. Second, subjects with obvious hypertension and/or CVD-related outcomes were not evaluated. The other relevant measurements, such as hemoglobin A1c, CRP and autonomic nervous system (as expressed as body temperature, thermal and vibratory perception), were also not evaluated. The present study should only be considered a preliminary study at this point. Prospective evaluations of various populations and other relevant measurements are required to further confirm our findings.

In summary, a positive correlation between the HRs and SAA levels can present under hyperglycemic conditions. The findings may be useful for understanding and managing the CVD-related pathologies associated with hyperglycemia. Further studies are warranted to further explore this topic.

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