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LETTER TO THE EDITOR

rs1801253 Gly/Gly carriage in the *ADRB1* gene leads to unbalanced cardiac sympathetic modulation as assessed by spectral analysis of heart rate variability

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Introduction

The analysis of heart rate variability (HRV) has long been used as a standard non-invasive method for assessing autonomic nervous system (ANS) functions [1, 2]. By computerized analysis of an electrocardiographic trace of sufficient length, heart rate components can be extrapolated using two methods: time domain analysis and frequency domain analysis. The values obtained from the analysis of HRV reflect differences in the activity of the two branches of the ANS. In fact, in the presence of parasympathetic activation, an increase in standard deviation of RR intervals (SDNN), root mean square of successive differences between normal heart beats (RMSSD), and HRV values is observed [3]. Also, high frequency (HF) is taken as an index of modulation of the parasympathetic branch, whereas low frequency (LF) is taken as an index of modulation of the sympathetic branch; therefore, their ratio, namely LF/HF, is considered as indicative of sympathetic to parasympathetic balance [4].

The β-adrenergic receptors (β-ARs) are responsible for signaling in the sympathetic nervous system. The *ADRB1* gene encodes β1-adrenergic receptors, which account for 70–80% of the cardiac β-ARs [5]. In contrast, β2-adrenergic receptors, coded by the *ADRB2* gene, are located primarily in central nervous system, heart, kidney, and muscle. It has been demonstrated, both by in vivo and in vitro studies, that single nucleotide polymorphisms (SNPs) in the *ADRB1* and *ADRB2* genes are involved in the modulation of the physiologic variability of neural parasympathetic/sympathetic discharge [5], as well as in the effectiveness of drug therapy [6]. There is also evidence that β-ARs affect cardiac electrical stability and susceptibility to sudden cardiac death [7]. However, to what extent parameters evaluated at spectral analysis of healthy individuals observed at rest, reflecting their sympathetic to parasympathetic balance, are affected by genetic variability of β-ARs is unknown. With this paper, we aimed to fill this gap.

Methods

Patients

The study population included 241 healthy volunteers (female: $n = 159$, median age = 54 years, median body mass index = 23 kg/m^2; male: $n = 82$, median age = 54 years, median body mass index = 25 kg/m^2) recruited at an academic hospital in Northern Italy as part of a screening for cardiovascular risk. Of them, 116 were teetotalers, none consumed alcohol in excess on a regular basis while 44 were current smokers. Allelic and genotypic frequencies of the SNPs of interest are shown in Table S1.

β-Adrenergic receptor polymorphisms

All participants were genotyped, by means of restriction fragment length polymorphism (RFLP) analysis [6–8],

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for two SNPs in the *ADRB2* gene coding for the β2 surface receptor (rs1042713 and rs1042714), as well as for two SNPs in the *ADRB1* gene coding for the β1 surface receptor (rs1801252 and rs1801253).

Heart rate variability (HRV) analysis

The HRV variables were obtained by means of the computerized analysis of a 5-min 6-lead electrocardiogram (ECG; Easy ECG pocket and Software Easy View Plus Stress, Ates Medical Device, Colognola Ai Colli, Verona, Italy or ECG600G digital electrocardiograph, Contec Medical Systems Co., Ltd, Qinhuangdao, China), following the RR interval power spectral analysis, as previously described [9]. Collected data were analyzed by means of the Kubios HRV program version 3.1.0 (Kubios Oy, Kupio, Finland), both in the time domain and frequency domain [1, 10]. In addition, the sympathetic (SNS), parasympathetic (PNS) index, and stress index were examined through Kubios analysis of the registrations [11] (see supplementary material for further details).

Statistical analysis

Statistical analysis was conducted using the Stata statistical software, version 17.0 (StataCorp LP, College Station, Texas, USA). The allele and genotype frequencies were calculated for the biallelic sites of interest. Two multiple linear regression models were built to study the linear relationship between the dependent variables LF and HF and a set of independent variables (including confounders such as age, sex, body mass index, and systolic/diastolic blood pressure). For all tests used, the statistical significance threshold was 0.05 (two tailed).

Results

Univariate analysis

In the frequency domain, median (IQR) low frequency (LF) components were 58 (44–72) normalized units (NU) among rs1801253 A* reference allele carriers and 67 (54–76) in aa variant allele homozygotes ($p = 0.009$). Conversely, median (IQR) high frequency (HF) components were 41 (28–56) NU among rs1801253 A* carriers and 33 (25–46) in aa carriers ($p = 0.010$). Moreover, the median LF/HF ratio was 1 (1–3) in A* carriers vs. 2 (1–3) among aa carriers ($p = 0.013$). A similar though weaker association was observed for rs1801252. No significant differences were observed in the time domain, except for the longer root mean square of successive differences between normal heartbeats in rs1801252 a* carriers ($p = 0.040$).

Multivariate analysis

We built two multiple linear regression analysis models including as independent variables rs1801253 (AG/GG = 0; AA = 1; recessive model), sex (female = 0, male = 1), age (years), BMI (kg/m^2), systolic and diastolic blood pressure (mmHg), habits regarding smoking (never smoker = 0; former smoker = 1; current smoker = 2) and drinking (teetotalers = 0; drinkers = 1), and either LF (NU) or HF (NU) as dependent variable. In both models, carriage of the rs1801253 ancestral allele was a strong predictor of the observed LF and HF values, together with the diastolic blood pressure (R-squared 0.1327, $F < 0.001$ and R-squared 0.1315, $F < 0.001$, respectively). Table S2 summarizes the results of two similar models in which rs1801253 is analyzed genotypically.

Discussion

The present study suggests that in a population of middle-aged healthy subjects an SNP in the *ADRB1* gene (rs1801253; Arg389Gly) may influence frequency domain HRV (LF, HF, LF/HF)—a proxy measure of ANS activity—at supine rest, independently of multiple possible confounders. Under the same conditions, a second *ADRB1* SNP (rs1801252; Ser49Gly) also appears to affect time and frequency domain parameters (RMSSD, HF), though to a far lesser degree, with an association observed only at univariate analysis. Two other well-characterized SNPs in the *ADRB2* gene did not contribute significantly to the variability observed either in time or frequency domain HRV.

β-ARs SNPs have already been shown to be involved in the regulation of cardiovascular function, both as a direct action on the cardiac activity and through the regulation of the systemic vascular resistances and the renin–angiotensin–aldosterone system [12, 13]. In addition, in healthy subjects β1-AR rs1801252 and rs1801253 and β2-AR rs1042713 and rs1042714 appear to correlate with variables of cardiac function and HRV, and with arterial blood pressure [13].

The present data pinpoint SNPs in the *ADRB1* gene as likely important contributors to HRV variations in the frequency domain, consistent with the fact that most heart β-ARs are β1. The association we found between carriage of the Gly allele in the *ADRB1* gene and the sympathetic-related HRV variables is consistent with the observation that carriers of this allele may be less responsive to beta-blockers [14].

Conversely, we found a negative association between rs1801253 and one frequency domain variable

representative of the vagal activity, namely HF. These data are also not surprising since, as noted above, our study population was composed mainly of women, in which the parasympathetic tone overwhelms that of the sympathetic system.

Taken together these data suggest that carriage of the Gly allele in the *ADRB1* gene have an imbalance of the sympathetic/parasympathetic tone, in favor of the former, which could justify the greater propensity to develop alterations in arterial blood pressure and an increased risk for cardiovascular diseases. About this issue, it is worth noting that the sympathetic activity is the primary determinant of the circadian changes in arterial blood pressure and that any alteration in the sympathetic/parasympathetic balance might negatively affect the physiological drop in blood pressure during sleeping [15].

Limitations

For a study analyzing SNPs, our sample size is relatively small, though larger in comparison to the existing literature on the topic. Moreover, our results only apply to supine rest conditions, as we did not attempt to verify response to orthostasis and/or other physical or mental challenges. Also, being based on short electrocardiographic registrations, our study cannot provide data about cardiac reactions to a greater range of environmental stimulation as it occurs with longer recording periods (24 h). In fact, in addition to cardiorespiratory regulation, extended measurement periods can index the heart's response to changing workloads, anticipatory central nervous activity involving classical conditioning, and circadian processes, including sleep–wake cycles.

Conclusion

The present findings suggest that β1-adrenergic receptor gene variability, specifically at the 389 locus of the *ARDB1* gene (rs1801253), is a plausible explanation for the contribution of genetics to HRV in healthy subjects of either sex at supine rest. These data are consistent with the preferential expression of β1-adrenergic receptors in the heart as compared to β2-adrenergic receptors, as well as with what is known on how SNPs affect *ADRB1* gene function and phenotype under physiological and pathological conditions.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10286-023-01001-4.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest relevant to this paper.

Ethical approval All participants gave written informed consent to their participation in the study and their data were handled in pseudonymized conditions. The study protocol was approved by the local Ethical Committee (http://www.comitatoeticonovara.it/comitatoetico.html, document number 157/18) and has been conducted in strict accordance with the principles of the Declaration of Helsinki.

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