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Adrenergic hyperactivity: A missing link between multiple sclerosis and cardiovascular comorbidities?

Mario Habek[1,2], Tomislav Mutak[1]*, Bojana Nevajdić[1]*, Dunja Pucić[1]*, Luka Crnošija[2], Magdalena Krbot Skorić[2]

*These authors contributed equally.

[1] School of Medicine, University of Zagreb, Zagreb, Croatia

[2] University Hospital Center Zagreb, Department of Neurology, Referral Center for Autonomic Nervous System Disorders, Zagreb, Croatia

Corresponding author:

Mario Habek, MD, PhD

Department of Neurology, University Hospital Center Zagreb

Kišpatićeva 12

HR-10000 Zagreb

Croatia

Phone/Fax: +38512388033; e-mail: mhabek@mef.hr

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Abstract

Background and objective: To investigate differences in non-standard adrenergic baroreflex sensitivity (BRS) indices in patients with different phenotypes of multiple sclerosis (pwMS) and healthy controls (HC).

Methods: Retrospective analysis of types of systolic blood pressure (BP) curves during Valsalva maneuver (VM) (balanced (BAR), augmented (AAR) and suppressed (SAR) autonomic responses) and adrenergic baroreflex sensitivity (BRSa) measured with $BRSa_1$, α-BRSa and β-BRSa in patients with clinically isolated syndrome (CIS), relapsing remitting multiple sclerosis (RRMS), progressive multiple sclerosis (PMS) and HC. We also investigated correlations between $BRSa_1$, α-BRSa, β-BRSa and resting catecholamines levels.

Results: pwMS had higher α-BRSa compared to HC (p=0.02). There was no difference in $BRSa_1$, α-BRSa and β-BRSa between patients with CIS, RRMS and PMS. There was no association between pwMS and HC and the type of sBP curve ($\chi(2)=4.332$, p=0.114). pwMS and BAR or AAR had higher supine systolic and diastolic BP compared pwMS and SAR. There was a significant correlation between α-BRSa and upright systolic BP (r_p =0.194, p=0.017), α-BRSa and norepinephrine (r_s =0.228, p= 0.021) and $BRSa_1$ and epinephrine (r_s =0.226, p=0.040).

Conclusion: pwMS and HC exhibit different alpha-adrenergic response to Valsalva maneuver. These results may explain the connection between MS and increased cardiovascular risk.

Key words: multiple sclerosis, Valsalva maneuver, cardiovascular autonomic dysfunction, adrenergic baroreflex sensitivity

Introduction

Impaired autonomic control of cardiovascular function has been reported in a large proportion of patients with multiple sclerosis (pwMS). (1) The implications of cardiovascular autonomic dysfunction may be numerous, however the most important one is the recent finding that pwMS may have an increased risk of ischemic heart disease and congestive heart failure when compared with the general population. (2) Furthermore, it seems that there is a markedly increased risk of myocardial infarction in the first year after MS diagnosis. (3) Theoretically, the explanation for this might be a selective involvement of different branches of the autonomic nervous system (ANS) in pwMS depending on the stage and/or activity of the disease. In line with this, recent studies have shown frequent involvement of sympathetic adrenergic and cholinergic parts of the autonomic nervous system in pwMS at the stage of diagnosis of MS. (4)

There are several ways of investigating sympathetic adrenergic function, and the interpretation of the blood pressure (BP) response to Valsalva maneuver (VM) represents the cornerstone of autonomic evaluation. (5) The curve of the BP response to VM has four phases, with the BP increment in late phase II mediated by the alpha adrenergic influence, and BP overshoot in the phase IV mediated by the beta adrenergic influence. (6) The most accepted way of interpretation of the BP response to VM is in the form of Composite Autonomic Scoring Scale (CASS). (7) Another possibility is to calculate baroreflex sensitivity (BRS), which is widely used to quantify the vagal component of the baroreflex. The problem of interpreting sympathetic adrenergic function of the BRS was overcome by introducing standard adrenergic BRSa and alternative adrenergic $BRSa_1$ indices. (8) Both indices were validated with microneurographically recorded muscle sympathetic nerve activity studies and it has been shown that they faithfully record the systemic adrenergic sympathetic neural response to changes in BP. (8) However, the main limitation of both BRSa and $BRSa_1$ is that they can be calculated

only if typical systolic BP response is present during VM. It has been shown that in healthy young individuals, there are three distinct patterns of systolic BP in response to VM: balanced (BAR), augmented (AAR) and suppressed (SAR) autonomic responses, so for individuals with AAR and SAR, calculating BRSa and $BRSa_1$ is not possible. (9) In order to overcome this problem, Palamarchuk and colleagues developed a new method of discrete estimation of α- and β-adrenergic components in BRSa. (10) They speculate that evaluation of both alpha and beta adrenergic components in BRSa, may allow clinicians to identify mild autonomic dysfunction. (10)

Given the fact that BP response to VM is frequently changed in pwMS (4) and that pwMS have reduced spontaneous muscle sympathetic nerve activity (MSNA) compared with healthy controls (11), we aimed to investigate differences in recently developed, non-standard adrenergic BRS indices in patients with different phenotypes of multiple sclerosis and healthy controls (HC). Furthermore, we compared non-standard adrenergic BRS indices with standardized interpretation of BP response to VM and catecholamine levels.

Methods

Study design: We retrospectively analyzed data of all patients with the diagnosis of clinically isolated syndrome (CIS), relapsing remitting multiple sclerosis (RRMS), progressive forms of multiple sclerosis (PMS) and healthy controls (HC), who were examined in the Referral Center for Autonomic Nervous System Disorders, University Hospital Center Zagreb, from October 2014 - January 2017. CIS was defined as a first neurological symptom suggestive of MS with an acute or subacute onset, lasting at least 48 hours in the absence of fever or infection and not fulfilling revise McDonald criteria for MS. (12,13) RRMS and PMS were diagnosed according revised McDonald criteria. (13)

Ethical committees of the University Hospital Center Zagreb approved the study.

Autonomic nervous system testing: All ANS tests were performed in the morning and patients had to refrain from smoking, drinking coffee or alcohol. ANS tests were performed after a 10 min resting period and included deep breathing test, heart rate (HR) and blood pressure (BP) response to Valsalva maneuver and 70° head-up tilt table test. Only patients in whom BP response to Valsalva maneuver and head-up tilt table test were available were included in the final analysis. All tests were performed using Task Force Monitor (TFM) (CNSystems Medizintechnik AG, Austria). All patients receiving medications with the known influence on the autonomic nervous system were excluded from the analysis.

The Valsalva maneuver was performed in the supine position by blowing for 15 s through a mouthpiece connected to a mercury manometer. The height of the mercury column was maintained at 40 mm. There was a small air leak in the system to prevent closing of the glottis. The test was repeated until a reproducible response was obtained and the BP curves on visual inspection allowed measurements of the BP changes. (5,6) The following parameters were calculated from the mean BP curve: maximal drop of the mean BP during phase II (phase II_E) compared to the level before the start of the test, the peak of the mean BP at the end of late phase II (II_L - recovery), overshoot in the phase IV. Pressure recovery time (PRT) was calculated from the systolic BP curve. Maximal pulse pressure drop during phase II was calculated as well. The results of the BP response to Valsalva maneuver and 70° head-up tilt table test were interpreted according to the adrenergic index of the Composite Autonomic Scoring Scale (CASS). (7)

Three types of systolic BP curves during VM were identified (FIGURE 1) (9): balanced autonomic response (BAR) was defined if the sBP drops below baseline in phase II_L and rebounds, exceeding the baseline in phase IV; augmented autonomic response (AAR) was defined if the sBP recovery reaches or exceeds the baseline in phase II_L; and suppressed autonomic response (SAR) was defined if the sBP does not fall below baseline during the entire phase II_L.

Evaluation of adrenergic baroreflex sensitivity was calculated from the systolic BP curves during the Valsalva maneuver according to previously published methods (10).

$BRSa_1$ was calculated with the following formula: $BRSa_1 = (A + 0.75*B)/PRT$ (A - maximal drop of the sBP during phase II_E compared to the level before the start of the test; B - maximal drop of the sBP during phase III compared to the peak of the sBP at the end of phase II_L).

Alpha BRSa (α-BRSa) was calculated with the following formula: $\alpha\text{-BRSa} = (t*C)/\sqrt{(t^2+C^2)}$ (C - an increment from the end of phase II_E to the end of phase II_L; t - duration of phase II_L.

Beta BRSa (β-BRSa) was calculated with the following formula: $\beta\text{-BRSa} = (PRT*D)/\sqrt{(PRT^2 + D^2)}$ (D - sBP recovery during PRT).

Catecholamines: If available, plasma catecholamine levels obtained after 10 min of resting period before the beginning of the Valsalva maneuver were analyzed. Plasma levels of epinephrine (E), norepinephrine (NE) and dopamine (DA) were measured on high pressure liquid chromatography, as previously described. (4)

Outcomes: The primary outcome was to evaluate differences in BRSa indices ($BRSa_1$, α-BRSa and β-BRSa) between pwMS and HC.

Secondary outcomes were to see whether there is a difference in BRSa indices between patients with CIS, RRMS and PMS as a whole and depending on the type of sBP curve during Valsalva maneuver. Finally, we investigated correlations between $BRSa_1$, α-BRSa, β-BRSa and BP values in supine and tilted positions, and between $BRSa_1$, α-BRSa, β-BRSa and catecholamines (E, NE and DA).

Statistics: The Kolmogorov-Smirnov test was applied to see whether the data have a normal distribution. Differences in the distribution of qualitative variables were determined with the $\chi 2$ test, while the differences in quantitative variables were determined with the use of the parametric t-test, non-parametric Mann-Whitney test, ANOVA and Kruskal-Wallis test. Correlations were tested with Pearson's and Spearman's correlation methods. P values less than 0.05 were considered as significant. Software used for statistical analysis was IBM SPSS, version 20.

Results

We have analyzed data from 153 MS patients (109 females, mean age 34.65±10.44) and 20 healthy controls (8 females, mean age 23.18±1.89). In the MS cohort 78 had CIS, 57 had RRMS, and 18 had PMS. The distribution of all ANS parameters and catecholamines values is presented in Table 1.

pwMS had higher α-BRSa compared to HC (p=0.02). There were no differences in $BRSa_1$ and β-BRSa between groups (p=0.814 and p=0.580, respectively). Because the two groups were not matched according to age and sex, we performed a separate analysis on a matched sample of pwMS and HC in order to overcome the possibility that the age difference is responsible for observed changes. In this subanalysis the α-BRSa was still significantly higher in pwMS compares to HC (Table 2). Furthermore, when we analyzed all participants included in the study (153 MS and 20 HC), there was no difference in BRSa1, α-BRSa and β-BRSa depending on the sex (p=0.669, p=0.808 and 0.333, respectively). Finally, there was no difference in $BRSa_1$, α-BRSa and β-BRSa between patients with CIS, RRMS and PMS (p=0.332, p=0.414 and p=0.595, respectively).

In the MS cohort, 48 patients had BAR, 18 SAR and 87 AAR, while in the healthy controls 10 participants had BAR and 10 AAR type of sBP curve during VM. There was no association between the two groups of participants (pwMS and HC) and the type of sBP curve ($\chi(2)=4.332$, p=0.114). Also, there was no association between the different MS phenotypes and the type of sBP curve ($\chi(4)=5.164$, p=0.274). In the CIS cohort, 21 patients had BAR, 8 SAR and 49 AAR; in the RRMS cohort 18 patients had BAR, 9 SAR and 30 AAR; and in the PMS cohort 9 patients had BAR, 1 SAR and 8 AAR. When we analyzed differences in supine and tilted systolic and diastolic BP depending on the type of sBP curve during VM, we found significant differences in both supine systolic (BAR: 112.0±12.1 mmHg; SAR: 105.3±9.0 mmHg; AAR: 114.1±10.6 mmHg) and supine diastolic BP (BAR: 71.9±9.8 mmHg; SAR: 66.4±6.2 mmHg; AAR: 72.1±8.3 mmHg) between groups, p=0.008 and p=0.035, respectively.

In order to investigate possible influence of α-BRSa and β-BRSa on supine and tilted systolic and diastolic BP, we performed correlation analysis. The results have shown significant positive correlation between α-BRSa and systolic BP in the tilted position (r_p =0.194, p=0.017), Figure 2.

Finally, we found significant correlations between α-BRSa and norepinephrine (r_s =0.228, p= 0.021) and $BRSa_1$ and epinephrine (r_s =0.226, p=0.040), Figure 3.

Discussion

This first finding of this study is that pwMS have adrenergic hyperactivity expressed as an increase in α-BRSa compared with HC. It has been shown that adrenergic hyperactivity is a hallmark of arterial hypertension, (14) and arterial hypertension is on of the most important MS comorbidities linked to clinical outcomes, including walking speed, self-reported disability, and depression. (15) On the other hand, it has been shown that BRS is higher during acute psychological stress in healthy subjects under β-adrenergic blockade. (16) Whether the observed changes in pwMS are a consequence of the disease process itself as suggested by some (17), or they are a consequence of acute stress should be further investigated. Despite of this, one could speculate that adrenergic hyperactivity, regardless of its cause, may contribute to development of hypertension and increased risk of ischemic heart disease and congestive heart failure in pwMS. Although all participants in the present study were normotensive, the finding of positive correlation between α-BRSa and systolic BP in the tilted position may go in line with this hypothesis.

Furthermore, we found significant differences in supine BP depending on the type of systolic BP curves during VM, patients with BAR and AAR had higher supine systolic and diastolic BP compared to patients with SAR. These results suggest that there is a difference in supine BP levels depending on the type of systolic BP curves during VM. Palamarchuk and colleagues speculate that the different type of systolic BP curves during VM may be useful in the assessment of mild forms of autonomic dysfunction such as postural orthostatic tachycardia syndrome (POTS). If type of systolic BP curves

during VM may identify mild form of dysautonomia like POTS, this could explain our recent finding that POTS may be an indicator of a more active disease course in patients with CIS. (18) In that study POTS was independent predictor of disability progression in patients with CIS, which is an interesting finding in the light of the current study which has shown adrenergic hyperactivity in pwMS.

The second finding of our study was that there was no difference in $BRSa_1$, α-BRSa and β-BRSa between patients with CIS, RRMS and PMS. This is in line with previous studies showing that adrenergic sympathetic dysfunction is manly evident in the acute stages of MS (relapses)and that it does not progresses with time. (19)

The third important finding is that we found significant correlations between α-BRSa and norepinephrine and $BRSa_1$ and epinephrine. Studies performed on patients with with type 2 diabetes mellitus without structural heart disease have shown that high resting NE is associated with major adverse cerebral and cardiovascular events. (20) This association further supports the possible role of α-BRSa as a marker of adrenergic hyperactivity in pwMS which could explain increased cardiovascular risk.

The limitations of our study are retrospective design and a small sample of HC. Furthermore, the question remains weather α-BRSa and β-BRSa are valid measures of adrenergic ANS disturbance and in order to answer it, a validation study using microneurography is needed. Newer the less, the correlation between α-BRSa and resting NE levels further accentuate the possible usefulness of non-standard adrenergic BRS indices in research and clinical perspective. In conclusion, pwMS and HC exhibit different alpha-adrenergic response to Valsalva maneuver. Finally, correlation between α-BRSa and systolic BP values may explain the connection between MS and increased cardiovascular risk.

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Tables

Table 1. The distribution of all ANS parameters and catecholamines values.

Parameter	N	Mean/Median	SD	Min	Max
MS cohort					
$BRSa_1$	128	33.42	31.12	4.59	201.0
α-BRSa	153	6.36	2.44	0.19	11.76
β-BRSa	152	2.42	3.44	0.20	21.22
sBP supine	153	112.41	11.23	88.00	146.00
dBP supine	153	71.37	8.72	51.00	103.00
HR supine	153	71.08	11.03	49.00	105.00
sBP tilt	153	107.70	15.48	45.00	157.00
dBP tilt	153	72.66	11.69	30.00	109.00
HR tilt	153	90.51	14.43	57.00	147.00
Adrenergic index	148	0		0	3
E	103	0.17	0.10	0.08	0.68
NE	103	1.26	0.77	0.13	5.06
DA	77	0.29	0.22	0.14	1.53
CIS cohort					
$BRSa_1$	62	35.45	34.26	5.83	201.0
α-BRSa	78	6.61	2.33	1.50	11.30
β-BRSa	77	2.43	3.60	0.20	21.22
sBP supine	78	114.29	10.97	92.00	146.00
dBP supine	78	72.18	7.49	55.00	93.00
HR supine	78	71.71	10.66	53.00	105.00
sBP tilt	78	110.96	15.75	81.00	157.00
dBP tilt	78	73.86	10.87	42.00	95.00
HR tilt	78	91.22	14.54	57.00	121.00
Adrenergic index	77	0		0	3
E	72	0.17	0.11	0.08	0.68
NE	72	1.28	0.79	0.13	5.06
DA	55	0.24	0.10	0.18	0.68
RRMS cohort					
$BRSa_1$	50	33.63	29.90	4.60	190.25
α-BRSa	57	6.17	2.32	1.05	11.76
β-BRSa	57	2.31	3.37	0.20	15.90
sBP supine	57	109.49	10.13	88.00	126.00
dBP supine	57	68.84	8.52	51.00	88.00
HR supine	57	69.96	11.46	49.00	105.00
sBP tilt	57	104.39	14.12	45.00	134.00
dBP tilt	57	70.53	11.99	30.00	91.00
HR tilt	57	89.75	14.07	61.00	147.00
Adrenergic index	56	0		0	3
E	31	0.17	0.08	0.08	0.39
NE	31	1.23	0.72	0.23	3.43
DA	22	0.40	0.37	0.14	1.53
PMS cohort					
$BRSa_1$	16	24.92	20.24	5.20	80.10
α-BRSa	18	5.90	3.23	0.19	10.50

β-BRSa	18	2.71	3.12	0.50	13.61
sBP supine	18	113.67	14.05	92.00	143.00
dBP supine	18	75.89	11.81	58.00	103.00
HR supine	18	71.89	11.56	53.00	100.00
sBP tilt	18	104.28	16.25	73.00	145.00
dBP tilt	18	74.33	13.63	47.00	109.00
HR tilt	18	89.89	15.72	64.00	119.00
Adrenergic index	15	0		0	3
Healthy controls					
$BRSa_1$	20	32.07	27.80	5.37	121.42
α-BRSa	20	5.02	2.15	2.12	9.62
β-BRSa	20	1.53	1.16	0.30	4.43
Adrenergic index	20	0		0	0

BRSa adrenergic baroreflex sensitivity; sBP systolic blood pressure; dBP diastolic blood pressure; HR heart rate; MS multiple sclerosis; CIS clinically isolated syndrome; RRMS relapsing remitting multiple sclerosis, PMS progressive multiple sclerosis; E epinephrine; NE norepinephrine; D dopamine

Table 2. Differences in BRSa indices on an age and sex matched pwMS and HC.

Parameter	**pwMS (N=34)**	**HC (N=20)**	**p value**
Age (mean±SD)	24.0±3.1	23.2±1.9	0.410
Sex (females, N)	23	8	0.086
$BRSa_1$ (mean±SD)	33.87±26.14*	32.07±27.80	0.822
α-BRSa (mean±SD)	6.48±1.99	5.02±2.15	0.014
β-BRSa (median)	1.10	1.10	0.912

*BRSa1 was available for 27 patients in the MS cohort.

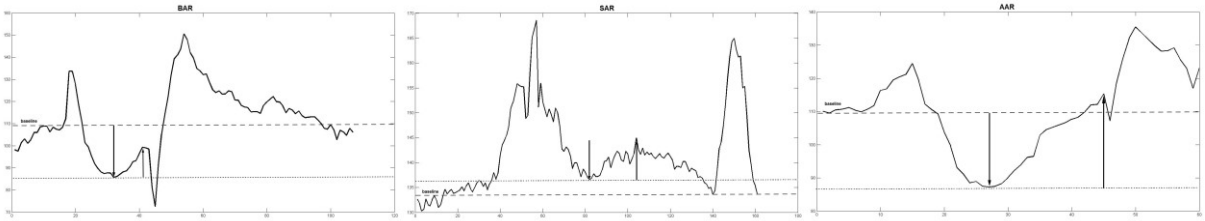
BRSa adrenergic baroreflex sensitivity; pwMS patients with multiple sclerosis, HC healthy controls

Figures

Figure 1. Three types of systolic blood pressure curves during Valsalva maneuver: balanced autonomic response (BAR). suppressed autonomic response (SAR) and augmented autonomic response (AAR).

Figure 2. Correlation between α-BRSa and systolic BP in the tilted position.

Figure 3. Correlations between α-BRSa and norepinephrine.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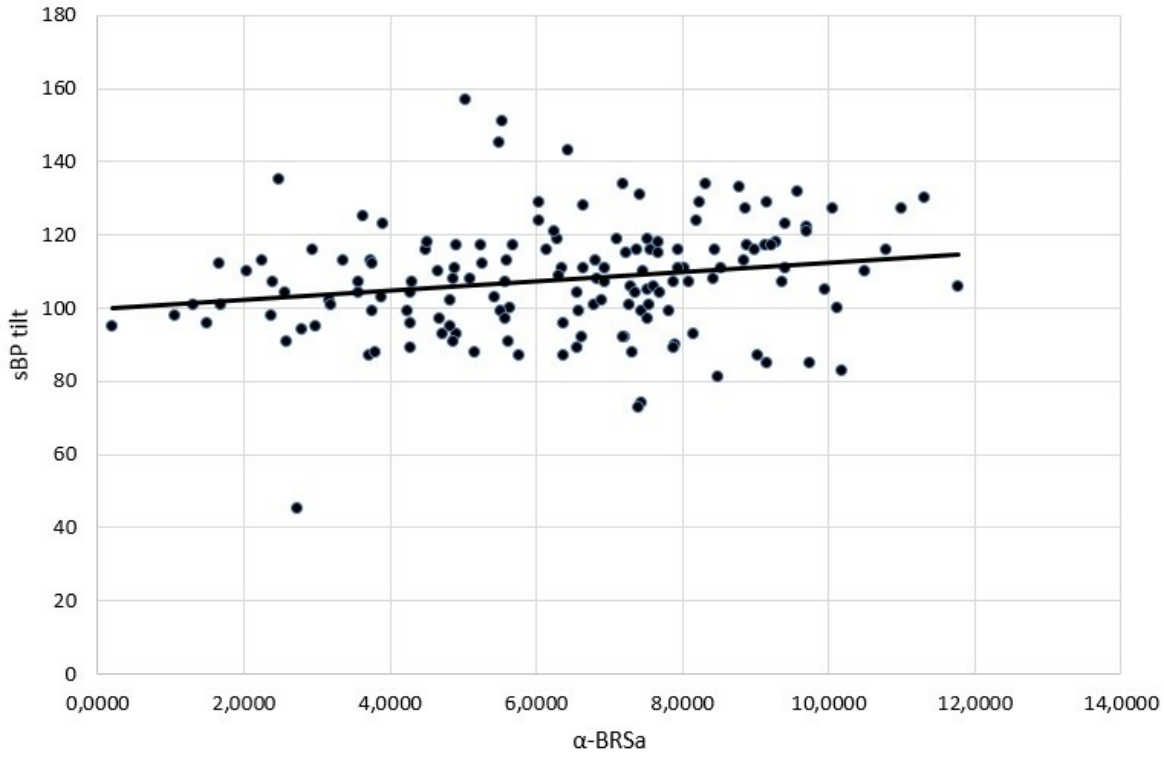
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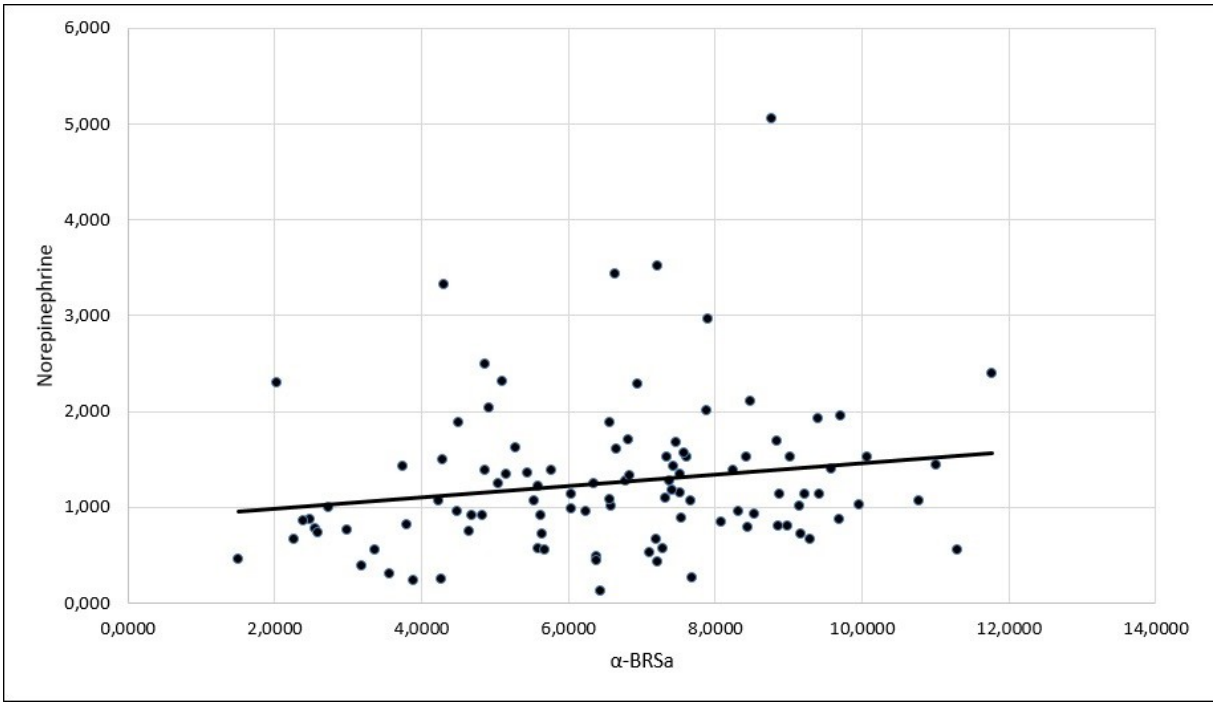
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