Negative association between lipoprotein associated phospholipase A_2 activity and baroreflex sensitivity in subjects with high normal blood pressure and a positive family history of hypertension

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Summary

The relationship between baroreflex sensitivity (BRS) and inflammatory vascular biomarker Lipoprotein associated phospholipase A_2 (Lp-PLA_2) in subjects with high normal blood pressure (HNBP, prehypertensives) with a positive family history of hypertension (FHH+) and hypertension history free control subjects (FHH-) was evaluated. A total of 24 HNBP participants (age 39.5 ± 2.5 years, 18 male/ 6 female) were studied. 14 HNBP subjects FHH+ were compared to 10 HNBP participants FHH-, being of similar age and body mass index. BRS (ms/mmHg) was determined by the sequence and spectral methods (five-minute non-invasive beat-to-beat recording of blood pressure and RR interval, controlled breathing at a frequency of 0.33 Hz). Venous blood was analysed for Lp-PLA_2 biomarker of vascular inflammation and atherothrombotic activity. A significant negative correlation between spontaneous BRS obtained by both methods and systolic blood pressure (BP) was present (BRS spect r = –0.54, P<0.001, BRS seq r = –0.59, P<0.001). BRS obtained by sequence and spectral methods were reduced in HNBP FHH+ compared to the group of HNBP FHH- (P = 0.0317 BRS seq, P = 0.0395 BRS spect). Lp-PLA_2 was significantly higher in HNBP FHH+ compared to FHH- controls (P< 0.05). Lp-PLA_2 was negatively correlated with BRS obtained by sequence method (r = -0.798, R^2 = 0.636, P< 0.001) in the HNBP FHH+ subjects. These findings demonstrate that reduced baroreflex sensitivity, as a marker of autonomic dysfunction, is associated with vascular inflammation, predominantly in otherwise healthy participants with a positive family history of hypertension who could predispose to increased risk of hypertension. We conclude that our transversal study suggests that a low baroreflex sensitivity could be an early sign of autonomic dysfunction even in the prehypertensive period, and to corroborate these findings, a longitudinal study is needed.

Key Words: Baroreflex Sensitivity, Autonomic Nervous System, Arterial Hypertension, Vascular Inflammation, High Normal Blood Pressure

Introduction

Arterial hypertension (AH) is the most common cardiovascular disease (Williams *et al*. 2018). Elevated blood pressure (BP) was the leading global contributor to premature death in 2015, accounting for almost 10 million deaths and over 200 million disability-adjusted life years (Forouzanfar *et al*. 2017). Hypertension rarely occurs in isolation, and often clusters with other cardio-metabolic risk factors (Williams *et al*. 2018). Population-based epidemiologic studies have established that a higher blood pressure leads to a higher cardiovascular risk (Williams *et al*. 2018). Subjects with high normal blood pressure (HNBP, prehypertensive stage) are at a greater risk of progression to hypertension than those individuals who are normotensives.

The arterial baroreflex is one of the most important physiological nervous mechanisms controlling homeostasis of blood pressure (BP) (Honzíková *et al*. 2009). It is involved not only in short-term, but also in long-term BP control (Persson 2005, Honzíková *et al*. 2009). Baroreceptors are mechanosensitive nerve endings that are activated by vascular and/or cardiac distension during increases in intraluminal BP (Chapleau 2012). The changes in baroreceptor activity evoke rapid reflex adjustments that buffer or oppose the changes in arterial blood pressure in a negative feedback manner (Chapleau 2012). Both vagal and sympathetic cardiovascular influences appear to be already altered under conditions in which BP may be still normal or in the high-normal range (Grassi 2010).

Baroreflex sensitivity (BRS) characterises the efficacy of blood pressure regulation. BRS is quantified in ms of RR interval duration to each mmHg of arterial pressure. BRS can reach resting values between 2 and 30 ms/mmHg in adults (Honzíková *et al.* 2003). Normal value is about 15 ms/ mmHg (La Rovere *et al.* 2001**).** Index BRSf expressed in Hz/mmHg is less dependent on pulse interval changes than BRS (Al-Kubati *et al.* 1997). The decrease of BRS/BRSf precedes a pathological BP increase (Honzíková *et al.* 2009). It was found not only in children with hypertension, but also in those with white-coat hypertension (Honzíková *et al.* 2006b).

There is substantial evidence indicating that a significant component of baroreflex function is genetically determined (Biaggioni 2012). A positive family history of hypertension (FHH+) in first-degree relatives is a common risk factor for the future development of hypertension. A few polymorphisms in several genes have been associated with reduced baroreflex function. Polymorphism in AT1 receptor gene was associated with reduced BRS in normotensive individuals (Jíra *et al*. 2010). Reduced BRS is found in offspring of

hypertensive parents, and predicts the development of hypertension (Ormezzano *et al*. 2010, Biaggioni, 2012). Decreased BRS with additional risk factors (obesity, diabetes mellitus, lack of exercise, smoking) in children and adolescents predisposes to the development of an early stage of essential hypertension (Krontorádová *et al.* 2008, Honzíková *et al*. 2016). It is not clear whether reduced baroreflex buffering contributes to the development of hypertension or is mostly a trait of an underlying abnormality in the autonomic regulation of blood pressure (Biaggioni 2012).

Impaired baroreflex function is associated with a shift in autonomic balance towards sympathetic dominance, which may play an important role in the long-term development of arterial hypertension and consequent hypertension induced organ damage (Grassi 2010). Sympathetic hyperactivity is involved in several metabolic and cardiovascular alterations accompanying the BP elevation. Chronic inflammation, particularly vascular inflammation, may lead to BRS dysfunction (Chapleau 2012). Sympathoexcitation and impaired arterial baroreflex are linked to vascular inflammation in individuals with elevated resting blood pressure (Fonkoue *et al*. 2019). Some studies have shown that inflammatory biomarkers such as C-reactive protein and interleukin 6 (IL-6) may be elevated in prehypertension (Nandeesha *et al.* 2015). Lipoprotein-associated phospholipase A_2 (Lp-PLA_2, platelet-activating factor acetylhydrolasa), known as a biomarker of atherothrombotic activity, is highly specific for vascular inflammation. It has a low biological variability (Franekova *et al.* 2013) and is a cross-link between LDL oxidative modification and inflammatory reaction of the intimal part of arteries. Vascular inflammation represented by higher Lp-PLA_2 activity is associated with the progression of endothelial dysfunction that may have a role in impairing BRS at the level of the nucleus tractus solitarius in the brainstem, or the baroreceptor nerve endings within the vasculature (Chapleau 2012, Fonkoue *et al*. 2019).

In the present study the relationship between baroreflex sensitivity (BRS) and inflammatory vascular biomarker Lipoprotein associated phospholipase A_2 (Lp-PLA_2) in subjects with high normal blood pressure (HNBP, prehypertensives) with a positive family history of hypertension (FHH+) and hypertension history free control subjects (FHH-) was evaluated.

Methods

We studied 24 subjects (18 male/ 6 female, mean age 39.5 ± 2.5 years) with high normal blood pressure (HNBP) without manifest cardiovascular or metabolic disease. HNPB, also termed as prehypertension in real-life clinical practice, was defined as a resting systolic BP 130-139 mmHg and/ or diastolic BP 85-89 mmHg as per Hypertension guidelines by the European Society of Hypertension/European Society of Cardiology 2018 (ESH/ESC 2018) (Williams *et al*. 2018). On the other hand, this subgroup of elevated resting BP is defined by American College of Cardiology/American Heart Association (ACC/AHA) guidelines as Stage I hypertension (Whelton *et al.* 2018). Despite being defined as hypertension, according to the ACC/AHA guidelines, in patients without diabetes mellitus or high CV risk only life-style modification without starting antihypertensive therapy is recommended.

Exclusion criteria included the following: atrial fibrillation, recordings of more than five ectopics per minute and other cardiac arrhythmias, stroke, myocardial infarction, unstable angina, history and evidence of left ventricular dysfunction, diabetes mellitus, renal function impairment (creatinine more than 100 μmol/l), any systemic disease, active smoking, excessive alcohol use (more than 1-2 drinks per day), non-cooperative subjects, end-stage diseases, drug use, any medications, including antihypertensive medication, chronic disease that may influence the autonomic nervous system, posttraumatic stress disorder.

24 HNBP subjects were divided into 2 groups according to a positive the family history of hypertension in first-degree relatives. The groups were well-matched for body mass index and age by an active selection process to eliminate the obesity and the age-dependent differences of BRS. All subjects were in sinus rhythm. All study participants were Caucasian males and females without any pharmacological treatment. Baseline characteristics of the subjects are given in Table 1. All subjects were examined according to a standardized protocol, provided written informed consent for study participation and the study was approved of by the local Ethics committee

Three seated BP measurements separated by 5 minutes were taken during at least 2 separate visits to confirm HNBP. We used an appropriately sized cuff placed on the upper arm with arm resting at the heart level according to the 2018 ESH/ESC Hypertension Guidelines. We used an automated BP device (OMRON, HEM-7221-E8(V), Omron Healthcare, Kyoto, Japan). Participants were asked to avoid alcohol, caffeine and exercise 24 hours prior to the procedure. The BRS measurement was performed in a quiet room at a constant temperature with subdued light. The subjects lay supine on a coach with their heads

propped up. During the experimental protocol BP was measured continuously and noninvasively by the BP monitor (COLLIN CBM 7000, Japan), with an appropriately sized cuff applied to the wrist. The cuff was held at heart level. Control BP was measured at the level of the brachial artery on the other arm by the automated BP device. Three surface electrocardiographic chest leads were attached for continuous ECG monitoring because RR intervals measure cardiac cycle length more precise than intervals between blood pressure pulsations (Janssen MJA *et al*. 1994). After 15 minutes of rest, after the achievement of satisfactory BP, ECG signal and stabilization of BP, the first recording followed**.** A pulse-sensing sensor using applanation tonometry (COLLIN CBM 7000, Japan) was placed around the wrist where radial artery is maximally pulsatile, for beat-to-beat indirect continuous 5-min blood pressure recordings and heart rate measurements. The recordings were taken during spontaneous and metronome breathing. The subjects were allowed to adjust the tidal volume according to their own comfort. Breathing was synchronized by a metronome at 0.33 Hz. Three consecutive 5-minute recordings of BP and RR intervals were obtained. In each subject the arithmetic mean of the three BP and RR interval recordings was calculated. BP and RR intervals were recorded simultaneously on a computer with an analogue digital converter.

BRS expressed in ms/mmHg was determined by the sequence (BRS seq) and spectral method (BRS spect) using a protocol of controlled breathing at a frequency of 0.33Hz. A five-minute non-invasive beat-to-beat recording of blood pressure and RR interval changes were analysed with the use of the Collin CBM-7000 monitor. We performed a cross-spectral analysis to assess the RR interval changes associated with systolic BP oscillations. The BRS seq was assessed by analysing the slopes of spontaneously occurring sequences of three or more consecutive beats in which systolic BP and RR interval of the following beat increased or decreased in the same direction in a linear fashion.

Venous blood samples were collected on the day of the experiment. We studied lipoprotein-associated phospholipase A_2 (Lp-PLA_2) and C reactive protein (CRP) in all participants. CRP was measured using the Multigent CRP Vario Standard method. Lp-PLA_2 is known as platelet-activating factor acetylhydrolasa (PAF-AH). The activity of Lp-PLA_2 was measured using an enzymatic method, immunoassay (diaDexus kit, PLAC test).

Statistics

The data were analysed using Scope Win 95 software. Statistical data were expressed as mean ± standard deviation (SD) of average, category variables in percentage. A chi-squared test for independence was used to compare the categorical variables of sex and family

history of hypertension. Comparisons between the continuous variables including Lp-PLA_2 in the two groups was performed by an independent t-test. The significance of the differences was evaluated by the Mann-Whitney U test for BRS. Correlations were evaluated by Pearson´s correlation coefficient. Logistic regression analysis was applied to the evaluation of association of BRS and Lp-PLA_2. A P value of <0.05 was considered to be significant.

Results

In the present study 14 HNBP subjects FHH+ were compared to 10 HNBP FHH- participants. The differences between cardiovascular and inflammatory parameters of the two groups are presented in Table 1. Comparison of Lp-PLA_2 activity in the HNBP subjects divided according to the family history of hypertension in first-degree relatives was performed. Mean Lp-PLA_2 activity in the group of HNBP FHH+ subjects was significantly higher compared to the HNBP FHH- subjects ($P < 0.05$). Figure 1 shows the results of the comparison of vascular inflammatory biomarker Lp-PLA_2 in the HNBP group divided according to the family history of hypertension in first-degree relatives. There was no significant difference in CRP between the HNBP FHH+ and HNBP FHH- groups.

Spectral BRS and sequence BRS showed a statistically significant negative correlation with systolic BP (BRS spect r = –0.54, P <0.001, BRS seq r = –0.59, P <0.001). Resting BRS obtained by sequence and spectral methods were reduced in the HNBP subjects with a positive family history of hypertension compared to the group of HNBP without family history of hypertension (P = 0.0317 BRS seq, P = 0.0395 BRS spect). BRS characteristics of the study population is in Table 2.

The relation between BRS and vascular biomarker Lp-PLA_2 was analysed using correlation analysis. The relationship between baroreflex sensitivity (BRS) and the inflammatory vascular biomarker Lipoprotein associated phospholipase A_2 (Lp-PLA_2) in the HNBP subjects divided according to the family history of hypertension in first-degree relatives was evaluated. Figure 2 shows the results of the correlation between BRS obtained by sequence method and Lp-PLA_2 in HNBP FHH + ($r = -0.798$, $R^2 = 0.636$, $P < 0.001$). Figure 3 shows the results of the correlation analysis between BRS obtained by sequence method and Lp-PLA_2 in the HNBP FHH - subjects. Lp-PLA_2 activity was negatively associated with BRS in the HNBP FHH+ subjects. There was no significant correlation between Lp-PLA_2 and BRS

in the HNBP FHH- group. Regression analysis revealed that low BRS and an increased level of Lp-PLA_2 were independent variables associated with an increased risk of prehypertension.

Discussion

The increased sympathetic activity in patients with arterial hypertension is an important etiopathogenetic factor that contributes not only to initiation, but also to progression of the disease, and the resultant cardiovascular risk. The baroreflex represents a link between neural and cardiac response in autonomic regulation. Several studies have confirmed that essential hypertension, and even the prehypertension period is connected with decreased BRS (Ormezzano *et al.* 2008, Krontoradova *et al*. 2008). In our study we have confirmed that in the HNBP FFH+ subjects the lower values of BRS are present than in other prehypertensive subjects. Individuals with prehypertension have an increased risk of full-blown hypertension, hypertension induced organ damage and cardiovascular-related morbidity and mortality (Grassi 2010). It was reported that obesity could lead to a reduction in spontaneous BRS not only in adults, but also in children (Lazarova *et al*. 2009). However, low BRS is an independent risk factor for the development of essential hypertension (Krontoradova *et al*. 2008). BRS for the control of the heart rate is impaired in normotensive subjects with a family history of hypertension (Iwase et al. 1984). Tank et al. (2001) assessed the genetic influence on BRS in monozygotic and dizygotic twins. A few polymorphisms in several genes have been associated with reduced baroreflex function, e.g. polymorphism in AT1 receptor gene (Jíra *et al*. 2010). Endothelin system may be involved in the regulation of BRS in humans (Ormezzano *et al*. 2005).

This study analyzed the association between autonomic dysfunction represented by reduced baroreflex sensitivity and vascular inflammation in otherwise healthy Caucasian population with BP in the range of high normal blood pressure, divided according to the family history of hypertension in first-degree relatives. In our study we have observed a noticeable negative correlation between BRS obtained by sequence and spectral method and systolic BP even in this population. The higher the systolic BP the lower BRS values were found. BRS values obtained by both methods were significantly lower in the HNBP FFH+ group compared to the HNBP FHH- subjects.

This exploratory study used the BP range for high normal blood pressure according to the current ESH/ESC guidelines. The inconsistency among the studies could be due to a different range and terminology of high normal blood pressure. In the present study we

analyzed whether reduced BRS was associated with vascular inflammatory activity more in the HNBP subjects with genetic predisposition for arterial hypertension in first-degree relatives. The prehypertensive stage is characterized by higher sympathetic and vascular inflammatory activity that could predispose long before the change of vascular structures (Chapleau 2012, Grassi 2010). Autonomic dysfunction and vascular inflammation in young people with a positive family history of hypertension may contribute to fixation of BP to higher levels and finally initiate arterial hypertension.

Chronic inflammation could modulate BRS and lead to BRS dysfunction in the brainstem and/or at the level of the baroreceptor nerve endings within vasculature, thereby perpetuating an increase in arterial BP by maintaining sympathetic overactivation (Chapleau *et al.* 2001, Fonkoue *et al.* 2019). E-selectin and ICAM-1 may have direct sympatoexcitatory effects, independent of their action on cardiovagal BRS (Fonkoue *et al.* 2019). Prehypertension may be associated with increased systemic inflammatory markers such as C-reactive protein and interleukin-6 (Nandeesha *et al.* 2015). The relationship between CRP and prehypertension was most evident with systolic BP (Nandeesha *et al* 2015). C-reactive protein in the HNBP subjects in our study was higher than it was to be in normotensives. However, we did not confirm a significant difference between the HNBP subjects divided according to the family history of hypertension. Increased levels of Lp-PLA_2 known as platelet-activating factor acetylhydrolasa (PAF-AH) and E-selectin were documented in individuals with elevated resting BP. E-selectin correlated also with impaired cardiovagal BRS in these individuals (Fonkoue *et al.* 2019), suggesting a link between vascular inflammation and impaired BRS in the HNBP participants. We have observed that Lp-PLA_2 activity was significantly higher in the HNBP subjects with a positive family history of hypertension compared to the HNBP subjects without a positive FHH ($P < 0.05$). Lp-PLA_2 activity was negatively associated with BRS in the HNBP FHH+ subjects. The principal result of this study showed that BRS and vascular inflammatory biomarker in relatively low-risk HNBP participants could identify subjects with a higher CV risk.

Measurement of BRS can identify and stratify high risk subjects with a wide spectrum of CV disease, including arterial hypertension and prehypertension. The ability to measure BRS noninvasively makes the clinical application feasible (Chapleau 2012). The strong inverse relationship between BRS and CV risk encourages targeting therapy to improve BRS. Measurement of vascular inflammatory biomarkers along with BRS measurement seems to be an additive method for the identification of cardiovascular risk in hypertensives and subclinical atherosclerosis in HNBP subjects.

There are several limitations to our study. The study population was small. The amount of the participants might have an impact on the statistical significance. Genetic predisposition, activation of other systems, such as the renin-angiotensin-aldosterone system, and oxidative stress could also contribute to sympathetic hyperactivity in prehypertension. We did not explore other systemic or vascular biomarkers. We did not observe patients with optimal BP and hypertensives in order to be able to compare these groups to prehypertensives and to detect a trend in BRS and BP values. The study needs to have a prospective focus in order to establish BRS as a novel risk stratifier in high normal blood pressure subjects that represent the grey zone where healthy people and subjects with a higher CV risk mix in the population. It is also unclear if there is a link between sympathetic overactivation and vascular inflammation with accelerated progression to hypertension. This should be evaluated in future longitudinal studies.

We conclude that our transversal study suggests that a low baroreflex sensitivity could be an early sign of autonomic dysfunction even in the prehypertensive period, and to corroborate these findings, a longitudinal study is needed. Lipoprotein associated phospholipase A_2 activity is negatively associated with baroreflex sensitivity in subjects with high normal blood pressure and a positive family history of hypertension. These findings demonstrate that reduced baroreflex sensitivity as a marker of autonomic dysfunction is associated with vascular inflammation predominantly in otherwise healthy participants with a positive family history of hypertension who could predispose to increased risk of hypertension.

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List of Tables:

List of Figures:

Table 1. Baseline characteristics of the study population

Variable	HNBP N=24		P value
	FHH+ N=14	**FHH-** N=10	
Gender male/female (N)	10/4	8/2	NS
Age in years	38 ± 6	41 ± 5	NS
BMI (kg/m^2)	27.42 ± 3.45	28.68 ± 4.42	NS
Impaired glucose tolerance	4 (28,57%)	3 (30%)	NS
Smoking in the past (N)	4 (28,57%)	3 (30%)	NS
Total Cholesterol (mmol/l)	5.09 ± 0.97	4.95 ± 1.13	NS
LDL-cholesterol (mmol/l)	3.42 ± 0.45	3.20 ± 0.32	NS
HDL-cholesterol (mmol/l)	0.96 ± 0.17	0.98 ± 0.28	NS
Triglycerides (mmol/l)	1.98 ± 0.60	1.67 ± 0.39	NS
Lp-PLA$_2$ (ng/ml)	163 ± 15.27	137 ± 13.73	P< 0.05
CRP (mg/l)	2,47 ± 1,15	2,19 ± 1,08	NS

The values are presented as mean ± standard deviation, category variables in percentage, HNBP – high normal blood pressure, FHH+ – positive family history of hypertension in first-degree relatives, FHH- – negative family history of hypertension in first-degree relatives, BMI – body mass index, LDL-cholesterol – low-density lipoprotein cholesterol, HDL-cholesterol – high-density lipoprotein cholesterol, Lp-PLA$_2$ – lipoprotein-associated phospholipase A$_2$, CRP – C reactive protein, NS – not significant

Table 2. Differences between parameters in high normal blood pressure subjects

Variable	HNBP N=24		P value
	FHH+ N=14	**FHH-** N=10	
Mean SBP (mmHg)	137 ± 2	133 ± 4	NS
Mean DBP (mmHg)	88 ± 2	87 ± 1	NS
RR-interval (ms)	817 ± 159	823 ± 135	NS
BRS seq (ms/mmHg)	9.47 ± 2.04	11.85 ± 2.19	0. 0317
BRS spect (ms/mmHg)	9.96 ± 2.59	11.19 ± 2.25	0.0395

The values are presented as mean ± standard deviation, HNBP – high normal blood pressure, FHH+ – positive family history of hypertension in first-degree relatives, FHH- – negative family history of hypertension in first-degree relatives, SBP – systolic blood pressure, DBP – diastolic blood pressure, BRS seq – baroreflex sensitivity values obtained by sequence method in ms/mmHg, BRS spect – baroreflex sensitivity values obtained by spectral method in ms/mmHg, NS – not significant

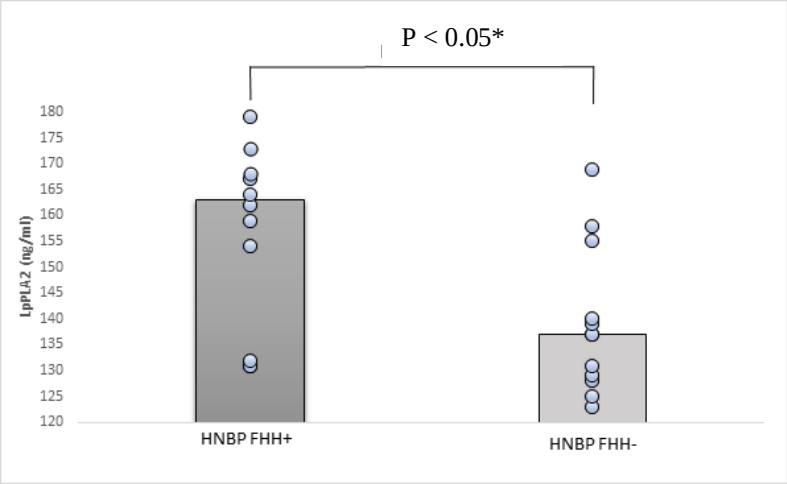

Figure 1. Lipoprotein-associated phospholipase A_2 (Lp-PLA_2) activity in high normal blood pressure participants divided according to the family history of hypertension in first-degree relatives.

Mean Lp-PLA_2 activity values were significantly higher in subjects HNBP FHH+ compared to HNBP FHH- group (* $P< 0.05$). HNBP – high normal blood pressure, FHH+ – positive family history of hypertension in first-degree relatives, FHH- – negative family history of hypertension in first-degree relatives, Lp-PLA_2 – lipoprotein-associated phospholipase A_2

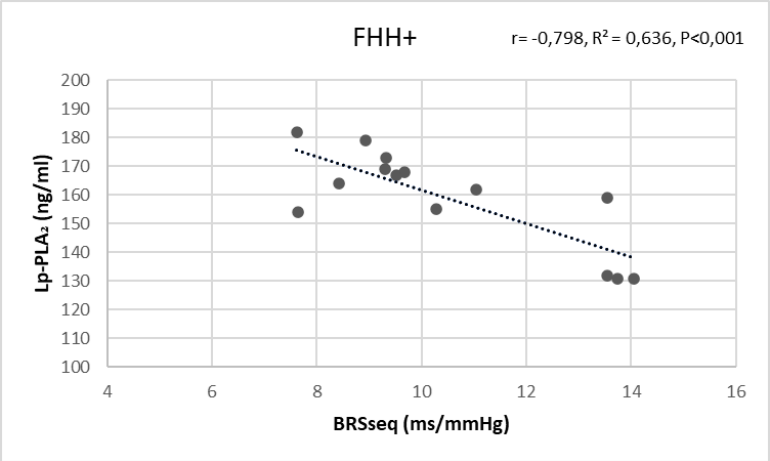

Figure 2. Correlation of BRS and Lipoprotein-associated phospholipase A_2 activity in high normal blood pressure subjects with a positive family history of hypertension in first-degree relatives.

Linear regression analysis shows a significantly negative correlation between BRS and Lp-PLA_2 in HNBP FHH + group, ($r = -0.798$, $R^2 = 0.636$, $P < 0.001$)
Lp-PLA_2 – lipoprotein-associated phospholipase A_2, BRS seq – baroreflex sensitivity values obtained by sequence method in ms/mmHg, FHH+ – positive family history of hypertension in first-degree relatives

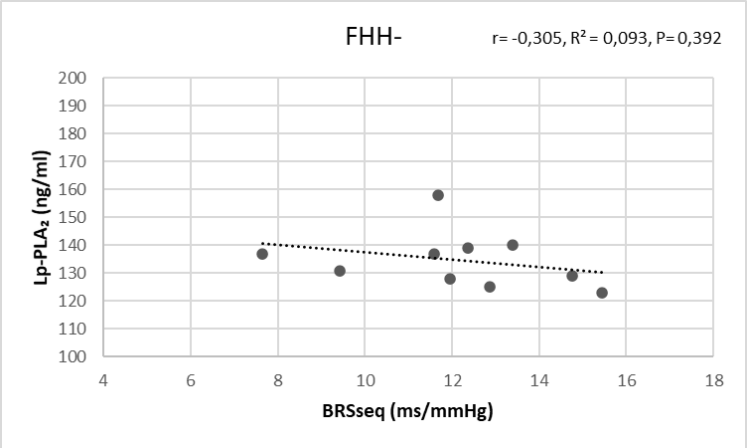

Figure 3. Correlation of BRS and Lipoprotein-associated phospholipase A_2 activity in high normal blood pressure subjects without a positive family history of hypertension in first-degree relatives.

Linear regression analysis shows no significant correlation between BRS and Lp-PLA_2 in HNBP FHH - group, r = -0.305, R^2 = 0.093, P = 0.392

Lp-PLA_2 – lipoprotein-associated phospholipase A_2, BRS seq – baroreflex sensitivity values obtained by sequence method in ms/mmHg, FHH- – without a positive family history of hypertension in first-degree relatives