THE MEDICAL BULLETIN OF
SISLI ETFAL HOSPITAL

DOI: 10.14744/SEMB.2024.64188
Med Bull Sisli Etfal Hosp 2024;58(3):363–370

Original Research

Can Galanin Be Used as a Marker of Microvascular Dysfunction in Prehypertensives?

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Abstract

Objectives: Coronary microvascular dysfunction is present in large percentage of the population, and it has been shown to have a pathological and prognostic role in many conditions. Therefore, early detection of microvascular dysfunction is important, especially in selected populations. The aim of this study was to investigate the association of galanin with coronary flow reserve (CFR) in prehypertensive individuals to determine whether it can be used as a marker to detect microvascular dysfunction.

Methods: A total of 100 participants, 50 prehypertensive and 50 normotensive were included in this prospective study. Serum galanin levels were measured and CFR was calculated by detailed transthoracic echocardiography.

Results: CFR was significantly lower in the prehypertensive group ($p<0.001$). Also, galanin values were numerically lower in the prehypertensive group, but the difference between the groups did not reach statistical significance ($p=0.062$). There was no significant correlation between CFR and galanin ($r=-0.161$, $p=0.11$).

Conclusion: Lower CFR values in prehypertensives suggest that microvascular dysfunction starts above normotensive values even if hypertension does not develop. The reason why low galanin levels were not statistically significant in prehypertensives and no correlation was found between galanin and CFR may be due to the small study population. Relationship between galanin, prehypertension and microvascular dysfunction will become clearer if large-scale population studies are carried out.

Keywords: Coronary flow reserve, galanin, microvascular dysfunction, prehypertension

Please cite this article as "Cekin ME, Kul S, Aciksari G, Erdal E, Ozcan FB, Caliskan M. Can Galanin Be Used as a Marker of Microvascular Dysfunction in Prehypertensives? Med Bull Sisli Etfal Hosp 2024;58(3):363–370".

Prehypertension (pHT) was first defined in the JNC-7 report published by the Joint National Committee in 2003 and was also mentioned in the JNC-8 report in 2013. According to these reports, blood pressure (BP) levels between 120/80 and 140/90 are defined as "prehypertension".[1] Since hypertension (HT) and pHT are usually asymptomatic, their prevalence is probably underreported.[2] A meta-analysis reported prevalence of pHT of 11% to 42%.[3] pHT causes subclinical atherosclerosis and has been associated with damage to target organs and an increased risk of total cardiovascular disease.[2] The risk of developing a cardiovascular disease increases two-fold for every 20/10 mmHg increase in

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Submitted Date: February 05, 2024 **Revised Date:** April 30, 2024 **Accepted Date:** June 24, 2024 **Available Online Date:** September 30, 2024

BP.[4] Effective control of PHT can prevent more than 10% of cardiovascular disease cases.[5] Therefore, early recognition of vascular damage in prehypertensives is essential.

Coronary flow reserve (CFR) is a parameter that indirectly assesses the global function of the coronary circulation. It is considered a measure of flow in both the epicardial coronary arteries and the microcirculation. Deterioration in CFR is a sensitive indicator of subclinical atherosclerosis and increases the risk of cardiovascular morbidity and mortality.[6] It has been shown that transthoracic echocardiography can be used to assess microvascular function with >95% success rate in CFR measurement.[7]

Galanin, an orexigenic neuropeptide commonly found in the central and peripheral nervous systems of mammals, regulates physiological processes such as nociception, sleep-wake regulation, nutrition, and BP regulation.[8] Galanin has been shown to play a role in cardiovascular regulation[9] and may lower BP by inhibiting the sympathetic nervous system.[10] So, we thought that galanin may be associated with PHT and subclinical atherosclerosis.

There is no study in the literature investigating galanin levels in individuals with PHT. Therefore, we aimed to investigate whether galanin can be used as a marker for microvascular dysfunction by examining its relationship with CFR in prehypertensives.

Methods

The study comprised 100 patients, 50 normal and 50 prehypertensive, admitted to Goztepe Training and Research Hospital between January 2018 and March 2018. Ethics approval was received from the Goztepe Training and Research Hospital Clinical Research Ethics Committee, and all participants gave written informed consent in accordance with the Declaration of Helsinki.

Inclusion criteria were determined as patients aged 18-65 years, with an office measurement of systolic BP (SBP) <140 mmHg and diastolic BP (DBP)<90 mmHg of BP. Exclusion criteria were having coronary artery disease, peripheral artery disease, heart failure, cardiac arrhythmia, heart valve disease, masked hypertension, bronchial asthma or chronic obstructive pulmonary disease, having a malignancy, diabetes mellitus (DM), chronic kidney/liver disease, or being pregnant.

Blood Pressure Measurements

All patients were examined with ambulatory blood pressure monitor (ABPM) and patients who were found not to have hypertension (24-hour average under 125/75 mmHg or daytime average under 130/80 mmHg or nighttime average under 110/65 mmHg) with ABPM were included in the study. Since the classification of prehypertension in the guidelines is based on office blood pressure measurements[1], the grouping of prehypertensive and normotensive patients was based on office measurements.

After confirming that the subjects did not use tea, coffee or cigarettes within 30 minutes and rested for at least 5 minutes, BP was measured in both arms and subsequent measurements were continued in the arm with the higher BP value. Three measurements taken at fifteen-minute intervals were averaged. Subjects, with SBP between 120 and 139 mmHg or DBP between 80 and 89 mmHg were included in the prehypertensive group, with SBP below 120 mmHg and DBP below 80 mmHg were included in the normotensive group.

Laboratory Measurements

To measure serum galanin levels, 3 ml of venous blood was transferred into an EDTA tube after blood pressure measurement and centrifuged at 3500 rpm for 10 minutes. Samples were stored at -80°C until testing. Galanin levels (Human GAL (Galanin) ELISA Kit 96 TEST, Elabsience, Cat. No: E-EL-H1301) were measured by ELISA in accordance with the manufacturer's instructions. Biochemical parameters and complete blood counts were analyzed from blood samples for each patient.

Echocardiographic Measurements

All measurements were performed by a single cardiologist experienced in echocardiography (MC), blinded to the clinical data, in the lateral decubitus position. A 7.5 MHz transducer was used with Vivid 7 Dimension® (GE Vingmed Ultrasound AS N-3190 Horten, Norway) echocardiography device. In parasternal long-axis images, the M-Mod cursor was placed at the level of the mitral valve cusps and intraventricular septum diastolic thickness, left ventricular posterior wall diastolic thickness, left ventricular end-diastolic diameter (LVEDD), and left ventricular end-systolic diameter (LVESD) were measured. Normal thicknesses of the interventricular septum and posterior wall were accepted as <11 mm. Ejection fraction (EF) was calculated by the formula EF: (LVEDC)2 - (LVESC)2 / (LVEDC)2 x 100. In the same image window, the diameter of the ascending aorta was measured by placing the M-Mod cursor 3 cm above the aortic valve.

Coronary Flow Reserve Assessment

Alcohol, theophylline and similar stimulant drugs, as well as caffeine-containing beverages, were discontinued for 24 h before the procedure. For the assessment of CFR, the transducer frequencies for B-mode and Doppler examinations were set to 8 MHz and 1.00-2.50 kHz, respectively. The color gain was adjusted by setting the maximum gain that showed

no abnormal flow in an anatomical region not expected to have blood flow (i.e. outside the pericardium), and the Nyquist limit was set to 0.16-0.50 m/s. Patients were monitored during the procedure, and heart rate and blood pressure data were recorded at baseline, during infusion, and after the procedure. Coronary flow velocities were recorded at baseline and after intravenous administration of dipyridamole at a rate of 0.56 mg/kg/min for 4 minutes. Heart rate was targeted to increase ≥10% from baseline.[11] If the pre-targeted heart rate was not achieved by the dipyridamole with this dose, an additional dose of 0.28 mg/kg/min was administered. In this way, the targeted heart rate was achieved in all patients. Imaging of left anterior descending (LAD) artery in the interventricular septum on modified two-chamber window was performed by positioning the transducer near the midclavicular line in the fourth and fifth intercostal spaces while the patient was in the lateral decubitus position. After obtaining appropriate image quality in all patients, the coronary blood flow velocities were recorded from the mid to distal LAD artery via a pulsed color Doppler (Fig. 1).[12]

Diastolic flow velocities measured at the beginning of the test before any drug administration were accepted as baseline diastolic peak velocity. Five highest diastolic velocities were recorded during maximal dipyridamole infusion and three minutes after cessation of dipyridamole and averaged to obtain the hyperemic diastolic peak flow velocities. CFR was defined as the ratio of hyperemic diastolic peak flow velocity to baseline diastolic peak velocities and value of 2 or above was considered normal.

Statistical Analysis

Mean, standard deviation, median, minimum, maximum, frequency, and ratio values were used in descriptive statistics of the data. The distribution of variables was measured using Kolmogorov-Smirnov test. Independent sample t-test and Mann-Whitney U-test were used to analyze quantitative independent data, and chi-square test was used for qualitative independent data. Correlation was assessed using Spearman correlation analysis. Data were analyzed using SPSS v22.0 (SPSS, Chicago, IL). Values of $p<0.05$ were considered statistically significant.

Results

There was no significant difference between the groups in terms of age, gender distribution, height, weight, BMI and smoking frequency.

Although all patients had normal wall thicknesses, septal wall thickness and posterior wall thickness were higher in prehypertensives. Also, while baseline diastolic peak velocity were higher in prehypertensives, CFR and hyperemic diastolic peak flow velocity were lower (Table 1).

Galanin levels were numerically lower in prehypertensives compared with normotensives, but it did not reach statistical significance. Total cholesterol, LDL, triglyceride, HbA1c, uric acid, creatinine, hs-CRP and uric acid/HDL levels were significantly higher in prehypertensives, and HDL was significantly lower (Table 2).

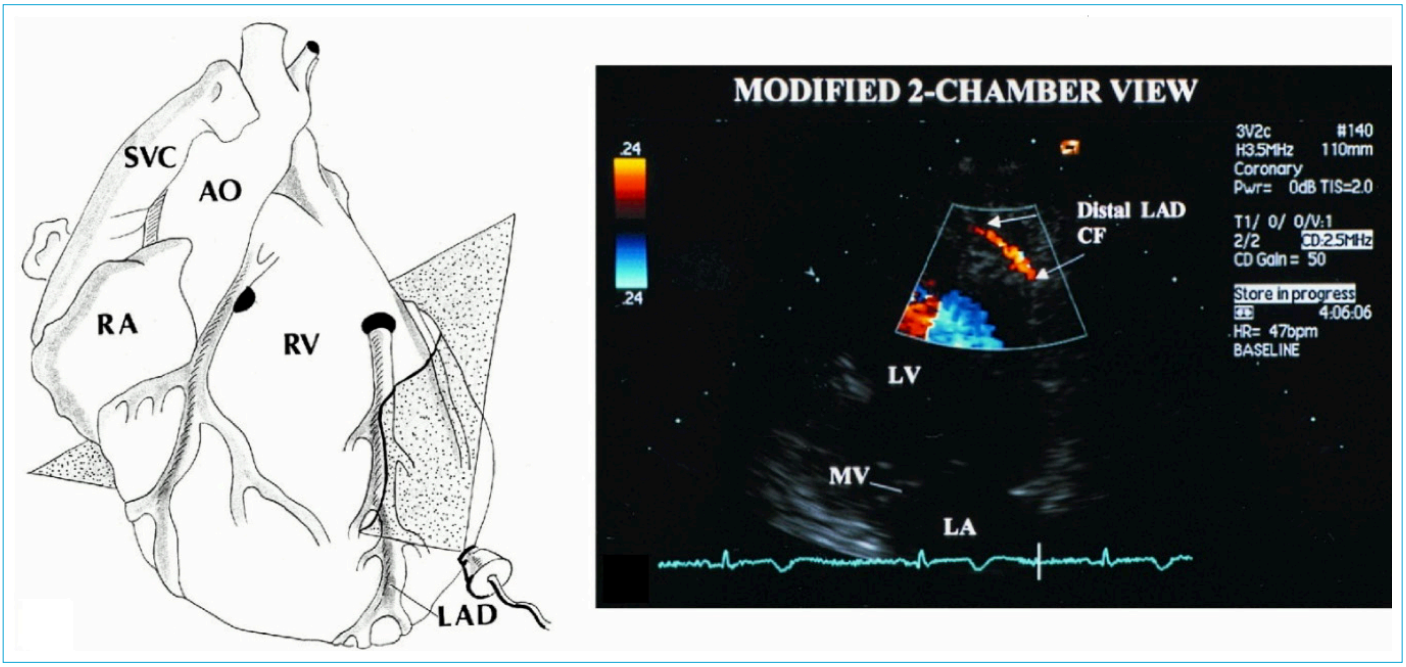


Figure 1. Transducer orientation for the mid-distal LAD and colour flow visualition in modified 2-chamber view. Figure created by Caiati et al.[12] (Open access).

Table 1. Blood pressure and echocardiographic & CFR values of groups

	Normotensive		Prehypertensive		p
	Avg±SD	Median	Avg±SD	Median	
Systolic BP, mmHg	111.3±6.7	113.0	129.6±6.4	128.5	>0.001
Diastolic BP, mmHg	66.4±5.9	68.0	75.9±7.8	75.0	>0.001
EF %	66.7±3.3	66.0	66.6±4.2	65.0	0.914
Lvedd, mm	45.2±4.7	44.0	46.7±5.6	46.0	0.134
Lvesd, mm	28.1±4.0	28.0	29.1±3.3	29.6	0.120
SWT, mm	8.8±1.0	9.0	10.0±1.1	10.0	<0.001
PWT, mm	8.2±1.0	8.0	9.2±1.1	9.0	<0.001
Ascending Aorta, mm	28.1±3.2	27.5	29.0±3.4	29.0	0.096
BDPFV, cm/sec	26.7±4.0	26.0	29.7±7.7	27.5	0.049
HDPFV, cm/sec	65.1±10.5	63.5	62.2±12.7	57.5	0.034
BasalPulse, beats/min	76.4±9.7	76.0	76.3±9.1	76.1	0.844
Peak Pulse, beats/min	100.4±10.1	100.2	100.0±12.2	101.5	0.915
CFR	2.4±0.2	2.4	2.1±0.2	2.1	<0.001

BDPFV: baseline diastolic peak flow velocity; BP: blood pressure; HDPFV: hyperemic diastolic peak flow velocity; Lvedd: left ventricular end diastolic diameter; Lvesd: left ventricular end systolic diameter; SWT: septal wall thickness; PWT: posterior wall thickness

Table 2. Laboratory data of groups

	Normotensive		Prehypertensive		p
	Avg±SD	Median	Avg±SD	Median	
Galanin, ng/L	7.0±1.8	7.0	6.4±1.5	6.2	0.062
Total Cholesterol, mg/dl	183.2±22.4	183.0	200.3±24.8	200.0	<0.001
HDL, mg/dl	50.7±10.1	50.0	46.6±9.9	46.0	0.004
LDL, mg/dl	109.4±22.4	109.0	127.8±21.1	127.0	<0.001
Triglycerides, mg/dl	104.0±43.4	104.0	123.1±58.5	123.0	0.012
Glucose, mg/dl	91.5±9.0	91.2	93.9±9.7	94.0	0.072
HbA1c, %	5.3±0.2	5.3	5.5±0.2	5.4	0.003
Uric Acid, mg/dl	4.5±0.8	4.4	5.0±1.0	5.0	<0.001
Urea, mg/dl	24.0±5.7	24.0	24.9±4.8	24.0	0.284
Creatinine, mg/dl	0.75±0.13	0.75	0.79±0.10	0.77	0.024
GGT, U/L	20.3±7.0	20.0	21.9±7.9	22.0	0.079
hs-CRP, mg/dl	0.6±0.6	0.6	0.9±1.3	0.9	0.040
ALT, U/L	18.7±9.0	17.0	20.3±8.8	20.0	0.120
AST, U/L	19.6±6.8	20.0	21.6±10.2	20.0	0.562

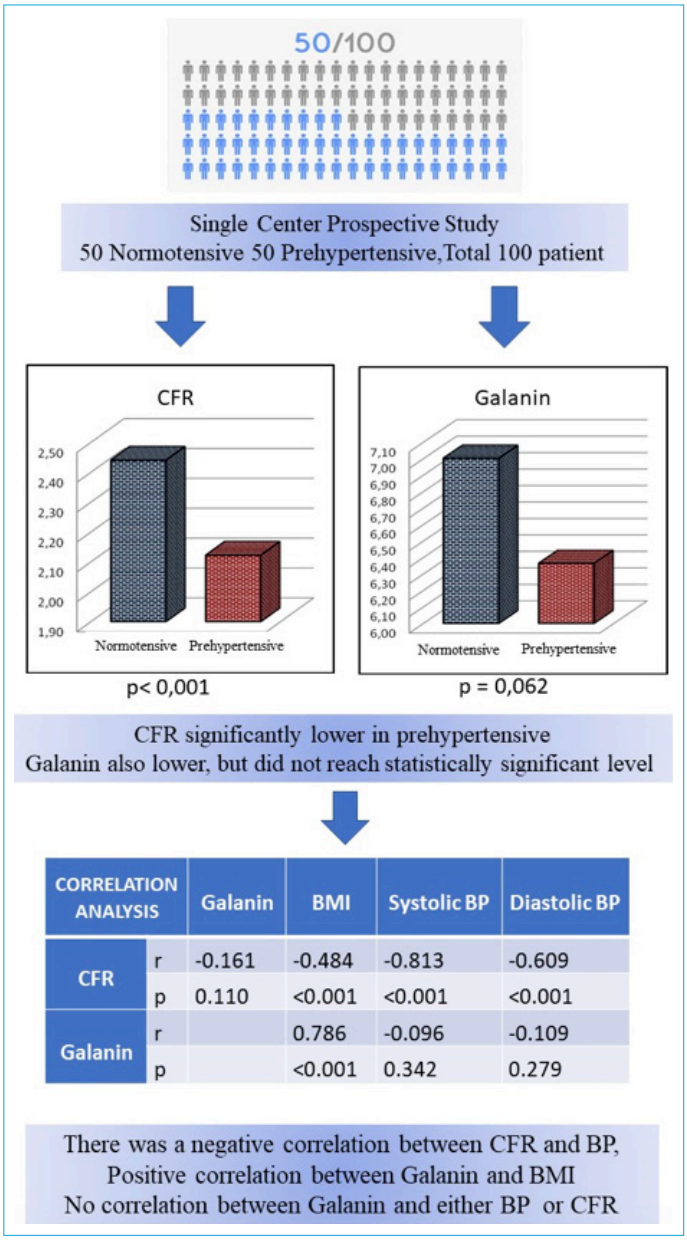
HDL: high density lipoprotein; LDL: low density lipoprotein; HbA1c: hemoglobin A1c; GGT: gamma glutamyl transferase; hs-CRP: high sensitivity C reactive protein; ALT: alanine aminotransferase; AST: aspartate aminotransferase.

There was a negative correlation between CFR and BP levels. No correlation was observed between galanin and either BP levels or CFR. However, a statistically significant positive correlation was found between galanin and BMI (Fig. 2).

Discussion

In this study, we aimed to investigate the relationship between serum galanin levels and BP and CFR and the possibility of using galanin levels as a marker for microvascular dysfunction in prehypertensives.

Because of the high prevalence and high cardiovascular risk of pHT, it is particularly important to investigate coronary microvascular function in prehypertensives. CFR is a sensitive parameter that shows coronary artery disease at very early stage.[13] International guidelines recommend CFR measurement as a diagnostic method for the implementation of targeted therapies in patients with microvascular angina.[14] Indeed, in a meta-analysis involving 8446



CORRELATION ANALYSIS		Galanin	BMI	Systolic BP	Diastolic BP
CFR	r	-0.161	-0.484	-0.813	-0.609
	p	0.110	<0.001	<0.001	<0.001
Galanin	r		0.786	-0.096	-0.109
	p		<0.001	0.342	0.279

Figure 2. Association of galanin and CFR in prehypertensives.

CFR: Coronary flow reserve; BP: Blood Pressure; BMI: Body-mass index r; Pearson's correlation coefficient.

patients, abnormal CFR increased the risk of death by 3.7-fold, and every 0.1 unit reduction in CFR was associated with a 16% increase in the risk of death.[6] Therefore, CFR may be an important parameter in the assessment of cardiovascular risk and microvascular function in prehypertensives, a vulnerable group.

CFR impairment has been suggested to occur generally due to changes in coronary resistance. Therefore, it has been emphasized that structural changes in the coronary vascular system are the main factor affecting the impaired CFR.[15] Medial wall hypertrophy is considered to be the most important mechanism in microvascular dysfunction.[16] This finding is supported by the fact that CFR may be impaired even in the absence of myocardial hypertrophy.[17] Likewise, we found that CFR values were lower in prehypertensives even in the absence of left ventricular hypertrophy.

Another cause of CFR impairment is a combination of decreased vasodilator mediators released from the endothelium, increased vasoconstrictor mediators and morphological changes in the vascular structure.[18] Polese et al.[19] suggested that the maximal cross-sectional area of the microcirculatory bed may be reduced due to vascular changes in the intramyocardial coronary arteries, and accordingly, the vasodilatory response of the microvascular bed to physiological or pharmacological stimuli may be limited.

We found baseline diastolic flow velocity and hyperemic diastolic peak flow velocity were significantly different between prehypertensives and normotensives, which are the two components that compose the CFR.

In our study, although myocardial wall thickness was below hypertrophic limits in both groups, there was a partial increase in prehypertensives. So higher baseline diastolic flow in prehypertensives, may be due to extravascular compression of intramyocardial coronary arteries caused by partial increase in myocardial wall thickness and higher blood flow rate caused by higher blood pressure. The lower hyperemic diastolic peak flow may be explained by a decrease in the maximal cross-sectional area of the microcirculatory bed and decreased vasodilatory response.[19]

We found HbA1c, total cholesterol, LDL, triglyceride, uric acid, creatinine, and hs-CRP levels were significantly higher in prehypertensives, and HDL was significantly lower.

DM causes hypertrophy of the media layer of coronary arteries, remodeling and dysplasia of arterioles, leading to diabetic microangiopathy and a decrease in CFR.[16] Patients with DM were not included in our study; however, elevated HbA1c in prehypertensives is remarkable. One of the reasons why CFR is found to be lower in prehypertensives may be these effects of high blood glucose.

Studies have shown that there is a relationship between prehypertension and lipid profile.[20] It is known that HDL has a protective effect against endothelial dysfunction because of its regulatory effects in the early stages of endothelial dysfunction, whereas LDL causes endothelial dysfunction.[21] Raitakari et al.[22] found that high LDL caused decrease in CFR. Lipid profile differences between the groups in our study can be explained by all these relationships.

HT causes impairment of renal function. Microalbuminuria, found in 10-40% of hypertensive patients, is an indi-

cator of diffuse microvascular damage and is recognized as an independent risk factor for cardiovascular morbidity and mortality.[23] Previous studies have shown microalbuminuria is higher in prehypertensives.[24] Microalbuminuria was not evaluated in our study, but creatine levels were found to be significantly higher in prehypertensives. Our findings support that renal function decreased and microvascular function deteriorated even at prehypertensive levels.

The relationship between atherosclerosis and inflammation has been clearly clarified. Moderately high hs-CRP values have been reported to be associated with an increased risk of cardiovascular events independent of other risk factors.[25] It has been found that hs-CRP causes decrease in nitric oxide level, increase in endothelin 1 level and up-regulation of angiotensin type-1 receptor, leading to increase in blood pressure.[26,27] In accordance with these findings, we found higher hs-CRP levels in prehypertensive.

In our study, we found that uric acid level was significantly higher in prehypertensives. Uric acid has been found to increase blood pressure by increasing renin, decreasing nitric oxide, causing interstitial inflammation, afferent arteriolopathy, increase in reactive oxygen products, vascular inflammation, suppression of endothelial cell growth and vascular smooth muscle cell proliferation.[28] In many studies[29,30], uric acid was found to be associated with HT, and it was reported that elevated uric acid was a predictor for development of hypertension.[31]

The association between prehypertension and galanin has never been studied before in the literature. There are a limited number of studies examining the relationship between BP and galanin. In a study, it was reported that galanin caused decrease in BP by inhibiting the sympathetic nervous system in humans and animals[9] and it was reported in another that high BP may decrease galanin synthesis.[32] Also, a positive correlation was found between the level of a member of the Galanin peptide family, alarin and BP.[33] In addition, alarin contributes to the development of HT by increasing renal sympathetic nerve activity.[34] Fang et al.[8] found that plasma galanin levels were significantly lower in hypertensive obese patients compared to obese controls and that there was a negative correlation between BP and galanin. In a recent study, it was determined that obese patients with HT had significantly higher blood galanin concentrations than controls.[35] Although both obesity and blood pressure have been found to affect galanin levels, multiple linear regression studies revealed that BMI was the biggest determinant of galanin levels.[36]

We also found a positive correlation between galanin and BMI. There was no correlation between galanin and CFR. Galanin levels were numerically lower in prehypertensives, although the difference was close to statistical significance, it did not reach level of significance. Perhaps, if the mean blood pressure values of the prehypertensive group (129.6/75.9 mmHg) in our study had been slightly higher, the difference in galanin between the groups may have reached statistical significance.

Another possible reason for the lack of significance can be the small relatively patient population in our study. In any case, we believe that future studies with more participants may further clarify the association of galanin with BP and microvascular function.

Limitations

The study design was cross-sectional and observational, patients were not followed up for adverse cardiac events or clinically, and it was a single-center study with a relatively small number of patients.

Conclusion

Galanin values were lower in the group with pHT, but this difference was not statistically significant. Also, no significant correlation was observed between CFR and galanin.

In prehypertensives, morphological changes in the left ventricle, deterioration in lipid parameters, increased blood glucose, hs-CRP and uric acid levels were found which are associated with many poor outcomes.

And CFR values were found to be significantly lower in people with pHT. Accordingly, impairment of microvascular function with an increase in blood pressure may begin even before hypertensive levels are reached. Evaluation with CFR can be important tool for cardiovascular risk assessment in prehypertensives. In this way, poor outcomes can be prevented by lifestyle changes and modification of risk factors in prehypertensives.

Moreover, we think that prospective studies with larger populations will reveal the relationship between galanin and BP and microvascular function better.

Disclosures

Conflict of Interest: The authors report there are no competing interests to declare.

Financial Support (Funder's name): No institutional and financial support received.

Ethics Committee Approval: This study was approved by the Istanbul Medeniyet University Goztepe Training and Research Hospital Clinical Research Ethics Committee (No. 2017/0294, Date: 26.12.2017).

Authorship Contributions: Concept – M.E.C., M.C., S.K.; Design – M.E.C., M.C., S.K.; Supervision – M.E.C., G.A., S.K.; Funding: M.E.C.; Materials – M.E.C., F.B.O., G.A.; Data collection and/or processing – M.E.C., F.B.O., G.A.; Analysis and/or interpretation – M.E.C., F.B.O., G.A.; Literature search – M.E.C., E.E., M.C., S.K.; Writing – M.E.C., E.E.; Critical Review – E.E., M.C., S.K.

Use of AI for Writing Assistance: None declared.

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