Cardiovascular Topics

The relationship between serum osteoprotegerin levels and right atrial and ventricular speckle-tracking measurements in essential hypertension patients with normal left ventricular systolic function

Ender Emre, Ezgi Kalaycıoğlu, Ahmet Özderya, Murat Gökhan Yerlikaya, Turhan Turan, Kaan Hancı, Tayyar Gökdeniz, Mustafa Çetin

Abstract

Objective: We planned to reveal the relationship between OPG (osteoprotegerin) level and right heart function in hypertensive patients with normal ejection fraction, using strain analysis, which is a sensitive method in demonstrating subclinical dysfunction.

Methods: Between February and June 2018, 625 consecutive patients with a diagnosis of hypertension who applied to the cardiology out-patient clinic of our hospital were evaluated for our study and 175 eligible patients were included. The patients were divided into two groups according to their OPG level. Strain analysis was performed in the echocardiographic evaluation.

Results: The mean OPG value was 6.33 ± 1.87 pg/l. There were 93 patients (age 51.1 ± 8.5 years) in the low OPG group and 82 patients (age 54.6 ± 10.4 years) in the high OPG group. A significant difference was found between the two groups with regard to age (p = 0.016), statin use (p = 0.026), C-reactive protein level (p = 0.048), office systolic blood pressure (SBP) (p = 0.001) and office diastolic blood pressure (DBP) (p = 0.001). A significant difference was found between values of strain during reservoir phase (RASr) (p = 0.01), strain during conduit phase (RAScd) (p < 0.001) and peak strain rate during reservoir phase (pRASRcd) (p = 0.044). In multivariate regression analysis, age (OR: 1.162, 95% CI: 1.064–1.269, p = 0.001), office DBP (OR: 1.089, 95% CI: 1.020–1.161, p = 0.011) and RAScd (OR: 0.890, 95% CI: 0.815–0.972, p < 0.010) were found to be independent predictors of high OPG.

Conclusion: In our study, we found high OPG level was inversely correlated with right atrial strain values and linearly associated with high blood pressure. In order to take advantage of the negative indicators of high OPG, positive results can be obtained in strain values of the right heart by indirectly reducing the afterload of the right heart. This can be done by reducing high systemic blood pressure and providing tight blood pressure control.

Keywords: osteoprotegerin, hypertension, strain, right heart function

Submitted 1/4/23, accepted 4/7/23

Cardiovasc J Afr 2023; online publication www.cvja.co.za

DOI: 10.5830/CVJA-2023-036

Department of Cardiology, Ahi Evren Chest and Cardiovascular Surgery Education and Research Hospital, Trabzon, Turkey

Ender Emre, MD, dr.enderemre@hotmail.com
Ezgi Kalaycıoğlu, MD
Ahmet Özderya, MD
Murat Gökhan Yerlikaya, MD
Turhan Turan, MD

Department of Cardiology, Akçaabat Haçkalı Baba State Hospital, Trabzon, Turkey

Kaan Hancı, MD

Department of Cardiology, Hitit University Erol Olçok Training and Research Hospital, Çorum, Turkey

Tayyar Gökdeniz, MD

Department of Cardiology, Medical Faculty, Recep Tayyip Erdoğan University, Rize, Turkey

Mustafa Çetin, MD

Osteoprotegerin (OPG) is a member of the tumour necrosis factor receptor superfamily and was first identified as a regulator of bone resorption.[1] OPG is highly expressed in many different cell types, such as osteoblasts, heart, kidney, liver, spleen and bone marrow.[2] There is a link between bone regulatory proteins and vascular biology, and OPG is considered a possible mediator of vascular calcification.[3] In many human studies, OPG level has been found to be associated with traditional cardiovascular risk factors, such as advanced age, low renal function, atherosclerosis, hypertension and duration of diabetes mellitus.[4-7]

Hypertension is an important risk factor that has a high prevalence worldwide and its role in adverse cardiovascular events is well known. Determination of the damage caused by hypertension in the heart can be done by echocardiography.[8] In patients with long-term hypertension, impaired left ventricular function, left ventricular hypertrophy and myocardial fibrosis are markers of end-organ damage.

The importance of right ventricular (RV) function has been overlooked for decades. However, with evidence obtained from healthy and ill individuals over time, understanding of the

importance of the right ventricle has increased.[9] Because of its complex RV geometry, evaluation of its function with traditional echocardiographic techniques is unreliable and conflicting results can be obtained. Numerous studies have shown the benefit of two-dimensional (2D) speckle-tracking echocardiography (STE) in the evaluation of right ventricular function. It has been found that 2D STE is a prognostic and clinically valuable instrument in many heart diseases affecting the right ventricle.[10]

In our study, we planned to reveal the relationship between serum OPG level and right heart function in hypertensive patients with normal ejection fraction, using strain analysis, which is a sensitive method of demonstrating subclinical dysfunction.

Methods

This study was planned as a cross-sectional registry study at Trabzon Ahi Evren Chest Cardiovascular Surgery Education and Research Hospital in Turkey. A multistage sampling method was used according to the exclusion and inclusion criteria. The data for our study were collected in the out-patient setting of an advanced heart centre with consecutive patients between February and June 2018.

The data of 625 patients with a diagnosis of hypertension were recorded. Among these, the patient group with isolated hypertension was selected according to the exclusion criteria. Excluded patients were 212 with coronary artery disease, 74 with ejection fraction < 50%, eight with a history of arrhythmia, 41 with chronic obstructive pulmonary disease and other major lung pathologies, 22 with symptoms of active infection, 35 with moderate and severe valve pathology and 10 with malignancy. Eight patients were excluded due to pulmonary hypertension, 18 due to advanced renal failure and four due to advanced hepatic failure. Eighteen more were excluded due to image limitations by our cardiology imaging specialist, who performed an echocardiographic examination independent of the study data.

The study was conducted with 175 consecutive patients. Age, gender, hypertension, diabetes mellitus history and drug use data of the patients were recorded. Office systolic and diastolic blood pressures of the patients were measured in accordance with scientific guidelines. Body mass index was calculated with the following formula: weight (kg)/height (m^2). Hypercholesterolaemia was defined as patients with total cholesterol level > 200 mg/dl (5.18 mmol/l), low-density lipoprotein cholesterol > 130 mg/dl (3.37 mmol/l), triglycerides > 150 mg/dl (1.7 mmol/l) or statin use.

Informed consent was obtained from all participants. The study protocol was approved by the local ethics committee in accordance with the Declaration of Helsinki and good clinical practice (approval number: 80576354-050-99/59).

For our study, the fasting blood glucose, creatinine, glycated haemoglobin (HbA_{1c}) and C-reactive protein (CRP) levels of the patients were recorded on an AU680 clinical chemistry analyser system; Beckman Coulter KK. For OPG analysis, venous blood taken from the antecubital vein after an overnight fast was placed into ethylenediaminetetraacetic acid (EDTA) tubes and centrifuged. The plasma obtained was stored at –80°C and quantified by a sandwich enzyme-linked immunosorbent assay (ELISA) assay using commercially procurable antibodies (Biovendor, Czech Republic). The study population was divided into two groups according to the mean value of the OPG results of all patients.

Echocardiographic examinations of the patients were performed with a VIVID S-5 (General Electric Medical System Vingmed Ultrasound AS, Horten, Norway) equipped with a 3.6-MHz transducer. Left ventricular ejection fraction (LVEF) was calculated according to the modified Simpson's method. With tissue Doppler imaging (TDI), tricuspid lateral annular systolic velocity (S′), early diastolic myocardial velocity (E′), late diastolic myocardial velocity (A′) from the apical four-chamber view in the lateral segment of the right ventricle were measured. Tricuspid annular plane systolic excursion (TAPSE) was calculated by applying M-mode to the junction between the RV lateral wall and the tricuspid annulus in the apical four-chamber view.

Frame rate was optimised for speckle tracking to provide the highest frame rate per cardiac cycle without significantly decreasing spatial resolution. Echocardiography 2D strain software (EchoPAC 108.1.12, General Electric Medical Systems, Horten, Norway) was used to evaluate strain imaging. RV four-chamber strain (RV4CSL) analysis was carried out in the apical four-chamber focused view and the RV borders were marked. It was first determined by automatic identification (by software) and then manual correction and modifications were made. For RV4CSL, the average of six segments, three free wall and three septum views, was taken. Although RV strain measurements are made at various stages of the cardiac cycle, the recommended

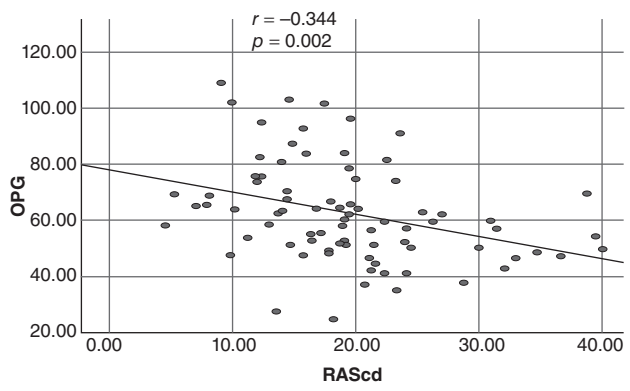

Fig. 1. The correlation between OPG and RAScd.

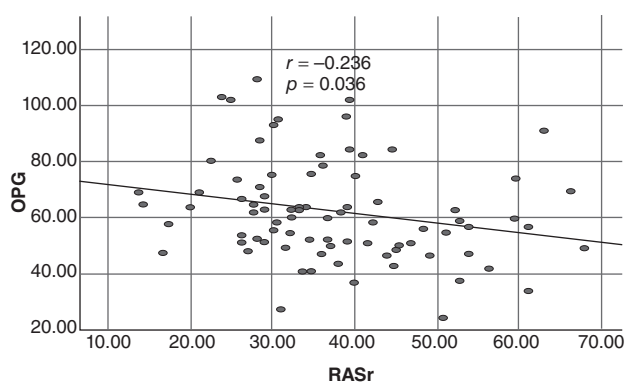

Fig. 2. The correlation between OPG and RASr.

RV peak systolic strain (maximum ventricular contraction) value should be used (Fig. 1).

For right atrial (RA) strain in the apical four-chamber view, contours were placed on the RA walls and six segments that were automatically separated by the software were observed (Fig. 2). It was adjusted to approximately 2–3 mm RA wall thickness. Manual adjustment was made to optimise imaging. The tracing was begun at the tricuspid valve annulus, along the endocardial border of the RA lateral wall, RA roof, RA septal wall, and ending at the opposite tricuspid annulus to avoid including the pericardium. Segments that failed to image atrial wall motion were excluded from the analyses. The end of diastole was calculated according to the R wave in electrocardiography as the beginning of the cardiac cycle for RA strain.

Strain and strain rates were recorded in various cardiac phases [strain during reservoir phase (RASr), strain during conduit phase (RAScd), strain during contraction phase (RASct), peak strain rate during reservoir phase (pRASRr), peak strain rate during conduit phase (pRASRcd), peak strain rate during contraction phase, (pRASRct)]. All echocardiograms were obtained and interpreted by two experienced cardiologists who were blinded to the patient's condition, in accordance with the recommendations of the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE).

Table 1. Demographic and laboratory parameters

Variables	*OPG < mean* (n = *93*)	*OPG > mean* (n = *82*)	p-*value*
Age (years)	51.1 ± 8.5	54.6 ± 10.4	0.016
Males, *n* (%)	49 (52.7)	36 (43.9)	0.167
Hypertension duration (years)	3.8 ± 4.7	3.9 ± 4.8	0.836
Newly diagnosed hypertension, *n* (%)	32 (34.8)	36 (43.9)	0.141
Diabetes mellitus, *n* (%)	49 (52.7)	36 (43.9)	0.157
Hyperlipidaemia, *n* (%)	60 (64.5)	53 (64.6)	0.557
BMI (kg/m^2)	31.5 ± 4.5	32.4 ± 4.5	0.155
ARB, *n* (%)	32 (34.4)	30 (36.6)	0.443
ACEI, *n* (%)	31 (33.3)	27 (33.3)	0.564
Beta-blocker, *n* (%)	21 (22.6)	24 (29.3)	0.201
Diuretic, *n* (%)	34 (36.6)	36 (43.9)	0.303
CCB, *n* (%)	17 (18.3)	24 (29.3)	0.063
Statin, *n* (%)	30 (32.3)	15 (18.3)	0.026
OAD/insulin, *n* (%)	46 (49.5)	36 (43.9)	0.280
FBG (mg/dl) (mmol/l)	123.1 ± 51 6.83 ± 2.83	122.6 ± 39.6 6.80 ± 2.20	0.954
Creatine (mg/dl)	0.8 ± 0.14	0.79 ± 0.16	0.831
CRP (mg/dl)	0.36 ± 0.31	0.49 ± 0.5	0.048
HbA_{1c}, (%)	7.7 ± 1.4	8 ± 1.37	0.446
Total cholesterol (mg/dl) (mmol/l)	208.3 ± 44.1 5.39 ± 1.14	208.4 ± 37.7 5.40 ± 0.98	0.992
LDL cholesterol (mg/dl) (mmol/l)	138.1 ± 36.3 3.58 ± 0.94	130.2 ± 33.5 3.37 ± 0.87	0.146
Triglycerides (mg/dl) (mmol/l)	170.2 ± 78.9 1.92 ± 0.89	182.5 ± 110.3 2.06 ± 1.25	0.391
HDL cholesterol (mg/dl) (mmol/l)	45.3 ± 9.7 1.17 ± 0.25	46.4 ± 10.4 1.20 ± 0.27	0.493
Office SBP (mmHg)	149.3 ± 15.3	157.1 ± 14.9	0.001
Office DBP (mmHg)	91.7 ± 11	97.2 ± 9.6	0.001

BMI: body mass index, ARB: angiotensin receptor blocker, ACEI: angiotensin converting enzyme inhibitor, CCB: calcium channel blocker, OAD: oral antidiabetic, FBG: fasting blood glucose, CRP: C-reactive protein, SBP: systolic blood pressure, DBP: diastolic blood pressure.

Statistical analysis

Statistical analysis was performed using the SPSS 17.0 program (SPSS Inc, Chicago, IL, USA) on Windows. The Kolmogorov–Smirnov and homogeneity of variance tests were performed and the normal distribution of the data was examined. For the two-group comparison of the variables showing normal distibution, the *t*-test was used on independent samples, and variables are indicated as mean ± standard deviation. For two-group comparison of non-normally distributed variables, the Mann–Whitney *U*-test was used and the variables are expressed with median (minimum–maximum) values. Categorical variables were compared using the chi-squared test and expressed as number and percentage.

All variables were evaluated with univariate regression analysis. Independent variables that were statistically significant in univariate regression analysis were evaluated in multivariate regression analysis. Predictors were determined by a multivariate logistic regression test. A p-value < 0.05 was considered statistically significant. Graphics were evaluated according to the value of the correlation coefficients (zero or very low if the coefficient r = 00.0–0.24, low if the coefficient r = 0.25–0.49, moderate to good if the coefficient r = 0.50–0.74, strong or excellent if the coefficient r = 0.75–0.99 and perfect if the coefficient r = 1).

Results

A total of 175 patients were included in our study. The mean OPG value was found to be 6.33 ± 1.87 pg/l. The patients were divided into two groups: low and high OPG levels. There were 93 patients (44 women and 49 men; mean age 51.1 ± 8.5 years) in the

Table 2. Echocardiography data

Variables	*OPG < mean* (n = *93*)	*OPG > mean* (n = *82*)	p-*value*
LVEF (%)	62.1 ± 6	61 ± 6.5	0.280
Tricuspid S′ (cm/s)	15.1 ± 2.7	14.1 ± 2.4	0.101
Tricuspid E′ (cm/s)	17.1 ± 2.8	11.9 ± 2.9	0.285
Tricuspid A′ (cm/s)	18.6 ± 5.1	17.6 ± 3.3	0.342
TAPSE (cm)	2.4 ± 0.37	2.3 ± 0.37	0.127
RASr (%)	40.5 ± 11.8	33.5 ± 11.7	0.010
RAScd (%)	–22.18 ± 7.8	–15.9 ± 6.4	< 0.001
RASct (%)	–18.5 ± 7.7	–17.6 ± 7.4	0.588
pRASRr	1.71 ± 0.52	1.52 ± 0.52	0.106
pRASRcd	–1.6 ± 0.53	–1.35 ± 0.42	0.044
pRASRct	–2.4 ± 0.85	–2.07 ± 0.81	0.087
RV4CSL (%)	–25.9 ± 5.4	–25.3 ± 5.9	0.579
Mitral E (cm/s)	72.5 ± 18	70.5 ± 18.2	0.484
Mitral A (cm/s)	81.2 ± 16.7	86.5 ± 22.3	0.087
Mitral EDT (ms)	204.9 ± 49.2	203.2 ± 49.5	0.063
Mitral S′ (cm/s)	5.1 ± 4.5	5.4 ± 4.6	0.433
Mitral E′ (cm/s)	5.8 ± 5.2	6.02 ± 4.9	0.962
Mitral IVRT (ms)	71.2 ± 27.3	72.8 ± 26.6	0.127
Mitral E/A	0.92 ± 0.29	0.85 ± 0.28	0.196
Mitral E/E′	4.3±3.8	4.4±3.9	0.913

LVEF: left ventricular ejection fraction, E′: early diastolic tissue velocity, S′: systolic tissue velocity, A′: late diastolic tissue velocity, TAPSE:tricuspid annular plane sysctolic excursion, RASr: strain during reservoir phase, RAScd: strain during conduit phase, RASct: strain during contraction phase, pRASRr: peak strain rate during reservoir phase, pRASRcd: peak strain rate during conduit phase, pRASRct: peak strain rate during contraction phase, RV4CSL: right ventricular four-chamber strain, EDT: E-wave deceleration time, IVRT: isovolumic relaxation time.

Table 3. Multivariate regression analysis on predicting factors of OPG levels

	Univariate analysis			*Multivariate analysis*		
Variables	*OR*	*95% CI*	*p-value*	*OR*	*95% CI*	*p-value*
Age	1.041	1.007–1.075	0.017	1.162	1.064–1.269	0.001
Statin use	–0.470	0.231–0.955	0.037	–0.443	0.133–1.468	0.183
CCB use	1.850	0.910–3.759	0.089			
CRP	2.243	0.977–5.148	0.057			
Office SBP	1.036	1.014–1.059	0.002			
Office DBP	1.053	1.020–1.086	0.001	1.089	1.020–1.161	0.011
RASr	–0.949	0.910–0.989	0.014			
RAScd	–0.875	0.807–0.949	0.001	0.890	0.815–0.972	0.010
pRASRcd	–0.369	0.135–1.003	0.051			
pRASRct	–0.613	0.347–1.081	0.091			

CCB: calcium channel blocker, CRP: C-reactive protein, SBP: systolic blood pressure, DBP: diastolic blood pressure, RASr: strain during reservoir phase, RAScd: strain during conduit phase, pRASRcd: peak strain rate during conduit phase, pRASRct: peak strain rate during contraction phase.

low OPG group and 82 patients (46 women and 36 men; mean age 54.6 ± 10.4 years) in the high OPG group.

Age, gender, hypertension, diabetes mellitus, hyperlipidaemia history, drug use, blood pressure and laboratory parameters of the individuals included in the study are given in Table 1. There was a statistically significant difference between the two groups with regard to age ($p = 0.016$), statin use ($p = 0.026$), CRP ($p = 0.048$), office systolic blood pressure (SBP) ($p = 0.001$) and office diastolic blood pressure (DBP) ($p = 0.001$). LVEF, and right atrial and right ventricular parameters of the patients are given in Table 2.

A difference was found between RASr ($p = 0.01$), RAScd ($p < 0.001$) and pRASRcd ($p = 0.044$) values. No statistically significant difference was found between the other parameters. In univariate regression analysis, age ($p = 0.014$), office SBP ($p = 0.002$) and office DBP ($p = 0.001$) were found to be directly proportional to high OPG level. Statin usage ($p = 0.037$), RASr ($p = 0.014$) and RAScd ($p = 0.001$) were found to be inversely proportional to high OPG level. In the multivariate regression analysis performed, age (OR: 1.162, 95% CI: 1.064–1.269, $p = 0.001$), office DBP (OR: 1.089, 95% CI: 1.020–1.161, $p = 0.011$) and RAScd (OR: 0.890, 95% CI: 0.815–0.972, $p < 0.010$) were determined independent predictors of high OPG level (Table 3). RASr ($p = 0.036$, r = –0.236) and RAScd ($p = 0.002$, $r = –0.344$) values showed an inverse correlation with OPG levels (Figs 3, 4).

Discussion

From this study, we found that OPG levels were associated with age, office DBP and RAScd, independent of other factors, in patients with hypertension with preserved LV function.

Hypertension is a serious public health problem worldwide due to its high prevalence and increasing risk of many cardiovascular diseases.[11] Cardiac remodelling in hypertension involves an imbalance in the production of collagen types 1 and 3, which bear the main stress in the extracellular matrix. Increased stress causes heterogeneous myocardial fibrosis and expansion to occur, especially in the subendocardial region.[12] OPG has been shown to have a key role in the development of vascular calcification and atherosclerosis in many studies and vascular calcification is considered to be an important cause of hypertension.[13,14]

OPG level has a strong correlation with age. The association of advancing age and atherosclerosis can be explained by the effect of OPG on vascular calcification.[15] In the studies of Mogelvang *et al.* and Røysland *et al.*, OPG level was found to be associated with increasing age.[15,16] In our study, age was found to be higher in the group with high OPG levels (51.1 ± 8.5 vs 54.6 ± 10.4 years, $p = 0.016$). It is particularly important that age was significant in univariate analysis (OR: 1.041, $p < 0.017$) and continued to increase in multivariate analysis (OR: 1.162, $p < 0.001$). High OPG levels were associated with age, independent of other factors, which was not surprising. Against the adverse effects of aging, OPG level could therefore be evaluated as a treatment target and a biomarker.

OPG is a biomarker of inflammation, as is CRP.[15] In our study, the CRP level was found to be higher in the group with high OPG levels (0.36 ± 0.31 vs 0.49 ± 0.5 mg/l, $p = 0.048$). In the JUPITER study, a decrease in CRP value was found in the group using rosuvastatin, and the study was terminated early due to a significant difference in endpoints.[17] Statins suppress inflammation and may cause positive clinical outcomes with negative effects on the development of atherosclerosis. The low use of statins in the group with high OPG levels may also have contributed to this situation [30 (32.3%) vs 15 (18.3%), $p = 0.026$]. Due to its role as a biomarker of inflammation and its impact on endothelial dysfunction, OPG may be a target molecule for both therapy and follow up in future therapeutic methods.

When the literature was examined, there was no study that directly examined the relationship between OPG and the

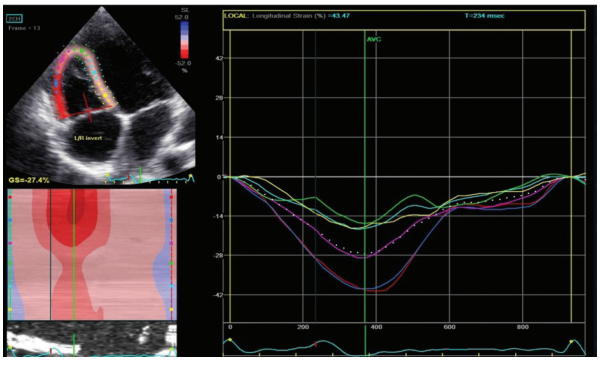

Fig. 3. Two-dimensional speckle-tracking imaging in the apical four-chamber view: right ventricular strain.

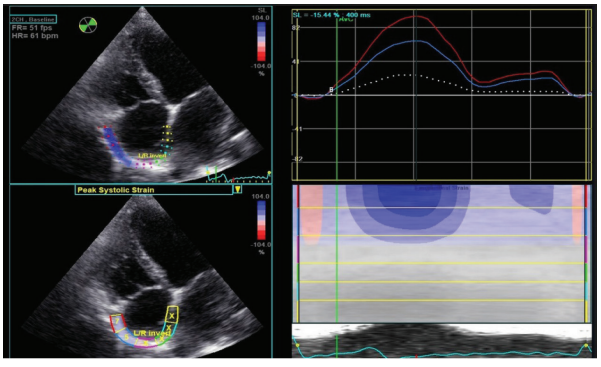

Fig. 4. Two-dimensional speckle-tracking imaging in the apical two-chamber view: right atrial strain.

right heart chambers. Studies have examined the relationship between pulmonary hypertension and OPG, or the relationship between pulmonary hypertension and right heart chambers. Pulmonary arterial hypertension (PAH) is a devastating disease with pulmonary vasculopathy, which adversely affects right heart function.[18] There are many molecular and cellular mechanisms in the pathogenesis of PAH, and there are many cross-signalling pathways among them.[19]

Activation of the bone morphogenetic protein receptor type-2 (BMPR2)–OPG pathway increases apoptosis and causes endothelial damage. Endothelial damage and proliferation are the basic processes that lead to endothelial dysfunction, which plays an important role in the pathogenesis of pulmonary vascular remodelling and hypertension.[20,21] In the study by Zhang *et al*., it was shown that the OPG level was higher in the group with pulmonary hypertension in heart failure patients, compared to the group without pulmonary hypertension.[22] Since OPG level is directly proportional to pulmonary hypertension, which increases the afterload of the right heart, right heart function may be adversely affected in the group with high OPG levels.

In the study by Bai *et al*., deterioration in RA strain values was found in the group of patients with pulmonary hypertension who had had an event.[23] In the study by Tadic *et al*., it was determined that RA and RV strain values in the controlled hypertension group were better than those in the uncontrolled or untreated group.[24] In our study, although no difference was observed in RV strain values in the group with high OPG levels, significant deterioration was found in RA strain values [RASr (40.5 ± 11.8 vs 33.5 ± 11.7%, $p = 0.010$), RAScd (–22.18 ± 7.8 vs –15.9 ± 6.4%, $p < 0.001$), pRASRcd (–1.6 ± 0.53 vs –1.35 ± 0.42, $p = 0.044$), pRASRct (–2.4 ± 0.85 vs –2.07 ± 0.81, $p = 0.087$). Besides, high OPG levels were associated with RAScd, independent of other factors.

When the correlation graph was examined, it was seen that there was an inverse relationship between OPG level and RAScd ($p = 0.002$) values. But the relationship was found to be low ($r = –0.344$). When examining the effects of hypertension on the heart, it is often focused on the left cavities of the heart. It should be considered that the right heart chambers may be adversely affected due to increased afterload, especially in hypertensive patients with high OPG levels. OPG could therefore be considered a biomarker for RA strain in patients with high blood pressure.

Measurement of systolic pulmonary artery pressure on echocardiography is dependent on the tricuspid regurgitation jet. Therefore, systolic pulmonary artery pressure could not be obtained in this study for every patient. If there were systolic pulmonary artery pressure values for each patient, we could have determined the relationship between strain values and OPG level more clearly.

High OPG levels have adverse effects on the pulmonary and systemic vasculature because they are linked to endothelial dysfunction. In our study, older age in the group with high OPG levels was to be expected. Likewise, increasing RA strain values and high blood pressure with age were also expected. The relationship between high OPG levels with RA strain values and poor blood pressure control is an important finding that was independent of other parameters. As a result of this relationship, close follow up for blood pressure control in individuals with high OPG levels may provide positive results, not only in systemic hypertension but also in functional parameters of the right heart.

Limitations

This study was carried out in a single centre with a limited number of patients. Another important limitation was the inability to measure systolic pulmonary artery pressure, since not every patient had tricuspid valve insufficiency. The lack of randomised and long-term follow up is also a limitation. Uncontrolled hypertension and the white-coat phenomenon could have affected the results. More reliable results could be obtained in a multicentre study with a larger patient population.

Conclusion

The correlation of OPG level, which is a biomarker of inflammation, with age was to be expected. High OPG level can be considered an indicator of deterioration in both systemic and pulmonary vasculature due to its negative effect on endothelial function. It was also important to determine that high OPG level was inversely related to RA tension and linearly associated with high blood pressure. This indicates that OPG level could be used as a biomarker for blood pressure control and RA strain. Therefore, in order to avoid the negative effects of high OPG level, which increases with advancing age, the afterload of the right heart could be reduced indirectly by providing improved systemic blood pressure with tighter blood pressure control.

The common mistake in evaluation of the heart is to focus on the left heart chambers and neglect the right heart chambers. While investigating the effects of systemic hypertension on organs such as the brain, kidney and eyes, the effects on the right heart should not be ommitted. For this, OPG level could serve as a biomarker.

References

1. Simonet WS, Lacey DL, Dunstan CR, *et al*. Osteoprotegerin: a novel secreted protein involved in the regulation of bone density. *Cell* 1997; **89**(2): 309–319.
2. Boyce BF, Xing L. Functions of RANKL/RANK/OPG in bone modeling and remodeling. *Arch Biochem Biophys* 2008; **473**(2): 139–146.
3. Flyvbjerg A. Diabetic angiopathy, the complement system and the tumor necrosis factor superfamily. *Nat Rev Endocrinol* 2010; **6**(2): 94–101.
4. Kudlacek S, Schneider B, Woloszczuk W, Pietschmann P, Willvonseder R; Austrian Study Group on Normative Values of Bone Metabolism. Serum levels of osteoprotegerin increase with age in a healthy adult population. *Bone* 2003; **32**(6): 681–686.
5. Kazama JJ, Shigematsu T, Yano K, *et al*. Increased circulating levels of osteoclastogenesis inhibitory factor (osteoprotegerin) in patients with chronic renal failure. *Am J Kidney Dis* 2002; **39**(3): 525–532.
6. Secchiero P, Corallini F, Pandolfi A, *et al*. An increased osteoprotegerin serum release characterizes the early onset of diabetes mellitus and may contribute to endothelial cell dysfunction. *Am J Pathol* 2006; **169**(6): 2236–2244.
7. Dawson S, Lawrie A. From bones to blood pressure, developing novel biologic approaches targeting the osteoprotegein pathway for pulmonary vascular disease. *Pharmacol Ther* 2017; **169**: 78–82.
8. Santos ABS, Foppa M, Bertoluci C, Branchi TV, Fuchs SC, Fuchs FD. Stage I hypertension is associated with impaired systolic function by strain imaging compared with prehypertension: A report from the prever study. *J Clin Hypertens (Greenwich)* 2019; **21**(11): 1705–1710.
9. Sanz J, Sánchez-Quintana D, Bossone E, Bogaard HJ, Naeije R.

Anatomy, function, and dysfunction of the right ventricle: JACC state-of-the-art review. *J Am Coll Cardiol* 2019; **73**(12): 1463–1482.
10. Cincin A, Tigen K, Karaahmet T, *et al.* Right ventricular function in hypertrophic cardiomyopathy: A speckle tracking echocardiography study. *Anatol J Cardiol* 2015; **15**(7): 536–541.
11. Sliwa K, Stewart S, Gersh BJ. Hypertension: a global perspective. *Circulation* 2011; **123**(24): 2892–2896.
12. Shahbaz AU, Sun Y, Bhattacharya SK, *et al*. Fibrosis in hypertensive heart disease: molecular pathways and cardioprotective strategies. *J Hypertens* 2010; **28**(Suppl 1): S25–S32.
13. Van Campenhout A, Golledge J. Osteoprotegerin, vascular calcification and atherosclerosis. *Atherosclerosis* 2009; **204**(2): 321–329.
14. Rattazzi M, Bertacco E, Puato M, Faggin E, Pauletto P. Hypertension and vascular calcification: a vicious cycle? *J Hypertens* 2012; **30**(10): 1885–1893.
15. Mogelvang R, Haahr-Pedersen S, Bjerre M, *et al.* Osteoprotegerin improves risk detection by traditional cardiovascular risk factors and hsCRP. *Heart* 2013; **99**(2): 106–110.
16. Røysland R, Bonaca MP, Omland T, *et al*. Osteoprotegerin and cardiovascular mortality in patients with non-ST elevation acute coronary syndromes. *Heart* 2012; **98**(10): 786–791.
17. Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. *Lancet* 2012; **380**(9841): 565–571.
18. Hoeper MM, Bogaard HJ, Condliffe R, *et al*. Definitions and diagnosis of pulmonary hypertension. *J Am Coll Cardiol* 2013; **62**(Suppl 25): D42–D50.
19. Hameed AG, Arnold ND, Chamberlain J, *et al.* Inhibition of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) reverses experimental pulmonary hypertension. *J Exp Med* 2012; **209**(11): 1919–1935.
20. Kim JY, Park YJ, Kim KJ, Choi JJ, Kim WU, Cho CS. Osteoprotegerin causes apoptosis of endothelial progenitor cells by induction of oxidative stress. *Arthritis Rheum* 2013; **65**(8): 2172–2182.
21. Lawrie A, Waterman E, Southwood M, *et al*. Evidence of a role for osteoprotegerin in the pathogenesis of pulmonary arterial hypertension. *Am J Pathol* 2008; **172**(1): 256–264.
22. Zhang H, Feng L, Wan Q, *et al*. Osteoprotegerin is associated with depletion of circulating endothelial progenitor cells and elevation in pulmonary arterial pressure in patients with systolic heart failure. *Acta Cardiol* 2015; **70**(4): 435–441.
23. Bai Y, Yang J, Liu J, Ning H, Zhang R. Right atrial function for the prediction of prognosis in connective tissue disease-associated pulmonary arterial hypertension: a study with two-dimensional speckle tracking. *Int J Cardiovasc Imaging* 2019; **35**(9): 1637–1649.
24. Tadic M, Cuspidi C, Suzic-Lazic J, *et al.* Is there a relationship between right-ventricular and right atrial mechanics and functional capacity in hypertensive patients? *J Hypertens* 2014; **32**(4): 929–937.