Original Research

Relationship between Sympathetic Overactivity and Left Ventricular Hypertrophy in Resistant Hypertension

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Introduction: Sympathetic overactivity plays an important role in the development of resistant hypertension (RH). However, the effect of sympathetic predominance on left ventricular hypertrophy (LVH) in RH is not very clear. In our study, we aimed to evaluate the association between sympathetic overactivity and LVH in RH.

Methods: One hundred forty-two RH patients were enrolled in this study. Transthoracic echocardiography was performed in each case and LVH parameters (interventricular septum and posterior wall thickness, left ventricular mass and left ventricular mass index) were assessed. Seventy-five patients had echocardiographic evidence of LVH (RH/LVH(+)) while the other 67 patients did not (RH/LVH(-)). Mean heart rate and time domain heart rate variability (HRV) values – standard deviation of NN intervals (SDNN), standard deviation of all five-minute NN intervals (SDANN), triangular index – that reflect sympathetic overactivity were obtained from 24-hour ECG recordings. Mean heart rate and HRV values were compared between the two groups.

Results: Demographic and clinical characteristics and blood pressure levels were similar between the groups. Echocardiographic parameters that reflect LVH were significantly higher in the RH/LVH(+) group than in the RH/LVH(-) group. Time domain HRV values were significantly lower (SDNN: 119.1 ± 34.6 vs. 138.1 ± 42.9, p=0.004; SDANN: 108.1 ± 41.6 vs. 127.9 ± 45.1, p=0.007; triangular index: 31.2 ± 10.5 vs. 36.3 ± 11.1, p=0.006) and mean heart rate was significantly higher (83.7 ± 16.4 vs. 78.3 ± 12.4, p=0.03) in the RH/LVH(+) group than in the RH/LVH(-) group.

Conclusions: Our study showed that, among patients with RH, sympathetic overactivity is significantly higher in those with LVH.

Resistant hypertension (RH) is defined as inadequate blood pressure control despite the use of at least three antihypertensive agents including a diuretic. Among the hypertensive population, the prevalence of RH is between 10% and 15%.[1] The etiology of RH is multifactorial, but sympathetic overactivity plays a major role in its pathophysiology. According to large scale trials, plasma norepinephrine levels were significantly higher in hypertensive patients.[2] Evidence from microneurographic studies proves that sympathetic nerve activity is higher in hypertensives compared to healthy controls.[3] In addition, autonomic innervation of the kidneys is thought to play an important role in the pathogenesis of RH through regulation of sodium reabsorption and renin secretion.[4]

One of the most serious types of target organ damage seen in RH is left ventricular hypertrophy (LVH). LVH and diastolic dysfunction have been related to cardiovascular morbidity and mortality.[5] The prevalence of echocardiographic

LVH in RH ranges from 55% to 75%.[6] The development of LVH has been linked to many factors, including high blood pressure levels, circulating epinephrine, and various growth-promoting substances such as angiotensin-II and insulin-like growth factor-1.

Since the treatment of RH is one of the most challenging problems in hypertension management, new interventional methods such as renal denervation,[7] which targets the renal sympathetic nerves, have increased in popularity. Although a few studies have investigated the effect of renal denervation on LVH,[8] for a better understanding of the value of renal denervation therapies it is necessary to determine the impact of sympathetic overactivity on LVH.

Heart rate variability (HRV) analysis has been used to detect sympathetic overactivity in hypertension. According to numerous data, HRV values seem to be a reliable indicator of sympathetic overactivity in hypertensive patients.[9,10] In particular, depression of time domain HRV parameters such as SDNN (standard deviation of NN intervals), SDANN (standard deviation of average NN intervals), and triangular index, which are derived from 24-hour ECG recordings, are strongly associated with sympathetic overactivity in hypertension.[11]

In our study, we aimed to investigate whether sympathetic overactivity is associated with LVH in patients with RH. For this purpose, the relation between HRV values and the echocardiographic parameters of LVH was assessed.

Methods

Study population

We recruited the cases for the present study from among patients who were referred to our clinic between January 2013 and January 2014. Our study was approved by the local ethics committee. During this period, 2912 hypertensive patients were screened and 142 patients with RH were enrolled in the study. The patients recruited were older than 18 years and had an office blood pressure of ≥160 mmHg, despite treatment with at least three anti-hypertensive drugs including a diuretic. Patients had been on the same medication for a minimum of three months before enrollment. Patients with secondary hypertension, heart failure and serious comorbidities that might influence the autonomic nervous system were excluded. Patients were divided into two groups according to their baseline echocardiographic parameters: 75 patients had

echocardiographic criteria of LVH and were defined as the RH/LVH(+) group, while 67 patients did not and were defined as the RH/LVH(-) group.

Blood pressure measurements

Office blood pressure (BP) was measured three times consecutively with a standard digital sphygmomanometer (Omron 5 blood pressure monitor, Omron Healthcare, Illinois, USA) on the right upper arm in a sitting position after a 10-minute rest. The average of the three measurements was calculated and recorded as the patient's BP value.

Holter ECG

All patients underwent 24-hour Holter ECG recording with a standard Holter ECG device (DL 800 Holter ECG device, Norav Medical Wiesbaden, Germany) in order to detect autonomic dysfunction. Mean heart rate, SDNN, SDANN, and triangular index values were obtained from time domain analysis of the 24-hour ECG recordings.

Transthoracic echocardiography

Transthoracic echocardiography was performed in each case using a standard echocardiography device (Philips HD 11 XE, Philips Healthcare Eindhoven, Netherlands) in the left lateral decubitus position at the time of the diagnosis. Standard echocardiographic measurements and LVH parameters were assessed: interventricular septum and posterior wall thickness, LV mass, LV mass index (indexed to body surface area). Measurements of interventricular septum and posterior wall thicknesses were made from a parasternal long-axis acoustic window. LVH parameters were calculated according to the criteria and formulae of the American Society of Echocardiography.[12] LVH is defined as an increase in the mass of the left ventricle that is secondary to an increase in wall thickness. The estimation of LV mass is derived from LV measurements obtained by two-dimensional echocardiography. According to guideline recommendations, LVH is defined as follows:

- Estimated LV mass of 201 to 227 g (103 to 116 g/m^2) for men and 151 to 171 g (89 to 100 g/m^2) for women is mildly abnormal;
- Estimated LV mass of 228 to 254 g (117 to 130 g/m^2) for men and 172 to 182 g (101 to 112 g/m^2) for women is moderately abnormal;

- Estimated LV mass >255 g (>131 g/m^2) for men and >193 g (>113 g/m^2) for women is severely abnormal.

Statistical analysis

Data were expressed as mean ± standard deviation for HRV measures. The chi-square test was used to compare demographic and clinical characteristics. The independent samples t-test was used to compare HRV values and LV echocardiographic parameters between groups. The level of statistical significance accepted was p<0.05. Data were analyzed using SPSS 17.0 software (SPSS IBM, Chicago, IL, USA).

Results

Demographic and clinical characteristics were similar between the groups (Table 1). Levels of systolic (175.6 ± 13.6 mmHg vs. 177.1 ± 10.7 mmHg, p=0.47) and diastolic BP (98 ± 7.4 mmHg vs. 98.1 ± 8.5 mmHg, p=0.92) were similar between the groups. The number of antihypertensive drugs per patient (3.9 ± 0.6 vs. 3.8 ± 0.6; p=0.46) and medications according to drug classes were similar between the groups. In particular, the rate of beta-blocker use (88% vs. 92.5%, p=0.41), which could affect sympathetic activity, did not differ between the groups.

Table 2 shows a comparison of the left ventricular structural echocardiographic parameters between the groups. Interventricular septum and posterior wall thickness, left ventricular mass, and left ventricular mass index values were significantly higher in the RH/LVH(+) group than in the RH/LVH(-) group.

All of the time domain HRV values, SDNN (119.1 ± 34.6 vs. 138.1 ± 42.9, p=0.004), SDANN (108.1 ± 41.6 vs. 127.9 ± 45.1, p=0.007), and triangular index (31.2 ± 10.5 vs. 36.3 ± 11.1, p=0.006), were

Table 1. Comparison of demographic and clinical characteristics between groups.

	RH/LVH(+) n=75	RH/LVH(-) n=67	p
Age	63.1 ± 13.5	59.3 ± 19.2	0.21
Male	25 (33.3%)	19 (28.4%)	0.58
BMI, kg/m^2	26.8 ± 3.6	26.39 ± 4.0	0.45
Type-2 diabetes	29 (38.7%)	32 (47.8%)	0.31
Hypercholesterolemia	56 (74.7%)	46 (68.7%)	0.45
Smoking	40 (53.3%)	39 (58.2%)	0.61
Atrial fibrillation	6 (8%)	10 (14.9%)	0.28
Coronary artery disease	28 (37.3%)	18 (26.9%)	0.21
Systolic BP, mmHg	175.6 ± 13.6	177.1 ± 10.7	0.47
Diastolic BP, mmHg	98 ± 7.4	98.1 ± 8.5	0.92
Stroke	8 (10.7%)	5 (7.5%)	0.57
No. of antihypertensive drugs	3.9 ± 0.6	3.8 ± 0.6	0.46
Patients receiving (drug class):			
ACE inhibitors/ARBs	74 (98.7%)	64 (95.5%)	0.34
Beta-blockers	66 (88%)	62 (92.5%)	0.41
Calcium channel blockers	50 (66.7%)	47 (70.1%)	0.71
Diuretics	75 (100%)	67 (100%)	1.00
Alpha-blockers	19 (25.3%)	16 (23.9%)	1.00
Central acting antihypertensives	11 (14.7%)	5 (7.5%)	0.19

BMI – body mass index; BP – blood pressure; ACE – angiotensin–converting enzyme; ARB – angiotensin receptor blocker; RH – resistant hypertension; LVH – left ventricular hypertrophy.

Table 2. Comparison of echocardiographic parameters between groups.

	RH/LVH(+) n=75	RH/LVH(-) n=67	p
IVS, mm	13 ± 1.6	9.7 ± 1.2	<0.001
PW, mm	12.6 ± 1.4	9.6 ± 1.0	<0.001
LV mass, g	250.4 ± 57.2	157.1 ± 36.6	<0.001
LV mass index, g/m^2	136.2 ± 27.6	87.6 ± 19.8	<0.001

IVS – interventricular septum; PW – posterior wall; LV – left ventricle; RH – resistant hypertension; LVH – left ventricular hypertrophy.
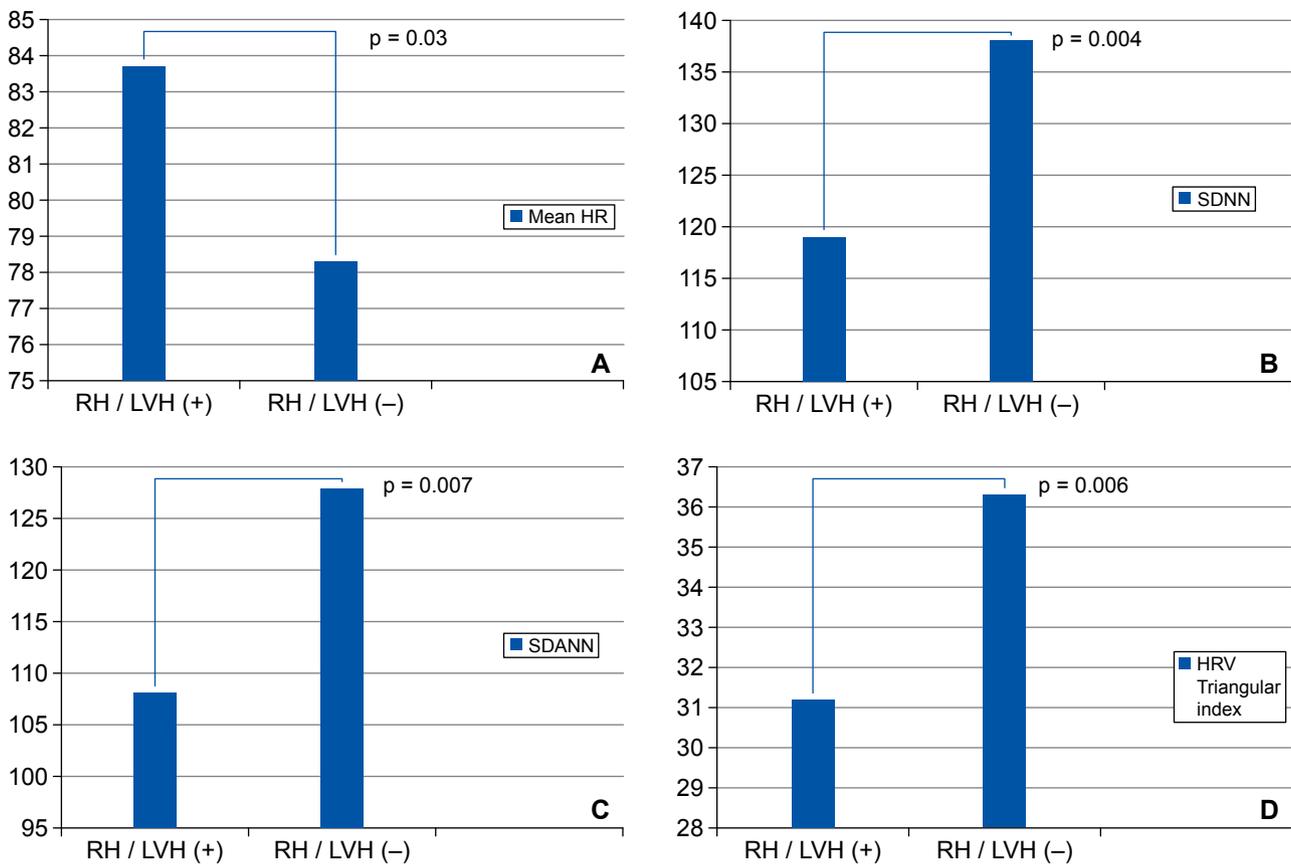
Figure 1. Comparison of mean heart rate (HR) and heart rate variability (HRV) values between groups. A. Mean HR. B. Standard deviation of NN intervals (SDNN). C. Standard deviation of all five minute NN intervals (SDANN). D. HRV triangular index.

significantly lower, whereas mean heart rate (83.7 ± 16.4 vs. 78.3 ± 12.4, p=0.03) was significantly higher in the RH/LVH(+) group (Figure 1). This result reflects clear sympathetic predominance in the RV/LVH(+) group compared to the RH/LVH(-) group.

Discussion

LVH can lead to diastolic dysfunction and, if hypertension is not adequately controlled, diastolic heart failure can develop. It has been previously shown that sympathetic overactivity plays an important role in the progression of hypertension and target organ damage.[13] However, as a specific subgroup, the effect of sympathetic system overactivity on LVH in RH deserves special attention. As invasive treatment modalities such as renal denervation become more popular, it is essential to examine the association between sympathetic overactivity and left ventricular structural changes in RH.

In our study, we divided resistant hypertensive patients into two groups according to echocardio-

graphic LVH criteria. We determined the grade of sympathetic overactivity using time domain HRV parameters in these patients, and found greater sympathetic activity in the RH/LVH(+) group than in the RH/LVH(-) group, independent of blood pressure level. Since factors that can affect the sympathetic state, such as age, sex, body mass index, history of type 2 diabetes, coronary heart disease, and use of blood pressure-lowering medications related to the sympathetic system, were similar in both groups, we believe that we can meaningfully compare the sympathetic activity between groups.

In RH, the etiology of LVH is multifactorial. The main mechanisms are pressure overload and neurohumoral factors that play a role in hypertension. Mediators like angiotensin II, prorenin, aldosterone, and norepinephrine accelerate cardiac hypertrophy and fibrosis. Clinical studies have shown significant correlations between circulating norepinephrine levels and LV mass.[14] In our study, LVH can be simply linked to greater sympathetic activity in the RH/LVH(+) group, but the interesting point is that BP

levels, which are greatly influenced by sympathetic overactivity, were similar in both groups. Thus, other mechanisms independent of BP level played a role in LVH in our RH/LVH(+) group.

The renin–angiotensin–aldosterone system (RAAS) plays a direct role in LVH. LV mass increases significantly in primary aldosteronism and renovascular hypertension compared with essential hypertension.[15] There is also a positive correlation between plasma aldosterone levels and LVH, independent of BP levels.[16] Some RAAS blockers have been proved to regress LVH in clinical studies.[17,18] The rate of RAAS blocker use was similar between our groups of patients, so this could not have biased the results. However, since patients in the RH/LVH(+) group in our study had greater sympathetic activity, their RAAS activity could have been higher and could have led to LVH without any difference in BP levels. Screening for conditions causing high angiotensin-2 and aldosterone may be valuable to differentiate the etiology of the RH/LVH(+) group.

Diabetes and insulin resistance is another causative factor for LVH. There are many studies that have revealed an association between insulin-like growth factor-1 and LV mass, independent of BP level.[19] In our study, the incidence of diabetes was similar between groups, but the degree of insulin resistance and levels of insulin-like growth factor-1 may have varied among the patients. Higher sympathetic activity can partially influence LVH via a higher insulin resistance mechanism, independently of a rise in BP. Thus, RH patients with serious LVH must be carefully screened for impaired glucose tolerance and uncontrolled diabetes.

Renal denervation is a new catheter-based system for treating RH. Catheter-based sympathetic denervation of the bilateral renal arteries is associated with significant BP reductions and is generally accepted as a safe procedure.[20,21] According to pilot studies, renal denervation has beneficial effects on LVH in RH.[8] A recent echocardiographic study showed that LVH and diastolic function improved six months after renal denervation without a significant relation to systolic BP in resistant hypertensives.[22] A more sensitive cardiac magnetic resonance study showed that renal denervation significantly reduced LV mass index, partly independently of BP level.[23] In this study, LV mass index was reduced in 15 of 18 patients who had a change in systolic blood pressure <10 mmHg six months after renal denervation. In light of our results, we can say that greater sympathetic overactivity can induce LVH and sympatholytic renal denervation therapy can reduce it, independently of BP level, in this patient group. In addition, our RH/LVH(+) group had greater sympathetic activity, so it can be postulated that this patient group was able to gain more benefit from renal denervation. In this group of patients, renal denervation was able to both reduce BP levels and regress LV mass effectively. Our study did not directly concern renal denervation therapy, but if the link between sympathetic overactivity and LVH becomes stronger, the indications for and beneficial effects of renal denervation therapies can be better evaluated.

However, some negative trials have also been published in recent years concerning renal denervation. The SYMPLICITY registry showed that the reduction in BP with renal denervation was below accepted levels in a selected population.[24] Finally, in the landmark SYMPLICITY HTN 3 trial, which randomized 535 treatment-resistant hypertensive patients, renal denervation therapy failed to achieve its primary efficacy endpoint.[25] However, the SYMPLICITY HTN 3 trial was primarily designed for the BP-lowering effect of renal denervation, not for the purpose of LVH regression. The impact of renal denervation on LVH in this patient group requires further analysis. Therefore, a prospective study examining HRV values and LV mass, both before and after renal denervation therapy, in RH/LVH(+) patients could be helpful in detecting the real effect of the therapy.

Our study has some limitations. In some studies, the rate of pseudo-resistant hypertension (white coat effect and non-compliance) can rise to 40%.[26] Therefore, defining the true resistant hypertensives is a difficult issue. Since ambulatory BP measurement is accepted as a more valuable tool in the diagnosis and follow up of RH,[27] categorizing the patients according to office BP values is a disadvantage of our study. Although we excluded patients with comorbidities that could affect LVH, the multifactorial origin of this pathology might have affected our results. Since our study was cross-sectional, its results cannot conclusively establish a causative relationship between autonomic dysfunction and LVH.

Conclusions

Our study included patients whose systolic blood pressure was over 160 mmHg. Since patients in this study are potential candidates for renal sympathetic denervation, the results of our study can make a

contribution to this field. The mechanism leading to LVH in resistant hypertensive patients currently eludes our understanding and is therefore an area that requires much more investigation to enhance our insight. Beyond pathophysiology, further studies that examine the effect of renal denervation on LVH are needed.

References

1. Persell SD. Prevalence of resistant hypertension in the United States, 2003-2008. Hypertension. 2011; 57: 1076-1080.
2. Grassi G. Role of the sympathetic nervous system in human hypertension. J Hypertens. 1998; 16: 1979-1987.
3. Anderson EA, Sinkey CA, Lawton WJ, Mark AL. Elevated sympathetic nerve activity in borderline hypertensive humans: evidence from direct intraneural recordings. Hypertension. 1988; 14: 177-183.
4. DiBona GF, Kopp UC. Neural control of renal function. Physiol Rev. 1997; 77: 75-197.
5. Redfield MM, Jacobsen SJ, Burnett JC Jr, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA. 2003; 289: 194-202.
6. Cuspidi C, Vaccarella A, Negri F, Sala C. Resistant hypertension and left ventricular hypertrophy: an overview. J Am Soc Hypertens. 2010; 4: 319-324.
7. Korovesis S, Giazitzoglou E, Pantos I, et al. Renal denervation for resistant hypertension: acute results and long-term follow-up. Hellenic J Cardiol. 2014; 55: 211-216.
8. Brandt MC, Mahfoud F, Reda S, et al. Renal sympathetic denervation reduces left ventricular hypertrophy and improves cardiac function in patients with resistant hypertension. J Am Coll Cardiol. 2012; 59: 901-909.
9. Wu JS, Lu FH, Yang YC, et al. Epidemiological study on the effect of pre-hypertension and family history of hypertension on cardiac autonomic function. J Am Coll Cardiol. 2008; 51: 1896-1901.
10. Rothschild AH, Weinberg CR, Halter JB, Porte D Jr, Pfeifer MA. Sensitivity of R-R variation and Valsalva ratio in assessment of cardiovascular diabetic autonomic neuropathy. Diabetes Care. 1987; 10: 735-741.
11. Pierdomenico SD, Bucci A, Costantini F, Lapenna D, Cuccurullo F, Mezzetti A. Twenty-four-hour autonomic nervous function in sustained and "white coat" hypertension. Am Heart J. 2000; 140: 672-677.
12. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005; 18: 1440-1463.
13. Malpas SC, Maling TJ. Heart-rate variability and cardiac autonomic function in diabetes. Diabetes. 1990; 39: 1177-1181.
14. Marcus R, Krause L, Weder AB, Dominguez-Meja A, Schork NJ, Julius S. Sex-specific determinants of increased left ventricular mass in the Tecumseh Blood Pressure Study. Circulation. 1994; 90: 928-936.
15. Rizzoni D, Muiesan ML, Porteri E, et al. Relations between cardiac and vascular structure in patients with primary and secondary hypertension. J Am Coll Cardiol. 1998; 32: 985-992.
16. Schlaich MP, Schobel HP, Hilgers K, Schmieder RE. Impact of aldosterone on left ventricular structure and function in young normotensive and mildly hypertensive subjects. Am J Cardiol. 2000; 85: 1199-1206.
17. Devereux RB, Dahlöf B, Gerdts E, et al. Regression of hypertensive left ventricular hypertrophy by losartan compared with atenolol: the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial. Circulation. 2004; 110: 1456-1462.
18. Schneider MP, Klingbeil AU, Delles C, et al. Effect of irbesartan versus atenolol on left ventricular mass and voltage: results of the CardioVascular Irbesartan Project. Hypertension. 2004; 44: 61-66.
19. Verdecchia P, Reboldi G, Schillaci G, et al. Circulating insulin and insulin growth factor-1 are independent determinants of left ventricular mass and geometry in essential hypertension. Circulation. 1999; 100: 1802-1807.
20. Schlaich MP, Esler MD, Fink GD, Osborn JW, Euler DE. Targeting the sympathetic nervous system: critical issues in patient selection, efficacy, and safety of renal denervation. Hypertension. 2014; 63: 426-432.
21. Stefanadis CI. Management of arterial hypertension: from no treatment to renal denervation. Hellenic J Cardiol. 2015; 56: 277-278.
22. Schirmer SH, Sayed MM, Reil JC, et al. Improvements in left ventricular hypertrophy and diastolic function following renal denervation: effects beyond blood pressure and heart rate reduction. J Am Coll Cardiol. 2014; 63: 1916-1923.
23. Mahfoud F, Urban D, Teller D, et al. Effect of renal denervation on left ventricular mass and function in patients with resistant hypertension: data from a multi-centre cardiovascular magnetic resonance imaging trial. Eur Heart J. 2014; 35: 2224-31b.
24. Böhm M, Mahfoud F, Ukena C et al; GSR Investigators. First report of the Global SYMPLICITY Registry on the effect of renal artery denervation in patients with uncontrolled hypertension. Hypertension. 2015; 65: 766-774.
25. Bhatt DL, Kandzari DE, O'Neill WW, et al. A controlled trial of renal denervation for resistant hypertension. N Engl J Med. 2014; 370: 1393-1401.
26. Taddei S, Bruno RM. Renal denervation: still more questions than answers. J Hypertens. 2014; 32: 28-29.
27. Grassi G, Bombelli M, Seravalle G, Brambilla G, Dell'oro R, Mancia G. Role of ambulatory blood pressure monitoring in resistant hypertension. Curr Hypertens Rep. 2013; 15: 232-237.