

## Editorial Comment

# Sympathetic Nervous System Activation and Left Ventricular Hypertrophy: Reflections of the Same Portrait of Resistant Hypertension?

COSTAS TSIIOUFIS, KYRIAKOS DIMITRIADIS, DIMITRIS TOUSOULIS

*First Cardiology Clinic, University of Athens, Hippokraton Hospital, Athens Greece*

Key words:  
**Sympathetic  
 overdrive, cardiac  
 adaptations,  
 resistant  
 hypertension.**

**A**ccording to the World Health Report 2002, suboptimal blood pressure (BP) control is the most common attributable risk for death worldwide, being responsible for 62% of cases of cerebrovascular disease and 49% of cases of ischemic heart disease.<sup>1</sup> Moreover, persistent resistant hypertension is accompanied by an almost threefold increase in cardiovascular risk, compared to never-resistant hypertensive patients during a follow up of 4 years.<sup>2</sup> An understanding of the mechanisms involved in the pathophysiology of treatment resistance and the development of its phenotype is crucial for achieving more effective therapeutic strategies (Figure 1).

The development of novel and sophisticated techniques for the direct and indirect assessment of adrenergic activity has changed our conception of the role of the sympathetic nervous system (SNS) in the regulation of BP, from a short-term regulator to a cornerstone of the pathogenesis and pathophysiology of hypertension.<sup>3</sup> Nowadays, the established theory is that SNS hyperactivity contributes to the initiation, maintenance and progression of hypertension.<sup>3,4</sup>

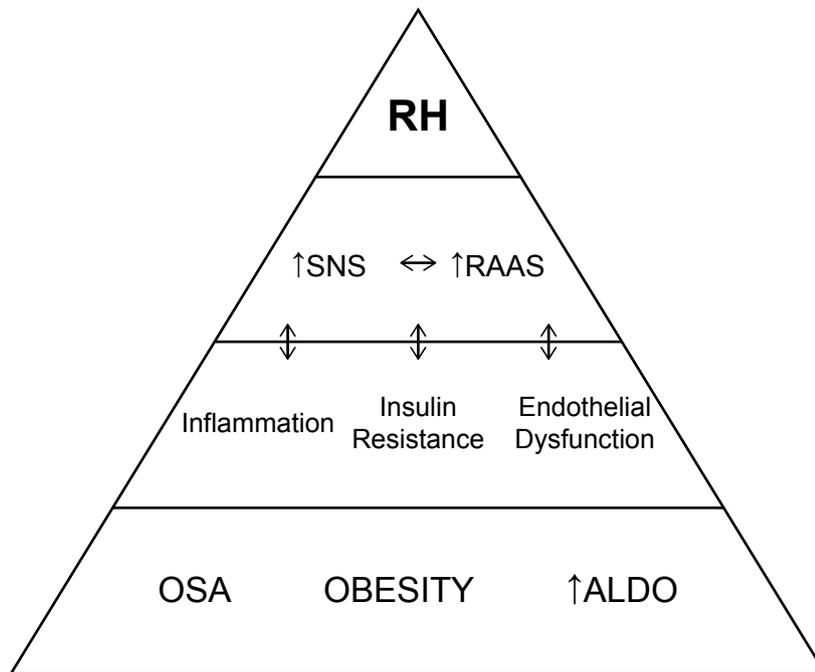
More specifically, increased SNS activity has been documented in systolic–diastolic and isolated systolic hypertension, in white coat and masked hypertension, and

in dipping conditions.<sup>3,5</sup> Furthermore, SNS activity increases progressively and in parallel with hypertension stages. This implies that the more advanced the stage of hypertension, the greater the adrenergic activity.<sup>5</sup> Whether this correlation could be extended to resistant hypertension remains unclear, given that the SNS activity in resistant hypertensives has been assessed in subgroups of populations of intervention studies without comparison with healthy controls.

In their study published in this issue of the HJC, Özel et al<sup>6</sup> investigated the relationship between SNS overactivity and left ventricular hypertrophy in resistant hypertension and found greater SNS activity in patients with left ventricular hypertrophy than in those without. Estimation of sympathetic drive was based on the mean heart rate and time domain heart rate variability, rather indirect indexes. Elevated heart rate values may depend not only on an augmented adrenergic outflow to the heart, but also on a reduced parasympathetic inhibition of sinus node activity.<sup>4</sup> In addition, power spectral analysis, a sophisticated mathematical approach, recognizes the high-frequency component in heart rate variability, determined primarily by vagal function, whereas low-frequency variability in heart rate does not strictly provide a measure of the rate of firing of the cardiac sympathetic nerves.<sup>4</sup> It pri-

Address:  
 Costas Tsioufis

3 Kolokotroni St.  
 152 36 Athens, Greece  
[ktsioufis@hippocratio.gr](mailto:ktsioufis@hippocratio.gr)



**Figure 1.** A “pyramid” of the main pathophysiological mechanisms involved in resistant hypertension phenotype, in which sympathetic nervous system overdrive plays a key role.

RH – resistant hypertension; SNS – sympathetic nervous system; RAAS – renin–aldosterone–angiotensin system; OSA – obstructive sleep apnea; ALDO – aldosterone.

marily investigates the baroreflex mechanisms and autonomic effector processes underlying circulatory rhythmicity, which bear no necessary relation to neural sympathetic drive.<sup>5</sup> More sophisticated methods, such as spill-over norepinephrine and muscle sympathetic nerve activity recording, have shown a close association between sympathetic overdrive and pronounced target organ damage (i.e. left ventricular hypertrophy, kidney dysfunction).<sup>2,5</sup>

The paper shares the common limitations of studies focused on populations with resistant hypertension.<sup>7,8</sup> First, the definition was based solely on office BP measurements that were not confirmed by

ambulatory recordings to exclude those with “white-coat” resistance. Second, any significant confounding effect of drugs on sympathetic activation and left ventricular geometry cannot be excluded. Third, left ventricular mass was not indexed for height, which is more accurate in patients with this phenotype.<sup>9</sup>

Despite the above limitations, the present work is of importance, since it highlights the close link between sympathetic overactivity and left ventricular hypertrophy in the setting of resistant hypertension. This strengthens the rationale for interventions to suppress SNS activity in hypertension and ameliorate cardiac organ damage (Table 1).<sup>2,9, 11-13</sup>

**Table 1.** Studies of sympathetic modulation’s effect on left ventricular mass in patients with resistant hypertension

Study	Time of follow up	Office systolic and diastolic BP reductions after neuromodulation	Method of LV mass estimation	LV mass changes
Brandt MC, et al. <sup>11</sup>	6 months	-27.8/-8.8 mmHg	Echocardiography	LV mass index from $53.9 \pm 15.6 \text{ g/m}^{2.7}$ ( $112.4 \pm 33.9 \text{ g/m}^2$ ) to $44.7 \pm 14.9 \text{ g/m}^{2.7}$ ( $94.9 \pm 29.8 \text{ g/m}^2$ ) ( $p < 0.001$ )
Doltra A, et al. <sup>12</sup>	6 months	-17.2/-5.2 mmHg	Cardiac MRI	LV mass index from $41.83 \pm 10.20 \text{ g/m}^{1.7}$ to $37.72 \pm 7.44 \text{ g/m}^{1.7}$ ( $p = 0.001$ )
Mafhoud F, et al. <sup>13</sup>	6 months	-22/-8 mmHg	Cardiac MRI	LV mass index from $46.3 \pm 13.6 \text{ g/m}^{1.7}$ to $43.0 \pm 12.6 \text{ g/m}^{1.7}$ ( $p < 0.001$ )
Tsioufis C, et al. <sup>9</sup>	6 months	-42/16 mmHg	Echocardiography	LV mass index from $136.1 \pm 20.1 \text{ g/m}^2$ ( $56.5 \pm 8.7 \text{ g/m}^{2.7}$ ) to $122.8 \pm 22.2 \text{ g/m}^2$ ( $51.2 \pm 9.2 \text{ g/m}^{2.7}$ ) ( $p = 0.004$ )

BP – blood pressure; LV – left ventricular; MRI – magnetic resonance imaging.

## References

1. World Health Organization. World Health Report 2002: Reducing Risks, Promoting Healthy Life, World Health Organization, Geneva, Switzerland, 2002
2. Tsioufis C, Kasiakogias A, Kordalis A, et al. Dynamic resistant hypertension patterns as predictors of cardiovascular morbidity: a 4-year prospective study. *J Hypertens.* 2014; 32: 415-422.
3. Tsioufis C, Kordalis A, Flessas D, et al. Pathophysiology of resistant hypertension: the role of sympathetic nervous system. *Int J Hypertens.* 2011; 2011: 642416.
4. Seravalle G, Dimitriadis K, Dell'Oro R, Grassi G. How to assess sympathetic nervous system activity in clinical practice. *Curr Clin Pharmacol.* 2013; 8: 182-188.
5. Grassi G, Seravalle G, Mancia G. Sympathetic activation in cardiovascular disease: Evidence, Clinical Impact and Therapeutic Implications. *Eur J Clin Invest.* 2015 Oct 19. doi: 10.1111/cci.12553. [Epub ahead of print]
6. Özel E, Taştan A, Öztürk A, Özcan EE. Relationship between sympathetic overactivity and left ventricular hypertrophy in resistant hypertension. *Hellenic J Cardiol.* 2015; 56: 501-506.
7. Bhatt DL, Kandzari DE, O'Neill WW, et al; SYMPPLICITY HTN-3 Investigators. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med.* 2014; 370: 1393-1401.
8. Tsioufis CP, Papademetriou V, Dimitriadis KS, et al. Catheter-based renal denervation for resistant hypertension: Twenty-four month results of the EnligHTN™ I first-in-human study using a multi-electrode ablation system. *Int J Cardiol.* 2015; 201: 345-350.
9. Tsioufis C, Papademetriou V, Dimitriadis K, et al. Effects of multielectrode renal denervation on cardiac and neurohumoral adaptations in resistant hypertension with cardiac hypertrophy: an EnligHTN I substudy. *J Hypertens.* 2015; 33: 346-353.
10. Tsioufis C, Dimitriadis K, Tsiachris D, et al. Catheter-based renal sympathetic denervation for the treatment of resistant hypertension: first experience in Greece with significant ambulatory blood pressure reduction. *Hellenic J Cardiol.* 2012; 53: 237-241.
11. 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.
12. Doltra A, Messroghli D, Stawowy P, et al. Potential reduction of interstitial myocardial fibrosis with renal denervation. *J Am Heart Assoc.* 2014 Dec;3(6):e001353. doi: 10.1161/JAHA.114.001353.
13. 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.