To the Editor:

We read with great interest the article by Schlaich et al.1 dealing with the issue of sympathetic augmentation in hypertension. In 1993, we demonstrated that neural sympathetic activity predominance is registered in essential hypertensive patients.2 These findings were supported by the overwhelming circulating noradrenaline (NA) versus adrenaline (Ad) levels registered throughout the oral glucose tolerance test. This NA versus Ad predominance has also been demonstrated through the supine-resting/1-minute orthostasis/5-minute moderate exercise test. This test is based on the findings of Robertson et al, who demonstrated that NA, but not Ad, peaks at 1-minute orthostasis. Thus, this test allowed the investigation of both neural and adrenal sympathetic release, separately. With respect to this, we have performed this test in some 25,000 normal and diseased subjects, and the results have been published in >50 research articles and in 3 books dealing with the autonomic nervous system.3,4 Our results might be summarized as follows: the normal NA/Ad plasma ratio is lower than 2 during the supine-resting situation. This NA/Ad ratio rises to 3 to 4 in normal subjects during 1-minute orthostasis. The NA/Ad ratio does not increase, but decreases in nonessential hypertensive and/or stressed subjects, despite the global assessment that plasma catecholamines show significant increases. Conversely, essential hypertensive patients show great NA rise but none or poor Ad rise at 1-minute orthostasis. Thus, the NA/Ad ratio shows maximal increase, reaching levels >8. Plasma dopamine (DA) values do not increase in essential hypertensive patients. Thus, the NA/DA ratio shows significant rise at the 1-minute orthostasis test. The opposite NA/DA profile is registered in neurogenic hypotension. This issue should be associated with the very well-known fact that DA modulatory pool exists at sympathetic terminals, and, acting at DA-2 presynaptic inhibitory receptors, is able to regulate the NA release from those terminals. Finally, in our experience, the measurement of circulating neurotransmitters in accordance with the orthostasis test is the more accurate procedure to differentiate neural sympathetic activity from adrenal-gland sympathetic activity. The former depends on the locus coeruleus (LC) pontine-NA nucleus, and the latter is ruled directly by medullary Cl-Ad nuclei. Additional information comes from the assessment of circulating indolamines. Free-serotonin in the plasma is raised in nonessential hypertensive, but not in essential hypertensive, patients. This phenomenon correlates with the raised Ad plasma levels responsible for the increased platelet aggregation that we also find in the former group. In addition to the above, we demonstrated that Ad, but not NA, plasma level shows an absolute fall during the rapid-eye-movement sleep stage in both essential hypertensive patients and essential hypertensive rats.4 Conversely, both NA and Ad reach almost zero values in nonessential hypertensive patients at this period. These findings are consistent with the well known fact that essential hypertensive humans and rats do not show the zero-firing activity of the LC-NA neurons necessary for the occurrence of rapid-eye-movement sleep stage.5 In effect, this sleep stage is not registered in them.1,4

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Response: Neural Sympathetic Activity in Essential Hypertension

We thank Prof Lechin et al for their interest in our study investigating mechanisms of sympathetic activation in hypertension.1 In his letter, Prof Lechin summarizes the vast experience of his group in assessing neural and adrenal sympathetic release in normal and diseased subjects. Prof Lechin’s group investigated the regulation of circulating plasma catecholamine and indolamine levels in response to various tests and revealed that the response to orthostasis, in particular, differs between normotensive and hypertensive subjects. Their work certainly contributed to our understanding of sympathetic neural and adrenal regulation in health and disease. However, plasma catecholamine ratios are only poor markers of sympathetic activation and do not account for regionalization of sympathetic activation, which is crucial when trying to investigate mechanisms of sympathetic augmentation in essential hypertension. In this context we have demonstrated that cardiac sympathetic activity is increased in essential hypertension and that the increased noradrenaline release contributes to cardiac structural changes typically evident in this patient group.2 We have also previously investigated the issue whether adrenaline acts as a sympathetic nervous cotransmitter, possibly enhancing cardiac noradrenaline release.3 Indeed, using a dual isotope dilution methodology, our group could demonstrate that adrenaline is released from the heart in patients with essential hypertension.
and that a proportionality exists between the rates of cardiac noradrenaline and adrenaline release.

In conclusion, essential hypertension is typically associated with neural sympathetic activation. The regulation of sympathetic tone and the mechanisms underlying sympathetic augmentation in essential hypertension are quite complex, depend on the region studied, and appear to include increased sympathetic nerve firing rates, reduced norepinephrine reuptake, adrenaline cotransmission, and several other factors.1

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