Sildenafil Does Not Influence Autonomic Neurocardiac Control Assessed by Standard Measurements of Heart Rate Variability

To the Editor:

Recently, an excellent study by Phillips and colleagues\(^1\) showed a significant increase in muscle sympathetic nerve activity (MSNA) in healthy young men after a single 100-mg dose of sildenafil. The MSNA increase did not, however, result in an increase in heart rate, from which the authors concluded that the sympathetic activation they observed was selective for the vascular sympathetic drive only. Given the highly differentiated nature of autonomic efferent activity, the measurement of MSNA as a pure index of peripheral sympathetic outflow might allow no definitive conclusions to be made about the autonomic control of the sinoatrial node.

A noninvasive method for evaluating autonomic neurocardiac control involves standardized investigations of heart rate variability (HRV). We recently investigated the 5-minute resting HRV. Measurements were obtained according to previously published protocols\(^2,3\) before and 90 minutes after a test dose of sildenafil (25 to 50 mg) in 21 men with an average age of 53.7 ± 11.5 years (M.W. Agelink, MD, et al., manuscript in preparation, 2000). Sildenafil exerted no notable influence on the spectral low frequency (0.04 to 0.15 Hz) and high frequency (0.15 to 0.4 Hz) components assessed in absolute and normalized units; the sympathovagal balance expressed as the low/high frequency ratio was not displaced by sildenafil (4.3 ± 2.9 before versus 4.7 ± 3.3 after sildenafil; \(P = 0.7\)). If one accepts the normalized low frequency power and the low/high frequency ratio as reasonable reflections of central nervous sympathetic outflow to the sinoatrial node, our results indicate that sildenafil does not influence the cardiac sympathetic resting tone or the sympathovagal balance. There was, however, a mean 8.9% reduction of systolic blood pressure combined with a mean 5.8% increase in heart rate 90 minutes after dosing with sildenafil, which suggests that the blood pressure decrease under sildenafil in older patients is more marked than in younger patients. Thus, an increased vascular sympathetic drive after application of sildenafil (expressed in the study of Phillips et al\(^1\) as a sildenafil-induced increase in MNSA burst frequency) may be important in opposing the systemic vasodilator effects of sildenafil and maintaining blood pressure levels.

Ben-David and Zipes\(^4\) emphasized that autonomic nervous system integrity is important for preventing, promoting, or precipitating cardiac arrhythmias and sudden cardiac death. Vagal activity seems to have myocardio protecti ve and anti-arrhythmogenic effects, which arise, on the one hand, because of direct inhibition of the myocardium and, on the other, through interference with sympathetic neurons.\(^5\) Against this background, the observation that sildenafil does not influence HRV and neurocardiac balance is certainly worthy of attention in the as-yet unresolved debate concerning a potential relationship between the autonomic nervous system effects of sildenafil and cases of sudden cardiovascular death.

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Response

We very much appreciate the interest of Drs Agelink, Brockmeyer, and Ulrich in our work.\(^1\) They are correct in that direct measures of sympathetic traffic to peripheral blood vessels do not necessarily provide accurate insights into the autonomic control of the sinoatrial node. Differential activation of the autonomic nervous system occurs in a number of situations, including REM sleep\(^2\) and the diving reflex.\(^3\) Even in healthy normal humans studied during resting conditions, there is considerable complexity in the interaction between sympathetic traffic and heart rate and their relative influences on blood pressure levels.\(^4\)

The interesting data described by Agelink and colleagues do indeed suggest the possibility of an age-dependent potentiation in the hemodynamic effects of sildenafil. The relatively modest increase in heart rate in the setting of a presumed 10 to 15 mm Hg reduction in blood pressure is also quite intriguing. We thank these investigators for sharing their data with us.

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