Letter to the Editor

Nitrovasodilators and heart rate: more than the arterial baroreflex

P. Musialek* , B. Casadei

Department of Cardiovascular Medicine, John Radcliffe Hospital, University of Oxford, Oxford OX3 9DU, UK

Received 5 May 2000; accepted 11 May 2000

We read with interest a recent study by Mésangeau et al. [1], which evaluates the development of cardiovascular autonomic neuropathy in a pig model of streptozotocin-induced diabetes.

In addition to spectral analysis of short-term arterial blood pressure (ABP) and heart rate (HR) variability, this investigation involved determination of the baroreceptor-HR reflex with vasoactive drugs. The sensitivity of the baroreceptor-HR reflex was calculated by plotting the HR response to changes in ABP obtained by a graded infusion (40–60 min) of the α-adrenoceptor agonist phenylephrine (used to increase ABP) or of the nitrovasodilator sodium nitroprusside (SNP; used to reduce ABP).

As a further contribution to the discussion on the use of nitrovasodilators to test baroreflex sensitivity [2], we would like to draw attention to the recent discovery of several extra-vascular actions of nitrovasodilators which may confound assessment of the baroreceptor-HR reflex. Nitrovasodilators have been shown to exert most of their biological effects by releasing nitric oxide (NO); thus at present these drugs are frequently referred to as ‘NO donors’ [3].

The principle behind employing NO donors to test the baroreceptor-HR reflex has been to achieve a reduction in blood pressure (and thus unload arterial baroreceptors) without directly affecting cardiac pacemaker activity, baroreflex transmission or the activity of autonomic nervous system. Although it is well-established that the NO-mediated vascular relaxation is the major effect of NO donors in the cardiovascular system [3], recent data indicate that exogenous NO may exert several other important actions. For instance, NO donors can inhibit peripheral sympathetic neurotransmission by reducing the synaptic release of noradrenaline [4,5]. Moreover, both exogenous and endogenous NO may contribute to the cholinergic antagonism of the positive chronotropic response to adrenergic stimulation [6,7], possibly by interfering with the β-adrenergic signal transduction pathway in the sinoatrial node (see e.g. Ref. [8]). In addition, large concentrations of exogenous NO can directly suppress baroreceptor activity [9,10] and affect baroreflex transmission in the central nervous system (though the functional relevance of these effects is still controversial; reviewed in Ref. [11]). Finally, NO donors have been shown to directly (i.e. independent of their effects on the autonomic nervous system) increase HR through a NO–cGMP-mediated stimulation of the pacemaker current \( I_f \) in isolated sinoatrial node cells and spontaneously beating atrial preparations [12,13]. Recent work indicates that the direct positive chronotropic effect of exogenous NO is functionally relevant in vivo, both in animals [14,15] and in humans [16]. For instance, topical administration of SNP to the sinoatrial node in the pig heart in situ (Fig. 1) increases HR in the absence of changes in ABP [14]. Furthermore, i.v. infusion of SNP or molsidomine increases HR independent of autonomic activation in the rabbit [15] and in humans when ABP is clamped by simultaneous application of phenylephrine [16].

The net effect of these potentially confounding extravascular actions of nitrovasodilators (e.g. direct increase in HR, inhibition of sympathetic neurotransmission, and accentuation of vagal responses) on the assessment of the baroreceptor-HR reflex is difficult to predict.

In humans, graded infusion of SNP (0.125–2 \( \mu g \cdot kg^{-1} \cdot min^{-1} \)) plus phenylephrine (to clamp ABP) had no detectable effect on the baroreceptor-HR reflex determined by the spontaneous sequence method, despite a 12% increase in HR [16]. However, spectral analysis of ABP variability in these subjects suggests that sympathetic control of ABP may be attenuated during the SNP+
phenylephrine infusion, consistent with previous findings on the sympatholytic action of NO [4,5].

In conclusion, there is increasing evidence that extravascular actions of NO (including the direct stimulatory effect of NO on the sinoatrial node activity [12]) may affect the HR response to nitrovasodilators. However, further studies will be needed to assess the impact of these potential confounders on the measurement of the baroreceptor-HR reflex.

References