CROSSTALK

CrossTalk proposal: Bradycardia in the trained athlete is attributable to high vagal tone

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Endurance trained athletes are well known to have low resting heart rates, with values below 30 beats min^{-1} reported. Such low resting heart rates result from long periods of endurance training (Carter *et al.* 2003). We argue here that an increase in cardiac parasympathetic activity (vagal tone) is a major contributor.

The factors contributing to heart rhythm are complex but essentially there are three, the cardiac parasympathetic (vagal) nerves, the sympathetic nerves and the pacemaker cells, that set the intrinsic rate. At rest in healthy individuals the heart rate is determined by the balance between a high parasympathetic and low sympathetic activity changing around a fixed intrinsic pacemaker cell rhythm of around 105 beats min^{-1} or lower depending on age (Jose & Collison, 1970). In humans and many large animals such as dogs, pigs and horses resting heart rate is lower than the intrinsic pacemaker rate. In healthy young humans heart rates of 60–70 beats min^{-1} are common and atropine, given to block the effect of parasympathetic cholinergic nerves, results in increased heart rate to above the intrinsic rate (Maciel *et al.* 1985). This is not the case in small animals such as guinea pigs, rats and mice, which have high sympathetic tone, and resting heart rates of 300–700 beats min^{-1} are normal, with intrinsic rates from 170–500 beats min^{-1} (Mohan *et al.* 2000; Danson & Paterson, 2003; D'Souza *et al.* 2014).

Studies to determine the underlying mechanisms causing the lowering of heart rate following endurance training have provided different explanations. This is partly due to interpretation of non-uniform methodology and partly to the difficulty of obtaining direct measurements of autonomic neural activity in humans. However, we consider there are clear indications that training bradycardia is largely caused by an augmentation of parasympathetic influence on the pacemaker cells. We are persuaded because it appears that neural pathways are necessary for post training resting bradycardia. For example, Ordway *et al.* (1982) showed that dogs with the cardiac autonomic nerves removed had no decrease in resting heart rate after endurance training compared to a control group, although other measures of the mild exercise training were similar in both groups. Furthermore, removal of baroreceptor influence by sinoaortic denervation in rats prevents an endurance training-induced increase in baroreflex–heart rate sensitivity and decrease in resting heart rate (Ceroni *et al.* 2009).

To appreciate the evidence it is essential to understand the organization of cardiac parasympathetic control.

Cardiac vagal tone

Cardiac parasympathetic nerves in dogs and cats have a low frequency (5 Hz) burst pattern of basal activity (Koizumi *et al.* 1985) oscillating in phase with each cardiac beat and with a superimposed respiratory rhythm. Closer analysis of the cardiac preganglionic neurones in the brainstem by McAllen & Spyer (1978) has shown that the main generator of the activity is an excitatory input from the arterial baroreceptors via the nucleus of the tractus solitarius that fire during each heart beat. The effect of this excitatory input to cardiac preganglionic neurones is lessened during inspiration by an inhibitory input from nearby inspiratory neurones and increased during expiration (Gilbey *et al.* 1984). The magnitude of the respiratory-related rhythm is responsible for the fluctuations in heart rate known as respiratory sinus arrhythmia (RSA). Importantly there is a linear relationship between frequency of vagal activity and cardiac R–R interval (Parker *et al.* 1984) so that an increment of vagal firing would prolong the R–R interval by a fixed value independent of the initial R–R.

In humans indirect measurements of vagal tone based on RSA have been devised (e.g. Eckberg, 1983), developed and validated by animal studies (Katona & Jih, 1975). The most reliable indicator of vagal tone is that using frequency analysis of the cardiac beat known as power spectral analysis (PSA; Task Force of the European Society of Cardiology, North American Society of Pacing and Electrophysiology, 1996). PSA of heart rhythm reduces an R–R interval time series to its constituent sine wave frequency components. The spectral density of the signal describes the magnitude of the signal causing the variance at a particular frequency. It is the variation in the length of the inter-spike interval not the absolute length that is measured. In the spectrum the high frequency (HF) peak occurring at

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the individual's respiratory rate is abolished by atropine (Hollander & Bouman, 1975; Maciel *et al.* 1985) and by section of the vagus nerve in experimental animals (Ordway *et al.* 1982). A higher cardiac parasympathetic activity results in a more dominant respiratory rhythm so the HF peak is a robust surrogate for vagal tone (Fouad *et al.* 1984). However, it is only of significant quantitative value when changes in HF power are compared within a single individual and respiratory frequency and depth is controlled (Task Force, 1996).

With these caveats in mind a spectral analysis was done in a longitudinal study on a group of untrained young individuals who then underwent an aerobic endurance-training programme for 6 weeks. There was a marked and significant increase in HF power (Al-Ani *et al.* 1996) together with a significant decrease in resting heart rate. An enhanced vagal influence was further supported by measuring the immediate decrease in R–R interval in response to muscle contraction during a selected point in expiration and in inspiration. The immediate increase in heart rate caused by small muscle afferent fibres excited by muscle contraction occurs within the central nervous system. Therefore, their action reflects the excitability of neurones participating in the heart rate control circuits. Al-Ani *et al.* (1996) showed that the muscle-initiated decrease in R–R interval was significantly greater than the pre-training value. This is consistent with an increase in cardiac parasympathetic activity. The interpretation is supported by other studies showing that contraction-induced or exercise-induced immediate increase in heart rate is blocked by atropine (e.g. Maciel *et al.* 1985). The results accord with other longitudinal studies (Hottenrott *et al.* 2006). Thus these data strongly suggest an augmented contribution of cardiac parasympathetic nerve activity to training bradycardia.

Consistent with this Herrlich *et al.* (1960) showed that a training-induced decrease in resting heart rate in rats was associated with a considerable increase in atrial acetylcholine content. In accordance with this Paterson and his colleagues (Mohan *et al.* 2000; Danson & Paterson, 2003) have shown that presynaptic NO–cGMP-dependent acetylcholine release from cardiac parasympathetic terminals is enhanced in atria from exercise-trained mice. The cardiac parasympathetic NO–cGMP–cholinergic signalling pathway plays an important role in the induction of bradycardia in guinea pigs, rats, mice, dogs and humans (Sears *et al.* 1998; Herring & Paterson, 2001, 2009; Chowdhary *et al.* 2002; Markos *et al.* 2002). Thus these studies clearly show that exercise-induced resting bradycardia is at least in part dependent on changes in parasympathetic activity.

A similar conclusion is reached by studies testing the efficacy or sensitivity of the baroreceptor–heart rate reflex. Activity in single fibres of the cardiac vagus nerve is increased by arterial baroreceptor stimulation (Kunze, 1972) and baroreflex sensitivity is increased in aerobic exercise-trained individuals (e.g. Lenard *et al.* 2005). Furthermore, removal of baroreceptor influence by sinoaortic denervation in rats prevents a training-induced increase in baroreflex–heart rate sensitivity (Ceroni *et al.* 2009).

Cardiac sympathetic activity

Using radiotracers to measure cardiac noradrenaline spillover from the coronary sinus in humans before and after endurance training, Meredith *et al.* (1991) found no significant change. However, skeletal muscle and kidney sympathetic activity is reduced following endurance training (Meredith *et al.* 1991; Grassi *et al.* 1994).

Concluding remarks

The foregoing evidence strongly suggests that resting bradycardia following endurance training is attributable to high cardiac vagal tone. However, we are aware that a study on rats by Bolter *et al.* (1973) showed that exercise training reduced the intrinsic heart rate in isolated atria. Boyett and colleagues (D'Souza *et al.* 2014) showed that this effect was due to down-regulation of the funny current I_f. Nonetheless, exercise training in rats also increases atrial acetylcholine, and vagal presynaptic NO–cGMP in trained mice. Therefore, it would seem reasonable to conclude that training-induced bradycardia in these small animals probably involves two mechanisms, an increase in cardiac parasympathetic activity and a decrease in intrinsic rate of pacemaker cells. In humans an increase in cardiac parasympathetic activity is a major contributor.

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Additional information

Competing interests

None declared.