CROSSTALK

CrossTalk opposing view: Bradycardia in the trained athlete is attributable to a downregulation of a pacemaker channel in the sinus node

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Out goes the old

It is well known that athletes have a low resting heart rate (bradycardia). The bradycardia can be moderate to severe: reports of heart rates of 40–60 beats min^{-1} in athletes are common (Boyett *et al.* 2013), and Jensen-Urstad *et al.* (1997) reported heart rates of <30 beats min^{-1} in elite athletes at night. Consistent with this, S. Sharma has studied 142 elite cyclists and rowers and observed heart rates over the range 30–70 beats min^{-1}; the distribution of heart rates in the athletes (and for comparison in a normal population) is shown in Fig. 1. The resting heart rate is easy to measure and it is clear that athletes use the resting heart rate as a measure of fitness and speak of it in terms of pride and bravado. This is despite evidence that veteran athletes are more likely to need an electronic heart pacemaker fitted in later life (Baldesberger *et al.* 2008). The bradycardia is widely believed to be the result of high vagal tone; this is a natural assumption because high vagal tone will reduce the heart rate. However, despite this widespread belief, efferent vagal nerve activity to the heart's pacemaker (the sinus node) has never been recorded. It is not obvious how it could be measured, because the vagus nerve carries afferent as well as efferent nerve fibres. Because of this, the scientific community uses what is assumed to be a surrogate of vagal nerve activity to the sinus node, heart rate variability. Heart rate variability is a beat-to-beat variability in the heart rate and is assumed to be the result of stochastic fluctuations in autonomic nerve activity to the sinus node and changes in heart rate variability are assumed to represent changes in this. PubMed lists more than 17,000 publications concerned with heart rate variability. Heart rate variability is higher in athletes (Aubert *et al.* 2003) and this is taken as evidence of high vagal tone in athletes, and this is then assumed to be responsible for the bradycardia. However, a causative link between autonomic nerve activity and heart rate variability has never been demonstrated (for reasons discussed above). Furthermore, we have recently analysed the biophysics underlying heart rate variability and we have shown that, regardless of whatever is responsible for heart rate variability, heart rate variability is a steep exponential function of heart rate (heart rate variability increases with a decrease in heart rate) and the majority of reported changes in heart rate variability can be explained by the concurrent change in heart rate (Monfredi *et al.* 2014). All published data concerning the increase in heart rate variability in athletes that we have analysed can be explained by the bradycardia in the athletes (Monfredi *et al.* 2014). To dissect the mechanisms underlying the low resting heart rate in athletes, investigators have blocked autonomic nerve activity to the heart by injection of blockers (frequently but not exclusively atropine and propranolol). We have reviewed these studies and in no study in which the evidence indicates that there was complete autonomic blockade was the bradycardia in athletes abolished (if the bradycardia is the result of high vagal tone it should not be present after block of vagal activity to the sinus node; Boyett *et al.* 2013). In fact, the bradycardia can be larger after complete autonomic blockade, such as in the study of Katona *et al.* (1982).

And in comes the new

If the bradycardia is not the result of high vagal tone, what is the underlying mechanism? The sinus node is the 'Cinderella' of the heart and is under-studied as compared to the working myocardium and, therefore, when discussing possible causes of change in sinus node function the investigator has had little to guide them. Older literature therefore ascribes dysfunction of the sinus node in disease to 'fibrosis' with little or no justification (in much the same way that bradycardia in athletes has been ascribed to high vagal tone). However, this has changed in the last 10 years and it has been demonstrated that change or dysfunction of the sinus node in familial bradycardia (Milanesi *et al.* 2006), ageing (Hao, 2011; Yanni *et al.* 2011*b*), heart failure (Zicha *et al.* 2005; Yanni *et al.* 2011*a*), pulmonary hypertension (Yamanushi *et al.* 2010), atrial fibrillation (Yeh *et al.* 2009), metabolic syndrome (Albarado-Ibañez *et al.* 2013) and pregnancy (El Khoury *et al.* 2013) is the result of a remodelling of ion channels and related molecules in the sinus node. This is unsurprising because

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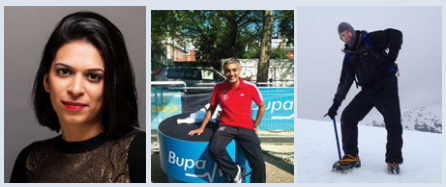

DOI: 10.1113/jphysiol.2014.284356

The Journal of Physiology

the function of the sinus node is electrical and as such depends on the expression of ion channels, etc. The most common reported cause of a bradycardia in these various conditions is a downregulation of the funny channel (HCN4) and the corresponding funny current, an important pacemaker mechanism (Zicha *et al.* 2005; Milanesi *et al.* 2006; Yeh *et al.* 2009; Yamanushi *et al.* 2010; El Khoury *et al.* 2013).

The arguments raised above prompted us to hypothesise that the bradycardia in athletes is the result of ion channel remodelling in the sinus node. We worked on rat and mouse models of athletic training (treadmill running for 3 months in the case of the rat and swim training for 1 month in the case of the mouse; D'Souza *et al.* 2014). There was a resting bradycardia *in vivo* in the trained animals that was still largely present after complete autonomic blockade. The spontaneous beating rate of the isolated (and therefore denervated) sinus node was also lower in the case of the trained animals. Analysis of tissue biopsies from the sinus node of the trained animals by quantitative PCR showed a widespread remodelling of ion channels and related molecules in the sinus node, including a downregulation of the important pacemaker channel HCN4. The corresponding funny current was also downregulated. *In vivo* and *ex vivo*, after block of the funny current, the heart rate (or spontaneous beating rate) of sedentary and trained mice was the same (or similar) and this suggests that the resting bradycardia in athletes (rats and mice at least) is the result of a downregulation of HCN4 and funny current. What is responsible for this change? Within the sinus node of the trained animals, we observed a downregulation of the transcription factor Tbx3, upregulation of another, NRSF, and upregulation of a micro-RNA, miR-1, and these changes are appropriate to explain the downregulation of HCN4. However, whatever is driving the changes in transcription factors and micro-RNA is unknown.

As well as sinus bradycardia, first degree heart block (slowing of atrioventricular node conduction), second degree heart block (intermittent heart block), and possibly third degree or complete heart block is more common among athletes especially at night (Northcote *et al.* 1989) and again this is attributed to high vagal tone (Maron & Pelliccia, 2006). However, once again this is doubtful (Stein *et al.* 2002) and we hypothesise that it is the result of a similar remodelling of ion channels etc. in the atrioventricular node. The popularity of sport in general, and of ultra-endurance events in particular, is increasing with >500 marathons held annually worldwide. This is expected to lead to a rise in the number of athletes with heart rhythm problems and a proper understanding of the underlying mechanisms will be central to tackling these issues.

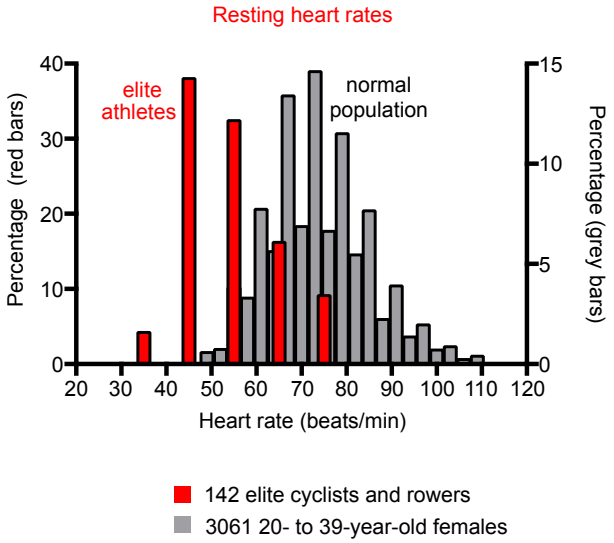

Figure 1. Distribution of resting heart rates in elite athletes and a normal population
Red bars, histogram of resting heart rate of 142 elite cyclists and rowers (S. Sharma, unpublished observations). Grey bars, histogram of resting heart rate of 3061 20- to 39-year-old female subjects (Ostchega *et al.* 2011).

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Additional information

Competing interests

None declared.