Viewpoint: Is the resting bradycardia in athletes the result of remodeling of the sinoatrial node rather than high vagal tone?

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It is well known that athletes have a low resting heart rate, i.e., a resting bradycardia and heart rates below 30 beats/min have been reported (7). For example, Wikipedia states that the Tour de France cyclist, Miguel Indurain, had a resting heart rate of 28 beats/min when race fit. The resting bradycardia in athletes is most often attributed to high vagal tone, i.e., high parasympathetic nerve activity (e.g., Ref. 1). However, over the years doubt about this explanation has been expressed (e.g., Ref. 26). Here we take a critical look at the two lines of evidence said to favor the high vagal tone hypothesis: 1) little or no change in the intrinsic heart rate in athletes and 2) an increase in heart rate variability in athletes.

Effect of training on intrinsic heart rate in humans. Jose and Taylor (9) investigated the effect of autonomic blockade in conscious human subjects and concluded that injection of 0.2 mg/kg propranolol (β-adrenergic receptor blocker) and 0.04 mg/kg atropine (M₂ muscarinic receptor blocker) effectively blocks autonomic influence on the resting heart rate in the human. They obtained dose-response curves for both drugs to ensure that there was complete blockade (9). This pioneering study established a technique that can be used to study the nature of the resting bradycardia in athletes. Since the effect of athletic training on the resting heart rate before and after autonomic blockade has been extensively investigated in the human and these studies are summarized in Table 1. In three studies (1–3 in Table 1), only the parasympathetic activity to the heart was blocked. In all three studies, there was a significant resting bradycardia as expected in the athletes [see heart rate (HR) data for studies 1–3 in Table 1]. The resting heart rate after parasympathetic blockade was also lower in the athletes (see HRab data for studies 1–3 in Table 1), and in all studies the difference in the heart rate after parasympathetic blockade was greater than the difference in the normal heart rate (compare ΔHR and ΔHRab data for studies 1–3 in Table 1). This suggests that high vagal tone is not the cause of the resting bradycardia in the athletes in these three studies at least. Instead it could be the result of either a decrease in sympathetic tone or a decrease in the intrinsic heart rate in the athletes.

In eight studies (4–11 in Table 1), the effect of complete autonomic blockade was studied. The heart rate after complete autonomic blockade is a measure of the intrinsic heart rate. In all eight studies, there was a significant decrease in the normal heart rate with training (see HR data for studies 4–11 in Table 1), and, in all but one study, the significant decrease in heart rate persisted after complete autonomic blockade (see HRab data for studies 4–11 in Table 1). The final column in Table 1 shows the decrease in the heart rate after complete autonomic blockade (ΔHRab) as a percentage of the decrease in the normal heart rate (ΔHR). In four out of the eight studies (4–6 and 11 in Table 1), the decrease in the heart rate after complete autonomic blockade was greater than the decrease in the normal heart rate (ΔHRab/ΔHR > 100%; bold in Table 1). This suggests that neither high vagal tone nor reduced sympathetic tone is the cause of the resting bradycardia in the athletes in these four studies at least and instead it is the result of a decrease in the intrinsic heart rate—in fact these data suggest that there may be a decrease in vagal tone (or an increase in sympathetic tone). However, in one of the studies (7 in Table 1) there was no significant decrease in the heart rate after complete autonomic blockade and, in three other studies (8–10 in Table 1), the decrease in the heart rate after complete autonomic blockade was less than the decrease in the normal heart rate (ΔHRab/ΔHR < 100%). In these studies (7–10 in Table 1), the decrease in the intrinsic heart rate accounts for between 11 and 60% of the decrease in the normal heart rate; it is possible, theoretically at least, that high vagal tone accounts for the remainder.

However, there is a surprising variation in the intrinsic heart rate, i.e., the heart rate after complete autonomic blockade, in untrained individuals from 83 to 108 beats/min in studies 4–11 in Table 1. The largest study of the intrinsic heart rate in humans was performed by Jose and Collison (8), who measured the intrinsic heart rate (after complete autonomic blockade) in 432 healthy adult human subjects. It was age dependent and for the 152 subjects 20–30 years of age in their study it was 105.5 ± 0.7 (mean ± standard error of the mean) beats/min (8). Studies 4–11 in Table 1 are ranked according to the reported heart rate after complete autonomic blockade in untrained individuals. In studies 4–7 in Table 1, the heart rate after complete autonomic blockade is within the mean ± 2 SD from Jose and Collison (8), i.e., from 89.4 to 121.6 beats/min. However, in studies 8–11 in Table 1, the heart rate after complete autonomic blockade is below this range. The reason for this is unclear, but it is a cause for concern. If only studies 4–7 in Table 1 are considered [in which the reported heart rate after complete autonomic blockade in young untrained individuals is within the range of the mean ± 2 SD from Jose and Collison (8)], the decrease in the heart rate after complete autonomic blockade was greater than the decrease in the normal heart rate (ΔHRab/ΔHR > 100%) in three of the four studies (4–6 in Table 1).

In summary, analysis of the heart rate in athletes after autonomic blockade shows that the resting bradycardia in athletes is in part at least and perhaps even completely the result of a decrease in the intrinsic heart rate.

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Table 1. Summary of the effect of athletic training on the resting HR under normal conditions and after HR<sub>ab</sub> in human subjects in different studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Authors</th>
<th>Sex, Age, Number of Subjects</th>
<th>Type of Study</th>
<th>Type of Athletic or Training</th>
<th>Autonomic Blockade, mg/kg</th>
<th>HR of Untrained Subjects, beats/min</th>
<th>HR of Trained Subjects, beats/min</th>
<th>ΔHR, beats/min</th>
<th>HR&lt;sup&gt;ab&lt;/sup&gt; of Untrained Subjects, beats/min</th>
<th>HR&lt;sup&gt;ab&lt;/sup&gt; of Trained Subjects, beats/min</th>
<th>ΔHR&lt;sup&gt;ab&lt;/sup&gt;, beats/min</th>
<th>ΔHR&lt;sup&gt;ab&lt;/sup&gt;/ΔHR, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Maciel et al. (14)</td>
<td>Male; 24–34; n = 7</td>
<td>I/E</td>
<td>10 wk cycling</td>
<td>0.04 atr; block not confirmed</td>
<td>69.0 ± 1.9</td>
<td>58.0 ± 1.7*</td>
<td>11.0</td>
<td>121.0 ± 4.6</td>
<td>105.0 ± 4.6*</td>
<td>16.0</td>
<td>145</td>
</tr>
<tr>
<td>2</td>
<td>Katona et al. (10)</td>
<td>Male; approximately 21–22; n = 9/8</td>
<td>C/E</td>
<td>National international rowers</td>
<td>0.04 atr; block confirmed by dose-response curve</td>
<td>63.2 ± 2.1</td>
<td>53.6 ± 1.4*</td>
<td>9.6</td>
<td>117.1 ± 3.9</td>
<td>93.9 ± 2.6*</td>
<td>23.2</td>
<td>242</td>
</tr>
<tr>
<td>3</td>
<td>Stein et al. (26)</td>
<td>Male; approximately 28–29; n = 6/group</td>
<td>C/E</td>
<td>Runners (∼50 km/week)</td>
<td>0.04 atr; block not confirmed</td>
<td>65.7 ± 5.9</td>
<td>58.3 ± 5.7*</td>
<td>7.5</td>
<td>91.9 ± 5.7</td>
<td>81.4 ± 6.0*</td>
<td>10.5</td>
<td>140</td>
</tr>
<tr>
<td>4</td>
<td>Dickhuth et al. (5)</td>
<td>Not specified</td>
<td>C/not specified</td>
<td>Not specified</td>
<td>0.2 pro or 0.04 atr; not known whether block confirmed</td>
<td>67.1 ± 10.2</td>
<td>53.0 ± 8.8*</td>
<td>14.1</td>
<td>108.0 ± 7.1</td>
<td>85.2 ± 12.8*</td>
<td>22.8</td>
<td>162</td>
</tr>
<tr>
<td>5</td>
<td>Lewis et al. (12)</td>
<td>Male; approximately 21–26; n = 8/group</td>
<td>C/E</td>
<td>Elite cyclists (450–700 km/week for 5–11 yr)</td>
<td>0.25 pro or 0.5 met +0.04 atr; block not confirmed</td>
<td>70.0 ± 7.3</td>
<td>53.0 ± 7.5*</td>
<td>17.0</td>
<td>103.0 ± 6.9</td>
<td>84.6 ± 7.5*</td>
<td>18.4</td>
<td>108</td>
</tr>
<tr>
<td>6</td>
<td>Katona et al. (10)</td>
<td>Male; approximately 21–22; n = 9/8</td>
<td>C/E</td>
<td>National/International rowers</td>
<td>0.2 pro or 0.04 atr; block confirmed by dose-response curve</td>
<td>63.2 ± 2.1</td>
<td>53.6 ± 1.4*</td>
<td>9.6</td>
<td>99.8 ± 3.3</td>
<td>79.8 ± 2.3*</td>
<td>20</td>
<td>208</td>
</tr>
<tr>
<td>7</td>
<td>Lewis et al. (11)</td>
<td>Male; approximately 22; n = 5</td>
<td>I/R</td>
<td>11 wk leg training</td>
<td>0.2 pro or 0.04 atr; block not confirmed</td>
<td>58.3 ± 9.1</td>
<td>52.1 ± 8.6*</td>
<td>6.2</td>
<td>93.0 ± 9.0</td>
<td>89.3 ± 8.7NS</td>
<td>3.7</td>
<td>60</td>
</tr>
<tr>
<td>8</td>
<td>Smith et al. (23)</td>
<td>Male; 20–31; n = 10/group</td>
<td>C/E</td>
<td>Endurance exercise trained for &gt;2 yr</td>
<td>0.2 met + 0.04 atr; block confirmed by Valsalva manoeuvre and injection of isoproterenol</td>
<td>70.0 ± 4.0</td>
<td>54.0 ± 2.0*</td>
<td>16.0</td>
<td>87.0 ± 2.0</td>
<td>80.0 ± 3.0*</td>
<td>7.0</td>
<td>44</td>
</tr>
<tr>
<td>9</td>
<td>Smith et al. (24)</td>
<td>Male; approximately 25; n = 10/group</td>
<td>C/E</td>
<td>Runners (running competitively for several years; &gt;50 miles/week)</td>
<td>0.2 met + 0.04 atr; block confirmed by Valsalva manoeuvre only</td>
<td>70.2 ± 3.1</td>
<td>54.7 ± 3.0*</td>
<td>15.5</td>
<td>86.6 ± 2.5</td>
<td>79.5 ± 2.8*</td>
<td>7.1</td>
<td>46</td>
</tr>
<tr>
<td>10</td>
<td>Shi et al. (22)</td>
<td>Male; approximately 28; n = 8</td>
<td>I/E</td>
<td>8 mo walk/jog training</td>
<td>0.2 met + 0.04 atr; block confirmed by Valsalva manoeuvre and injection of isoproterenol</td>
<td>66.0 ± 4.0</td>
<td>57.0 ± 4.0*</td>
<td>9.0</td>
<td>85.0 ± 3.0</td>
<td>84.0 ± 3.0</td>
<td>1.0</td>
<td>11</td>
</tr>
<tr>
<td>11</td>
<td>Stein et al. (26)</td>
<td>Male; approximately 28–29; n = 6/group</td>
<td>C/E</td>
<td>Runners (∼50 km/week)</td>
<td>0.2 pro or 0.04 atr; block not confirmed</td>
<td>65.7 ± 5.9</td>
<td>58.3 ± 5.7*</td>
<td>7.5</td>
<td>83.1 ± 4.7</td>
<td>72.2 ± 5.7*</td>
<td>10.9</td>
<td>145</td>
</tr>
</tbody>
</table>

Values are means ± SE. atr, Atropine; C, case control study; E, endurance trained; ΔHR, difference in normal resting heart rate between trained and untrained subjects; ΔHR<sup>ab</sup>, difference in resting heart rate after autonomic blockade between trained and untrained subjects; I, interventional study; iso, isoprenaline; met, metoprolol; NS, not significantly different from same heart rate measured in untrained subjects; R, resistance trained; *significantly different from same heart rate measured in untrained subjects. Values of ΔHR<sup>ab</sup>/ΔHR >100% (indicating no role for high vagal tone) are in bold.
Table 2. Summary of the effect of athletic training on the resting HR under normal conditions, the HR\textsuperscript{ab}, and the IHR; measured in an isolated heart preparation) in animal models in different studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Authors</th>
<th>Species, Strain, Sex, and Number of Animals</th>
<th>Type of Study</th>
<th>Type of Training</th>
<th>Procedure for Autonomic Blockade (mg/kg) or Determination of IHR</th>
<th>HR of Untrained Animals, beats/min</th>
<th>HR of Trained Animals, beats/min</th>
<th>ΔHR, beats/min</th>
<th>HR\textsuperscript{ab} or IHR of Untrained Animals, beats/min</th>
<th>HR\textsuperscript{ab} or IHR of Trained Animals, beats/min</th>
<th>ΔHR\textsuperscript{ab} or IHR/ΔHR, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>De Angelis et al. (4)</td>
<td>Mouse; male; (n = 8/\text{group})</td>
<td>C/E</td>
<td>Treadmill running for 4 wk</td>
<td>In vivo; 1 pro +1 atr</td>
<td>612 ± 6</td>
<td>485 ± 9*</td>
<td>127</td>
<td>504 ± 9</td>
<td>473 ± 18(\text{NS})</td>
<td>31</td>
</tr>
<tr>
<td>2</td>
<td>Sanches et al. (19)</td>
<td>Rat; female (n = 7/\text{group})</td>
<td>C/E</td>
<td>Treadmill running for 8 wk</td>
<td>In vivo; 4 pro +3 atr</td>
<td>357 ± 10</td>
<td>332 ± 7*</td>
<td>25</td>
<td>368 ± 8</td>
<td>353 ± 6(\text{NS})</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>Barnard et al. (2)</td>
<td>Rat; male</td>
<td>C/E</td>
<td>Treadmill running for 12 wk</td>
<td>In vivo; 4 pro +5 atr</td>
<td>359 ± 6</td>
<td>331 ± 4*</td>
<td>28.2</td>
<td>401.4 ± 5.32</td>
<td>382.5 ± 6.34*</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>Rossi et al. (17)</td>
<td>Rat; male; (n = 14/\text{group})</td>
<td>C/E</td>
<td>Treadmill running for 10 wk</td>
<td>In vivo; 4 pro +5 atr</td>
<td>366 ± 8</td>
<td>333 ± 5*</td>
<td>33</td>
<td>389 ± 8</td>
<td>359 ± 4*</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>Souza et al. (25)</td>
<td>Rat; male; (n = 14/\text{group})</td>
<td>C/E</td>
<td>Swimming for 8 wk</td>
<td>In vivo; 5 pro +4 atr</td>
<td>346 ± 5</td>
<td>314 ± 6*</td>
<td>32</td>
<td>392 ± 6</td>
<td>332 ± 4*</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>Negrao et al. (15)</td>
<td>Rat; male; (n = 12/15)</td>
<td>C/E</td>
<td>Treadmill running for 13 wk</td>
<td>In vivo; 4 pro +3 atr</td>
<td>308 ± 3</td>
<td>299 ± 3*</td>
<td>9</td>
<td>369 ± 5</td>
<td>329 ± 4*</td>
<td>40</td>
</tr>
<tr>
<td>7</td>
<td>Lin and Horvath (13)</td>
<td>Rat; male; (n = 6/\text{group})</td>
<td>C/E</td>
<td>Swimming for 6 wk</td>
<td>In vivo; 8 pro +1 atr</td>
<td>382 ± 12</td>
<td>344 ± 10.5*</td>
<td>38</td>
<td>426 ± 25</td>
<td>372 ± 9*</td>
<td>54</td>
</tr>
<tr>
<td>8</td>
<td>Schäffer et al. (20)</td>
<td>Rat; male; (n = 9) control, 7 trained</td>
<td>C/E</td>
<td>Treadmill running for 10 wk</td>
<td>Ex vivo; isolated right atrium and (10^{-6}) M pro +10(-6) M atr</td>
<td>320 ± 6</td>
<td>301 ± 8*</td>
<td>19</td>
<td>264 ± 14.21</td>
<td>243 ± 8.4*</td>
<td>21</td>
</tr>
<tr>
<td>9</td>
<td>Bolter and Atkinson (3)</td>
<td>Rat; male; (n = 9) control, 7 trained</td>
<td>C/E</td>
<td>Treadmill running for 16 wk</td>
<td>Ex vivo; isolated right atrium</td>
<td>373 ± 4</td>
<td>353 ± 7*</td>
<td>20</td>
<td>299 ± 22</td>
<td>231 ± 22*</td>
<td>68</td>
</tr>
</tbody>
</table>

Values are means ± SE. HR\textsuperscript{ab} is a measure of the intrinsic heart rate, if autonomic blockade is complete. See Table 1 legend for meaning of abbreviations.
Effect of training on intrinsic heart rate in animals. Table 2 summarizes analogous data from animal studies. In animal studies, the intrinsic heart rate can be measured either in vivo following autonomic blockade or in an isolated denervated heart preparation. In six of the nine studies summarized in Table 2, at least 90% of the resting bradycardia in the trained animals can be attributed to a decrease in the intrinsic heart rate. However, in three of the studies there is a potential role for high vagal tone (or decreased sympathetic tone).

Problem with heart rate variability as a measure of vagal tone. The ideas here are a further development of the original idea of Zaza and colleagues (16, 29) concerning heart rate variability. Al-Ani et al. (1) described an individual who prior to training had a heart rate of 62 beats/min and a standard deviation of the normal beat-to-normal beat interval (SDNN; measure of heart rate variability) of 169 ms. After training (cycling) for 6 wk, the subject’s heart rate was 50 beats/min and the SDNN was 247 ms (1). The increase in heart rate variability (increase in SDNN) was interpreted as evidence of an increase in vagal tone (1). When the heart rate was 62 beats/min (value in untrained individual) and assuming the sinoatrial node action potential duration was 160 ms (typical value), then the diastolic interval was 808 ms. If the membrane potential covers 20 mV from the maximum diastolic potential (approximately −60 mV) to the threshold potential (approximately −40 mV), then the rate of change of membrane potential during diastole in the sinoatrial node cell, \( \frac{dV_m}{dt} \), was 0.025 V/s or 25 mV/s. Now consider a perturbation (perhaps a change in autonomic nerve activity) that results in an ionic current, \( I_{per} \), flowing across the cell membrane of a sinoatrial node cell with a membrane capacitance, \( C_m \). This will change \( \frac{dV_m}{dt} \). Because the cell membrane behaves as a capacitor, the change in \( \frac{dV_m}{dt} \), i.e., \( \Delta \frac{dV_m}{dt} \), is given by:

\[
\Delta \frac{dV_m}{dt} = - \frac{I_{per}}{C_m}
\]

\( I_{per} \) is a fluctuating current giving rise to heart rate variability. It will be assumed that during one diastolic period \( I_{per} = 0.2 \) pA, and this is the perturbing current necessary to give rise to a 1 SD change in the cycle length. \( C_m \) is typically 50 pF. Therefore,

\[
\frac{dV_m}{dt} = \frac{0.2 \times 10^{-12}}{50 \times 10^{-12}} = 0.004 V/s
\]

or 4 mV/s. Therefore, during diastole \( \frac{dV_m}{dt} = 25 -4 = 21 \) mV/s. Consequently, the diastolic interval will be 977 ms and the cycle length will be 1,137 ms. Therefore, there will be a change in cycle length of 169 ms. This is the SDNN (measure of heart rate variability) and it is the same as in the untrained individual in the study of Al-Ani et al. (1).

After training, when the subject’s heart rate was 50 beats/min in the study of Al-Ani et al. (1), the diastolic interval was 1,040 ms and \( \frac{dV_m}{dt} \) was 19 mV/s. Assume that \( I_{per} \) is the same, i.e., 0.2 pA. The change in \( \frac{dV_m}{dt} \) it gives rise to will be the same, i.e., 4 mV/s. During diastole \( \frac{dV_m}{dt} = 19 -4 = 15 \) mV/s and consequently the diastolic interval will be 1,338 ms and the cycle length will be 1,498 ms. Therefore, there will be a change in cycle length of 298 ms. This will be the SDNN of cycle length (measure of heart rate variability) after training. In summary, simply a decrease in the heart rate from 62 to 50 beats/min, with no change in the underlying perturbing current, is predicted to increase the heart rate variability, i.e., SDNN, from 169 to 298 ms. This is more than sufficient to explain the observed increase in heart rate variability (SDNN) from 169 to 247 ms in the study of Al-Ani et al. (1). There is no need to invoke any change in vagal tone. Analysis shows that the increases in heart rate variability with training reported in other studies (7, 18, 21) can similarly be accounted for by the reported decreases in heart rate. In conclusion, studies of heart rate variability provide no evidence of high vagal tone in athletes.

Calculations like those above show that there is an exponential-like relationship between SDNN and heart rate. Although the calculations above are based on some simplifying assumptions, using biophysically detailed models of the sinoatrial node action potential, we have confirmed this relationship (data not shown).

Ion channel remodeling as alternative to high vagal tone. The pacemaker activity of the heart is the result of the concerted action of ion channels and \( \text{Ca}^{2+} \)-handling proteins in the sinoatrial node (6). There is (or can be) a bradycardia in familial sinoatrial node disease, in the elderly, in heart failure, and with atrial fibrillation, and in each of these conditions the evidence suggests that the bradycardia is the result of a remodeling of ion channels and/or \( \text{Ca}^{2+} \)-handling proteins (6). For example, the bradycardia associated with ageing can be attributed to a downregulation of RYR2, which is involved in the \( \text{Ca}^{2+} \) clock mechanism of pacemaking (28). The review above suggests that there is little evidence of involvement of high vagal tone in the athletic training-induced bradycardia. If ion channels and \( \text{Ca}^{2+} \)-handling proteins are responsible for bradycardia in the diverse conditions discussed above, it is likely that they are also responsible for the bradycardia associated with athletic training. In 170 elite athletes, Whyte et al. (27) reported a decrease in the maximum heart rate (measured using a standard ramp protocol to volitional exhaustion) by −5 beats/min. Although this could be the result of a remodeling of the sinoatrial node (27), it cannot be explained by high vagal tone.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS


REFERENCES


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