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## Contemporary Review

# Symptomatic bradyarrhythmias in the athlete—Underlying mechanisms and treatments

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## ABSTRACT

Bradyarrhythmias including sinus bradycardia and atrioventricular (AV) block are frequently encountered in endurance athletes especially at night. While these are well tolerated by the young athlete, there is evidence that generally from the fifth decade of life onward, such arrhythmias can degenerate into pathological symptomatic bradycardia requiring pacemaker therapy. For many years, athletic bradycardia and AV block have been attributed to high vagal tone, but work from our group has questioned this widely held assumption and demonstrated a role for intrinsic electrophysiological remodeling of the sinus node and the AV node. In this article, we argue that bradyarrhythmias in the veteran athlete arise from the cumulative effects of exercise training, the circadian rhythm and aging on the electrical activity of the nodes. We consider contemporary strategies for the treatment of symptomatic bradyarrhythmias in athletes and highlight potential therapies resulting from our evolving mechanistic understanding of this phenomenon.

**KEYWORDS** Endurance exercise; Bradyarrhythmia; Electrophysiology; Vagal tone; Pacemaking

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## A. Introduction

Long-term participation in sports, especially endurance-type sports, results in a spectrum of surface electrocardiographic patterns that would be considered abnormal in untrained individuals. Among these patterns, bradyarrhythmias including sinus bradycardia, sinus arrhythmia, and atrioventricular (AV) conduction block are commonly observed.<sup>1</sup> The prevalence of sinus bradycardia and sinus arrhythmia in the athletic population is up to 90% and 20%, respectively, whereas sinus pauses exceeding 2 seconds are present in up to a third of athletes<sup>2</sup>; both sinus bradycardia and pauses are particularly evident during sleep.<sup>3</sup> Profound bradycardia with a heart rate of <35 beats/min is occasionally observed in highly conditioned athletes at rest (Figure 1A).<sup>4</sup> The cyclist Miguel Induráin has been reported to have had a resting heart rate of just 28

beats/min (source: *Wikipedia*). Senturk et al<sup>5</sup> published a systematic review of cardiac pauses in active trained athletes, and these pauses ranged from 1.35 to 30 seconds in duration. Disturbances in AV conduction, including first-degree AV block and Mobitz type I second-degree (Wenckebach) AV block, are also common in athletes, especially during sleep.<sup>3</sup> In 24-hour Holter recordings, first-degree AV block is present in up to 27.5%–40% of athletes while type I second-degree block is present in 15%–22%.<sup>6,7</sup> In the absence of symptoms of structural heart disease, current consensus guidelines consider sinus bradycardia > 30 beats/min, PR interval < 400 ms, Mobitz type I second-degree AV block, and junctional escape rhythms as benign physiological adaptations accompanying a long training history.<sup>8</sup> However, some evidence suggests that these changes may be on a continuum with

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symptomatic bradyarrhythmia necessitating the implantation of an electronic pacemaker. For example, Hood and Northcote<sup>9</sup> studied 19 veteran endurance athletes (mean age 67 years) and reported 2 had implanted pacemakers, a further 6 had significant bradycardia (heart rate < 35 beats/min), and of the 6, 1 had third-degree AV block and asystolic pauses and 1 had second-degree AV block. In a study of 134 Swiss male former professional cyclists (mean age 66 years) and 62 relatively sedentary male age-matched golfers by Baldesberger et al,<sup>10</sup> sinus node disease was more frequent (10% vs 2%) and pacemaker implantation for bradyarrhythmias was more common (3% vs 0%) in former cyclists. Similarly, Zadvorev et al<sup>11</sup> reported on a cohort of 36 former athletes (mean age 60 years) and 52 age-matched nonathletes in which pacemaker implantation (14% vs 3%), asystolic pauses (27.3% vs 9.3%), and sinoatrial block (16% vs 3%), including sinus node exit block (first- to third-degree) and arrest, were significantly higher in former athletes. A much larger study of 52,755 long-distance cross-country skiers by Andersen et al<sup>12</sup> demonstrated that a high level of endurance exercise (high number of races completed) and a high intensity of exercise (fast finishing time) conferred a significantly increased risk of hospitalization for sinus node dysfunction and high-degree AV block (Figure 1A). Evidence shows that the likelihood and severity of bradyarrhythmias increase with the degree of training (Online Supplemental Figure S1).<sup>11–13</sup> Table 1 summarizes data from the studies referred to above as well as some other related studies. The studies show that bradyarrhythmias are associated with many types of sports. However, the studies primarily report an association with endurance training rather than power training. The effects of endurance and power training were studied by Bondarev et al,<sup>14</sup> who compared 18 former professional athletes (9 former endurance athletes and 9 former power/mixed athletes) with 20 nonathletes, all of whom required pacemaker implantation and had no history of heart disease. The ages of diagnosis and pacemaker implantation were significantly lower in former endurance athletes (age 64 and 65 years, respectively) than in both former strength/mixed athletes (72 and 73 years of age) and nonathletes (74 and 75 years of age).<sup>14</sup> Furthermore, the former endurance athletes showed a higher prevalence of second- or third-degree AV block (78%) than did the power/mixed athletes (44%).<sup>14</sup>

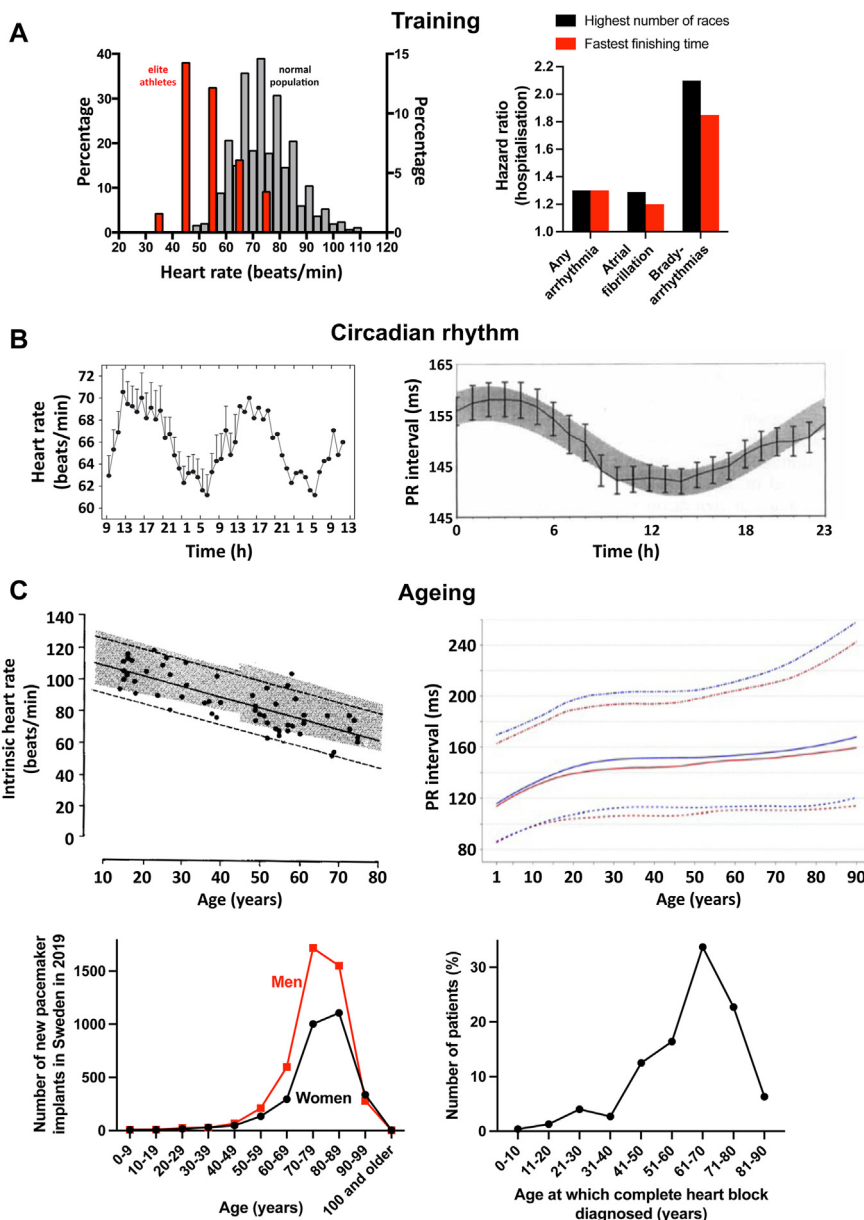
These data indicate that some veteran athletes represent a subpopulation with acquired cardiac conduction system disease, although clinical experience and anecdotal evidence suggest that conduction disturbances in athletes are much more frequent than hitherto described. With media coverage of our work on this topic,<sup>15,16</sup> we regularly receive correspondence from concerned symptomatic athletes. A common theme has emerged from this correspondence, which is corroborated by clinical practice: symptomatic bradyarrhythmias occur in veteran endurance athletes (frequently but not exclusively male, ~45–80 years of age, marathon runners or cyclists) who have been exercising at a high level for decades, and bradyarrhythmias are most pronounced at night. In these accounts, clinical management of individuals varies substan-

tially: some athletes already had implanted pacemakers or were considering pacemaker implantation (with trepidation), whereas others had been advised to detrain and 1 athlete was advised to undergo cardioablation. These apparent ambiguities prompted us to review, in the present article, mechanisms underlying athletic bradyarrhythmias and current, upcoming, and potential treatments. We present evidence that symptomatic bradyarrhythmias in the athlete result from the summation of the effects of exercise training, circadian rhythm, and age on the electrical activity of the sinus and AV nodes (Graphical Abstract) and highlight areas of potential therapeutic innovation on the basis of our evolving mechanistic understanding of this commonly encountered condition.

## B. Mechanisms underlying sinus bradycardia and AV block in athletes

Sinus bradycardia and AV block in athletes have been commonly attributed to high vagal tone; we have previously addressed the role of vagal tone,<sup>17</sup> and we briefly summarize the arguments for and against this hypothesis in the Online Supplement. Here, we address new mechanisms proposed to explain sinus bradycardia and AV block in athletes. Electrical activity is ultimately the result of the activity of ion channels, and our work over the last 2 decades has demonstrated that plasticity in the expression profile of pacemaking ion channels is an important mechanism by which heart rate and AV node conduction are regulated in response to chronic physiological and pathological stimuli.<sup>18</sup> Endurance exercise is one such stimulus for change.

We and others have shown in the human and rodent models, after exercise training, there is a decrease of the intrinsic heart/pacemaker rate in the absence of autonomic tone measured after complete autonomic blockade, in the isolated denervated sinus node, or isolated denervated sinus node myocyte (Figures 2A and 2B). Similarly, we have shown in the human, horse, and mouse that after exercise training, there is an alteration of intrinsic AV node electrophysiology (prolongation of the Wenckebach cycle length, a related prolongation of the AV node effective refractory period, prolongation of the PR interval, or decrease in the pacemaker rate) in the absence of autonomic tone (Figures 2C and 2D). In rodent models, we have shown that swim- or treadmill running–training results in a diffuse transcriptional remodeling (downregulation) of key ion channels in both the sinus and AV nodes.<sup>19–22</sup> According to work on the rat, mouse, and horse, there is an exercise training–dependent downregulation of the hyperpolarization-activated cyclic nucleotide-gated (HCN) and L- and T-type  $\text{Ca}^{2+}$  channels at the protein and/or messenger RNA (mRNA) levels in both nodes (eg, Figure 3A).<sup>19–22</sup> There is also a downregulation of the corresponding ionic currents, funny current ( $I_f$ ), L-type  $\text{Ca}^{2+}$  current ( $I_{\text{Ca,L}}$ ), and T-type  $\text{Ca}^{2+}$  current ( $I_{\text{Ca,T}}$ ), in sinus and AV node myocytes from swim-trained mice (eg, Figure 3A).<sup>19–22</sup>  $I_{\text{Ca,L}}$  and  $I_{\text{Ca,T}}$  are well known to play an important role in both sinus node pacemaking and AV node

**Figure 1**

Effect of endurance exercise (panel A), circadian rhythm (panel B), and aging (panel C) on functional properties of sinus and atrioventricular nodes. **A (left panel):** Distribution of resting heart rates in elite athletes and a normal population. The red bars correspond to histogram of the resting heart rate of 142 elite cyclists and rowers. The gray bars correspond to histogram of the resting heart rate of 3061 20- to 39-year-old female subjects. From D'Souza et al.<sup>79</sup> **A (right panel):** Risk of any arrhythmia, atrial fibrillation, and bradyarrhythmias for cross-country skiers either completing the highest number of races or with fastest finishing times as compared with cross-country skiers completing just 1 race or with slowest finishing times. Drawn from Andersen et al.<sup>12</sup> **B (left panel):** Mean heart rate of 8 male subjects plotted against time of day. Mean + SEM shown for the first 28 hours; for next 24 hours, only mean shown for clarity. Modified from Vandewalle et al.<sup>80</sup> **B (right panel):** Mean ( $\pm$ SEM) hourly PR interval of 50 subjects plotted against time of day. The shaded area corresponds to the fitted curve. Modified from Dilaveris et al.<sup>28</sup> **C (top left panel):** Relationship between the intrinsic heart rate measured after complete autonomic blockade and age in 56 human subjects. The dashed lines correspond to  $\pm 1$ SD. Modified from Kuga et al.<sup>36</sup> The shaded area corresponds to the 95% confidence limit for the intrinsic heart rate from Jose and Collison.<sup>35</sup> **C (top right panel):** 2nd, 50th, and 98th percentiles for the PR interval of 486,014 male (blue curves) and female (red curves) subjects plotted against age. Modified from Palhares et al.<sup>81</sup> **C (bottom left panel):** Relationship between the incidence of sick sinus syndrome (as measured by the number of new pacemaker implants in Sweden in 2019) and age in male and female subjects. Based on Härtel and Talvensaarri<sup>82</sup> and Benditt et al.<sup>33</sup> **C (bottom right panel):** In 224 patients with complete heart block, the relationship between the percentage of patients and age of patients. Drawn from Penton et al.<sup>34</sup>

conduction.<sup>23</sup> Although the role of  $I_f$  in pacemaking is well known, its role in AV node conduction is only now emerging: reduction in  $I_f$  slows not only pacemaking but also AV node conduction as seen in studies of  $I_f$  blockers,<sup>24</sup> HCN4 loss-of-function mutations,<sup>25</sup> and HCN4 knockout<sup>26</sup>; genome-wide association studies have also shown that polymorphisms at

the HCN4 locus associate not only with the risk of sinus node dysfunction but also with first-degree and complete AV block and pacemaker implantation.<sup>27</sup>

Pharmacological block of  $I_f$  abolishes the difference in heart rate between swim-trained and sedentary mice in vivo and in the isolated sinus node.<sup>21</sup> In an attempt to extend these

**Table 1** Studies reporting bradyarrhythmias in athletes

Study	No. of subjects studied	Age of athletes	Gender of athletes	Sport	Sports level	Extent of exercise training	Duration of exercise training	Main findings in athletes
Meytes et al <sup>59</sup>	126 Athletes	Not stated	Not stated	Swimming, athletics, volley ball, gymnastics	Professional	Israeli national team athletes	Not stated	9% First-degree AV block and 2% second-degree (Wenckebach) AV block
Beswick and Jordan <sup>13</sup>	60 Athletes and 47 normal control subjects	Not stated	Male	Short distance (sprint, field events, ring events, etc) and long distance ( $\geq 1$ mile)	Professional	Participants in 1958 Sixth British Empire and Commonwealth Games	Not stated	Lower heart rate (heart rate of long-distance athletes lower than that of short-distance athletes)
Cohen et al <sup>84</sup>	30 Ballet dancers and 15 sedentary control subjects	18–32 y	~ 50% Male; ~ 50% female	Ballet	Professional	Not stated	Mean: 14 y	Higher prevalence of sinus bradycardia and sinus arrhythmia
Murayama and Kuroda <sup>58</sup>	356 athletes	17–50 y	82% Male; 18% female	Various	Professional	Japanese athletes from 1964 Olympic games	Not stated	Higher prevalence of sinus bradycardia and first- or second-degree AV block
Talan et al <sup>6</sup>	20 runners and 50 age-matched sedentary control subjects	19–28 y	Male	Running	Nonprofessional; university track and team club members	$\geq 50$ miles/wk for 250–365 d/y	$\geq 3$ y	Lower heart rate; prolonged sinus pauses; higher prevalence of AV block
Palatini et al <sup>7</sup>	40 Athletes (20 runners and 20 cyclists) and 40 age- and sex-matched sedentary control subjects	20.3 $\pm$ 7 y	Male	Running or cycling	Nonprofessional; members of sports clubs and schools	Runners: ~ 75 km/wk; cyclists: ~ 16,500 km/y	>3 y	Lower heart rate; higher prevalence of first- and second-degree (Wenckebach) AV block
Northcote et al <sup>3</sup>	20 Runners and 20 age- and sex-matched sedentary control subjects	56 $\pm$ 7 y	Male	Running	Nonprofessional	47 $\pm$ 23 miles/wk	>25 y	Lower heart rate; higher prevalence of sinus bradycardia, asystolic pauses, and first-, second-, and third-degree AV block; prolonged PR interval

Hood and Northcote <sup>9</sup>	19 Runners (12-y follow-up study of athletes from Northcote et al <sup>3</sup> )	56–83 y	Male	Running	Nonprofessional	34 ± 21 miles/wk	26–60 y	<ul style="list-style-type: none"> <li>• Low heart rate; bradycardia; AV block; asystolic pauses</li> <li>• 11% of veteran athletes now required pacemaker implantation</li> </ul>
Bjørnstad et al <sup>85</sup>	1299 Athletes and 151 age- and sex-matched sedentary control subjects	24.2 ± 4.3 y	58% Male; 42% female	Various	Nonprofessional; students of the Norwegian College of Physical Education and Sport	Males: ran 3 km in 12 min; females: ran 1.5 km in 7 min	Not stated	Lower heart rate; higher prevalence of sinus bradycardia; 0.9% had rhythms other than sinus rhythm; prolonged PQ interval
Bjørnstad et al <sup>86</sup>	30 Top athletes, 30 age- and sex-matched athletic students, and 30 age- and sex-matched sedentary control subjects	Mean: 24	50% Male; 50% female	Cross-country skiing, biathlon, long-distance running, orienteering, running	Professional	International/national level athletes	Not stated	Lower heart rate and paroxysmal bradycardia; higher prevalence of second-degree AV block
Sharma et al <sup>87</sup>	1000 Athletes and 300 age- and sex-matched sedentary control subjects	14–18 y	73% Male; 27% female	Soccer, tennis, rugby, cycling, swimming, athletics, boxing, rowing, and modern triathlon	Nonprofessional; junior elite athletes	9.7 ± 3.3 h/wk of intensive training	1–10 y at the county level	Higher prevalence of sinus bradycardia, sinus arrhythmia, and first-degree AV block; small number of rhythms other than sinus rhythm; prolonged PR interval
Baldesberger et al <sup>10</sup>	62 Former professional cyclists and 62 age-matched sedentary control subjects	66 ± 7 y	Male	Cycling	Former professional cyclists but retired for 38 ± 7 y at the time of study	25,200 ± 9700 km/y when professional	11 ± 4 y as professionals	Lower heart rate; higher prevalence of sinus node disease and pacemaker implantation

(continued)

Table 1 Continued

Study	No. of subjects studied	Age of athletes	Gender of athletes	Sport	Sports level	Extent of exercise training	Duration of exercise training	Main findings in athletes
Andersen et al <sup>12</sup>	52,755 Cross-country skiers	15–65+ y	90% Male; 10% female	Cross-country skiing	Mixture of professional and nonprofessional	All Swedish finishers of a 90-km cross-country skiing event during 1989–1998	Not stated	<ul style="list-style-type: none"> <li>• Higher risk of bradyarrhythmias for those who completed the highest number of races or those with the fastest finishing time</li> <li>• Higher risk of hospitalization for bradyarrhythmias in skiers who completed more races</li> </ul>
Zadvorev et al <sup>11</sup>	36 Former athletes and 52 age-matched sedentary control subjects admitted to a cardiology ward	60.1 ± 10.6 y	83% Male; 17% female	Various	Former athletes	Various—ranked by sporting rank or title	Mixed	<ul style="list-style-type: none"> <li>• Higher prevalence of asystolic pauses, sinoatrial exit block, AV block, and pacemaker implantation</li> <li>• Prevalence of AV block increased with higher sporting rank/title</li> </ul>

Studies are listed chronologically with the exception of 2 related studies from Northcote and others.

AV = atrioventricular.



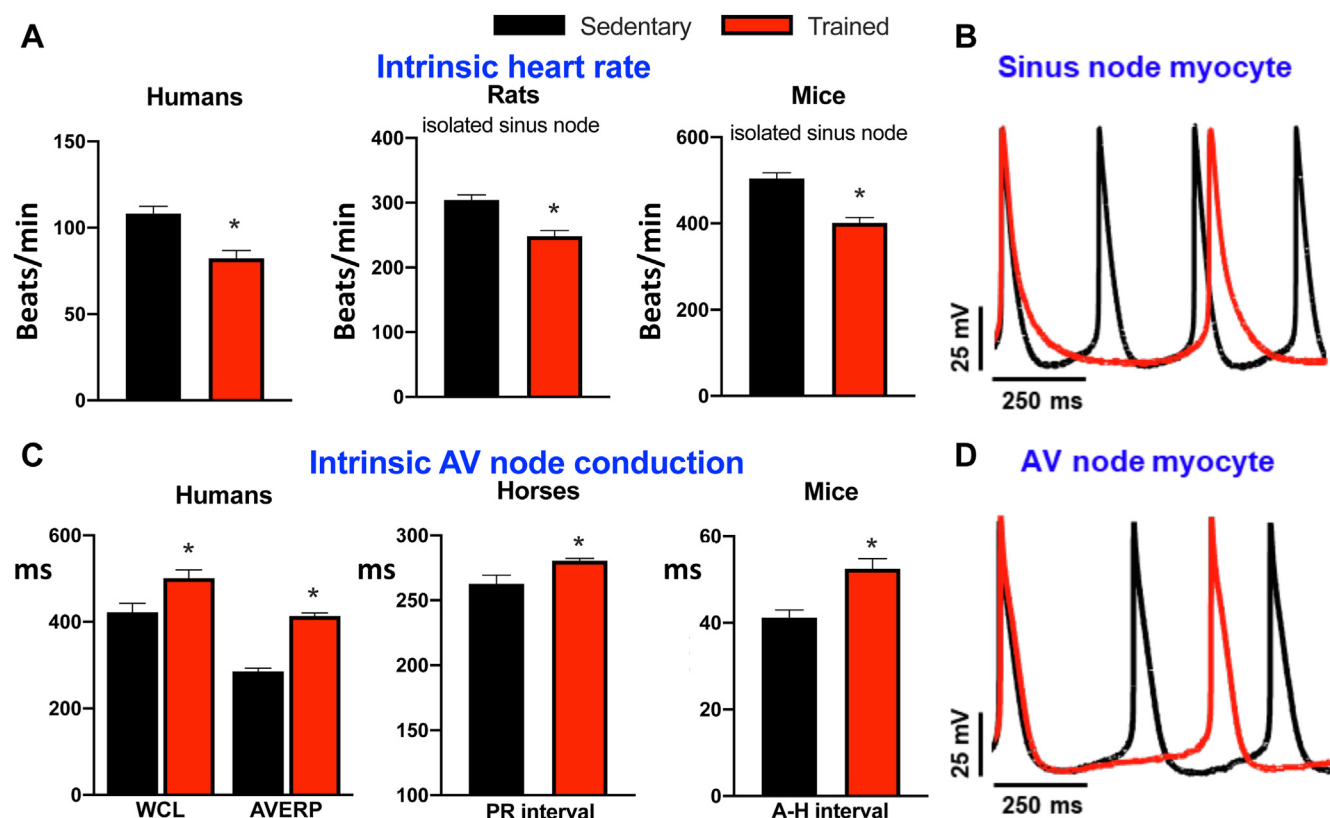
findings to humans, we have assessed the role of  $I_f$  remodeling in human endurance athletes using the  $I_f$  blocker ivabradine. We observed a significant correlation between the heart rate–lowering effect of oral ivabradine and the intrinsic heart rate (measured after complete autonomic blockade) of athletes and nonathletes: subjects with a lower intrinsic heart rate (generally athletes) had a blunted response to ivabradine.<sup>20</sup> This suggests that in both the human athlete and the exercise-trained rodent, the downregulation of HCN channels and  $I_f$  (Figure 3A) is at least contributing to sinus bradycardia.<sup>20</sup> In the case of the AV node, biophysically detailed modeling suggests that the downregulation of  $I_f$  and  $I_{Ca,L}$  is contributing to the slowing of AV node conduction after exercise training.<sup>19</sup> Furthermore, in the swim-trained mouse, the role of  $I_f$  is confirmed by the finding that a period of detraining restores HCN4 expression and AV conduction to pretraining levels.<sup>19</sup>

### C. Role of circadian rhythm in ion channel expression

Bradyarrhythmias in human athletes primarily occur at night.<sup>3</sup> In humans and laboratory animals, there is a circadian rhythm

in both the heart rate and the PR interval (Figure 1B).<sup>3,28</sup> The heart rate is higher during the awake period, presumably to anticipate the increase in demand for cardiac output during the awake period, and the PR interval is shorter (ie, AV conduction is faster) at the same time, presumably because there is less time during the shorter cardiac cycle for all events (the QRS duration and QT interval are also shorter). Once again, the circadian rhythm in heart rate and PR interval is commonly attributed to high vagal tone during sleep (see arguments for and against in the Online Supplement), but once again we address new proposed mechanisms here.

Measurement of the transcriptome of the mouse sinus node using RNA sequencing over 24 hours has shown that ~44% (7134 transcripts) of the measured sinus node transcriptome exhibits a circadian rhythm.<sup>29</sup> In the mouse sinus node, the rhythmic transcripts include the components of a functioning molecular circadian clock in the sinus node and this is presumably playing a role in the circadian rhythm in the sinus node.<sup>29,30</sup> Transcripts for many ion channels, including HCN channels, in the mouse sinus node exhibit a circadian rhythm,<sup>29,30</sup> and consistent with this, there is a circadian rhythm in  $I_f$  (Figure 3B).<sup>30</sup> In the mouse, pharmacological



**Figure 2**

Endurance exercise induces intrinsic sinus bradycardia and atrioventricular (AV) conduction slowing. **A** (left panel): Intrinsic heart rate (measured by electrocardiogram recording under complete pharmacological blockade of the autonomic nervous system) in human competitive endurance athletes and sedentary subjects. From D'Souza et al.<sup>20</sup> **A** (right panels): Intrinsic heart rate (measured in the isolated sinus node) in treadmill running–trained and sedentary rats and swim-trained and sedentary mice. From D'Souza et al.<sup>21</sup> **B**: Spontaneous action potentials recorded from myocytes isolated from the sinus node of swim-trained and sedentary mice. From Bidaud et al.<sup>22</sup> **C** (left panel): Wenckebach cycle length (WCL) and AV node effective refractory period (AVERP) recorded under complete pharmacological autonomic blockade in human endurance athletes and sedentary subjects. Digitized from Stein et al.<sup>83</sup> **C** (middle panel): PR interval recorded under complete pharmacological autonomic blockade from trained and sedentary racehorses. **C** (right panel): Atrio-His (A-H) interval recorded from isolated denervated AV node preparations from swim-trained and sedentary mice. From Mesirca et al.<sup>19</sup> **D**: Spontaneous action potentials recorded from myocytes isolated from the AV node of swim-trained and sedentary mice. From Mesirca et al.<sup>19</sup> Mean  $\pm$  SEM shown. \*Significantly different.

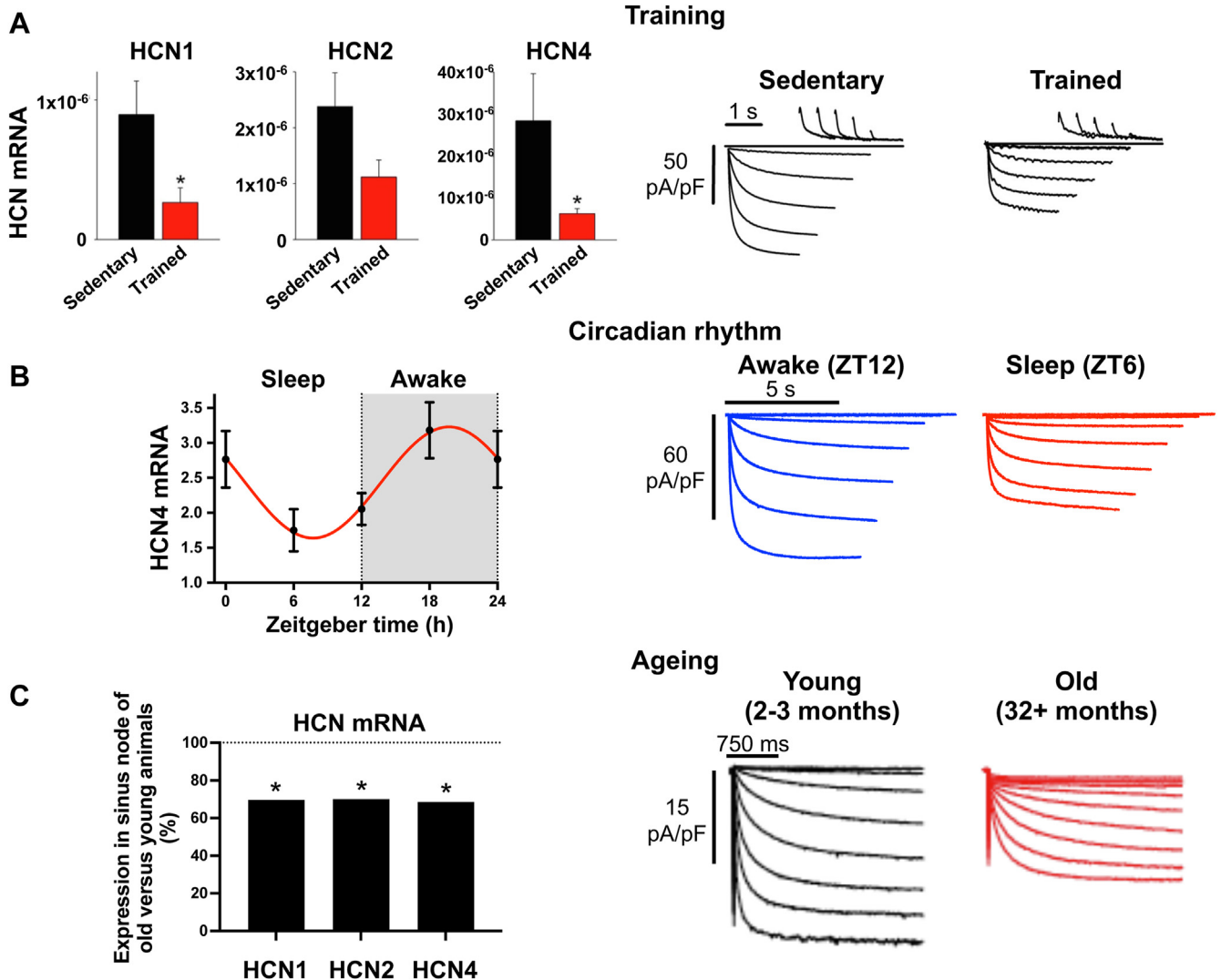


block of HCN channels and  $I_f$  both in vivo and in vitro (in the isolated sinus node) abolishes the circadian rhythm in heart rate and this suggests that the channels play an important role in the circadian rhythm in heart rate.<sup>30</sup> Many other transcripts in the mouse sinus node exhibit a circadian rhythm, and it is interesting that transcripts from genes identified by genome-wide association studies as determinants of the resting heart rate and transcripts from genes responsible for familial and acquired sick sinus syndrome all exhibit a circadian rhythm.<sup>29</sup> As in the case of the sinus node, we have shown that there is a circadian rhythm in the expression of circadian clock and ion channel (including HCN4) transcripts in the mouse AV node.<sup>18</sup> Although it is likely that the local circadian clocks in the 2 nodes are involved in the circadian rhythms of ion channel transcripts and so on and ultimately

pacemaker activity and AV node conduction, we have shown that circadian rhythms in the sympathetic nervous system and plasma glucocorticoids are also involved.<sup>31,32</sup>

#### D. Effect of aging on ion channel expression

Reports of symptomatic bradyarrhythmias in human athletes primarily concern the veteran athlete who has been exercising at a high level for decades rather than the young athlete.<sup>3,10,14</sup> This shows that age as well as exercise and time of day are important when considering symptomatic bradyarrhythmias in athletes. Age is important, because with age the functioning of both the sinus and AV nodes in the human declines; the prevalence of both sinus and AV node dysfunction increases in an exponential-like manner with age (Figure 1C).<sup>33–36</sup> The



**Figure 3**

Downregulation of HCN channels and  $I_f$  in mice with exercise training during the sleep period (day in the case of mouse) and during aging. **A (left panel)**: Mean ( $\pm$ SEM) expression of the 3 functionally important HCN transcripts in the sinus node of sedentary and treadmill running-trained rats. **A (right panel)**: Families of  $I_f$  recordings from isolated sinus node myocytes from sedentary and swim-trained mice. Data in panel A from D'Souza et al.<sup>21</sup> **B (left panel)**: Mean ( $\pm$ SEM) expression of the HCN4 transcripts in the sinus node of mice at 4 time points over 24 hours. Time given as Zeitgeber time (ZT): 0 h, start of the 12-hour light period; 12 h, start of the 12-hour dark period. **B (right panel)**: Families of  $I_f$  recordings from isolated sinus node myocytes from mice at ZT12 and ZT6. Data in panel B from D'Souza et al.<sup>30</sup> **C (left panel)**: HCN transient expression in the sinus node of  $\sim$ 24-month-old mice as a percentage of that in  $\sim$ 2-month-old mice. Data from D'Souza et al as published by Boyett et al.<sup>18</sup> **C (right panel)**: Families of  $I_f$  recordings from isolated sinus node myocytes from 2 to 3 and 32+-month-old mice. Data from Larson et al.<sup>52</sup> \*Significantly different. HCN, hyperpolarization-activated cyclic nucleotide-gated;  $I_f$ , funny current; mRNA, messenger RNA.

age-dependent decline in nodal function is also seen in animal studies.<sup>37,38</sup> The age-dependent sinus node dysfunction has been attributed to fibrosis (proliferation of the extracellular matrix),<sup>39–42</sup> although no evidence of this has been reported in the aged human, cat, and rat.<sup>43,44</sup> However, there is widespread evidence of an age-dependent downregulation of various ion channels and ionic currents in the sinus node of various animal species.<sup>18,38,40,44–51</sup> For example, in the mouse, there is an age-dependent downregulation of HCN channels<sup>18</sup> as well as  $I_f$ <sup>52</sup> (Figure 3C). Computer modeling has suggested that this electrical remodeling in the aged sinus node contributes to sinus node dysfunction.<sup>53</sup> Consistent with this, the decline in the intrinsic heart rate of the rat (measured in vivo after autonomic blockade)<sup>51</sup> as well as the beating rate of the isolated sinus node of the mouse from the adult to the senescent animal is reduced after pharmacological block of HCN channels and  $I_f$  (unpublished observations). It is likely that age-dependent downregulation of other ion channels (eg,  $Ca^{2+}$  channels) also contribute to age-dependent sinus node dysfunction.<sup>49,52</sup> Compared to the sinus node, less is known about the effect of age on the AV node. However, in the rat, once again there is evidence of electrical remodeling of the AV node (as well as fibrosis and apoptosis).<sup>37</sup>

## E. The whole is greater than the part<sup>54</sup>

In summary, exercise training results in electrical remodeling of the sinus and AV nodes and consequently a slowing of intrinsic sinus node pacemaking and AV conduction. Because of the circadian rhythm in the 2 nodes, this will be more marked at night (during sleep). For the young human athlete (eg, <50 years of age), this is well tolerated and not symptomatic. However, for the older veteran athlete with compromised nodal function as a result of aging, this is not necessarily the case. For the sinus node, this can be put in another way focusing on the HCN channels and  $I_f$  (although this does not mean that other factors are not involved): exercise training, nighttime (in the case of the human), and aging all result in a diminution of HCN channels and  $I_f$  (Figure 3), whereas any 1 of these or even 2 of these are unlikely to result in symptoms requiring medical intervention; symptomatic bradyarrhythmias may arise from the summation of all 3 physiological phenomena.

## F. Existing, new, and potential treatments

### F.1. Detraining

The most straightforward treatment of exercise training-induced bradyarrhythmias may be detraining. There is evidence from both human athletes and animal models of exercise training that detraining can reverse exercise training-induced bradyarrhythmias as well as exercise training-induced atrial tachyarrhythmia.<sup>55–59</sup> There is evidence that detraining is effective in young as well as veteran athletes: Giada et al<sup>56</sup> reported that after 2 months of detraining, exercise training-induced bradycardia was reversed by 15% in young (~24 years of age) and 50% in veteran (~55 years of age) cyclists. From clinical experience, we

know that the drawback of detraining is that the athlete may be reluctant or even refuse to detrain. Detraining can have adverse psychological effects<sup>60</sup>; individuals with a strong “athletic identity” are prone to high levels of psychological distress on detraining.<sup>61</sup> Studies suggest that individuals who are “addicted” to exercise will continue exercising regardless of physical injury, personal inconvenience, or disruption in other areas of life and addicted exercisers experience disturbing deprivation sensations when unable to exercise.<sup>62,63</sup>

### F.2. Pacemaker implantation

Adequately powered prospective studies assessing the prevalence of pacemaker implantation in athletes and consequences for sports practice have yet to be performed. However, as discussed above, athletes are more likely to need pacemaker implantation than nonathletes and the limited available evidence base indicates that this is a safe and effective strategy for bradyarrhythmia management in this population that does not impinge on the ability to perform endurance exercise of high intensity or duration.<sup>64</sup>

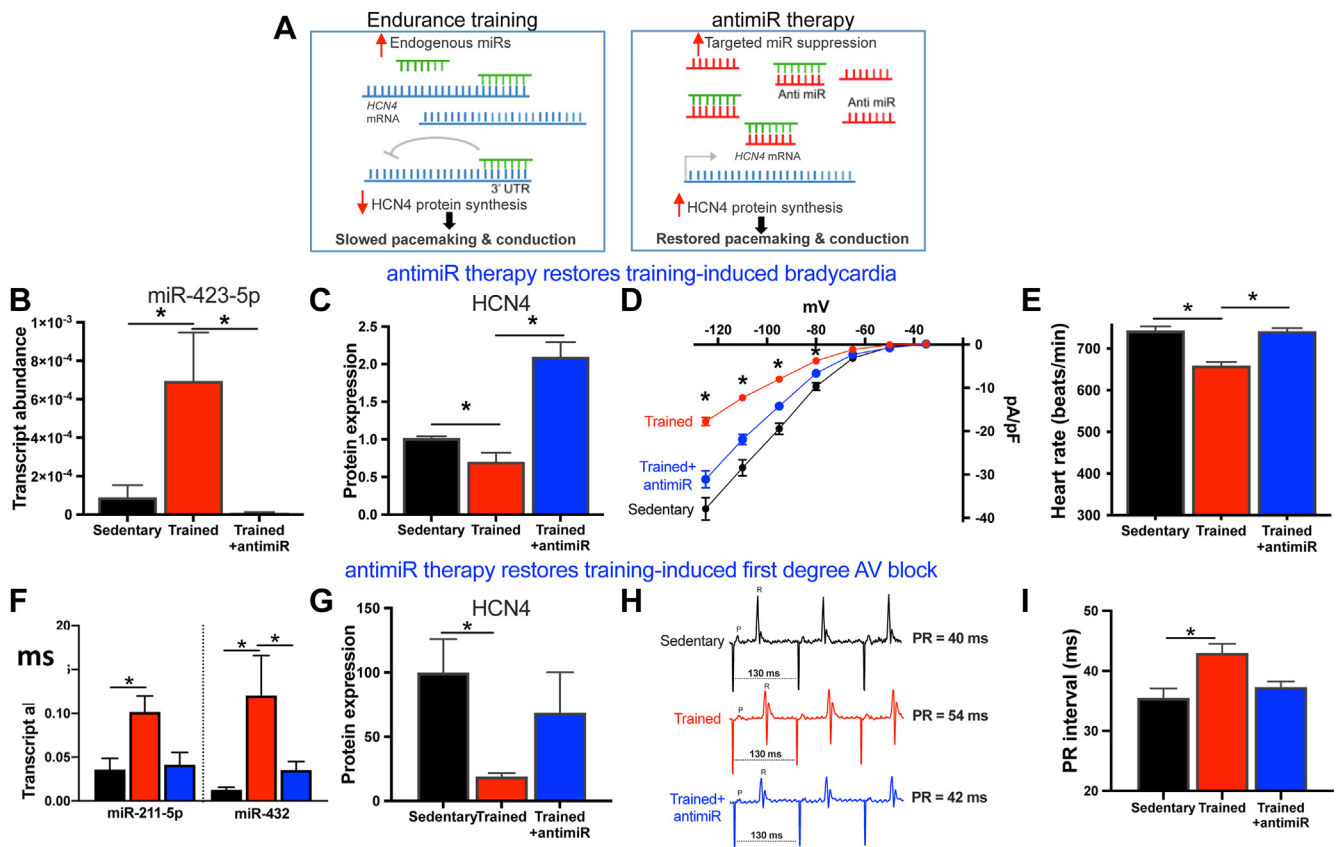
### F.3. Cardioneuroablation

Cardiac neuroablation (cardioneuroablation) is a new technique involving radiofrequency ablation of the vagal ganglia located on the outside of the atria or great vessels. Cardioneuroablation has been shown to relieve sinus node dysfunction and high-grade AV block (as well as neurally mediated reflex syncope) in carefully selected patients for at least 9–24 months with a low incidence of complications.<sup>65–69</sup> This is a promising new treatment of symptomatic bradyarrhythmias. However, currently, there are no recommendations for this method for the treatment of athletes with sinus node dysfunction.<sup>70</sup> Why is cardioneuroablation effective? The vagal nerves innervating the sinus and AV nodes are tonically active and act as a constant brake on both the heart rate and AV conduction; removal of this brake is expected to quicken the heart rate and reduce or eliminate AV block (by strengthening and quickening AV conduction). This mechanism will operate regardless of whether vagal tone is heightened in the athlete.

### F.4. Molecular targeting of ion channel remodeling as a potential therapeutic approach

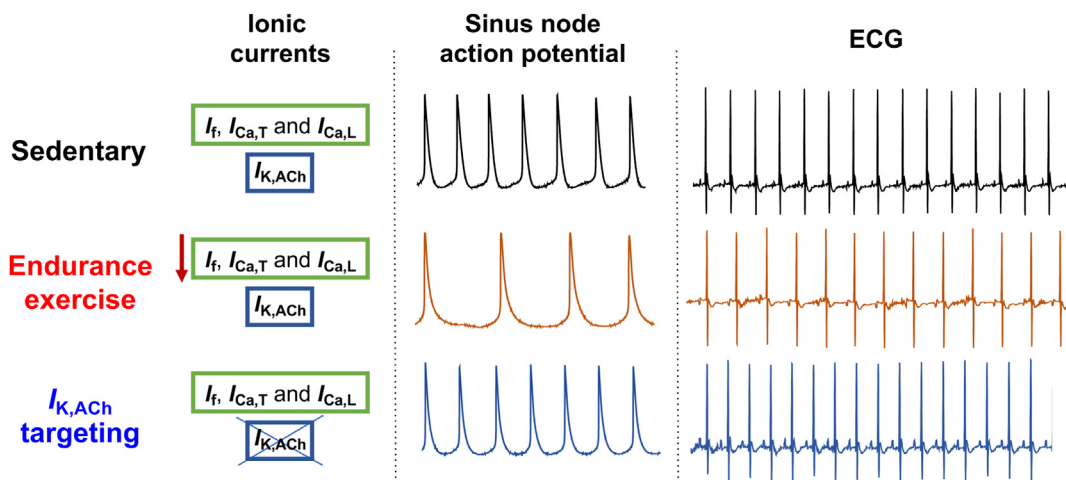
Insight into the molecular processes by which ion channels are remodeled in response to exercise-training presents possibilities for therapeutic innovation. The data reviewed above suggests that a downregulation of HCN4 and, therefore,  $I_f$  is playing an important role in exercise training-induced nodal dysfunction. What is responsible for the downregulation of HCN4? Currently there are 3 clues:

1. *micro-RNAs (miRs)*. miRs are endogenous small noncoding RNAs that have emerged as central regulators of gene expression, exerting posttranscriptional repressive effects on virtually all classes of protein-coding genes by degradation or translational inhibition of target mRNAs. The notion



**Figure 4**

In vivo suppression of hyperpolarization-activated cyclic nucleotide-gated channel 4-targeting micro-RNAs (miRs) using anti-miRs restores sinus node automaticity and atrioventricular (AV) conduction in swim-trained mice. **A:** Summary of miR-mediated sinus and AV node dysfunction in endurance training and its alleviation using anti-miRs. *Blue* correspond to messenger RNA; *green*, miR; *red*, anti-miR. **B–E:** Anti-miR treatment in mice suppresses the swim training-induced upregulation of miR-423-5p in the sinus node (panel B), downregulation of the HCN4 protein in the sinus node (panel C), reduction in funny current density in sinus node myocytes (panel D; mean current-voltage relationships shown), and decrease in heart rate measured in vivo (panel E). From D'Souza et al.<sup>20</sup> **F and G:** Combined administration of anti-miRs targeting miR-432 and miR-211-5p suppresses the swim training-induced upregulation of these miRs in the AV node (panel F) and downregulation of the HCN4 protein in the AV node (panel G) in mice. From Mesirca et al.<sup>19</sup> **H and I:** Restoration of PR prolongation in mice in vivo at a fixed pacing cycle length of 130 ms (panel H; electrocardiogram recordings shown; example P and R waves labeled) and in sinus rhythm (panel I). From Mesirca et al.<sup>19</sup> Mean  $\pm$  SEM shown. \*Significantly different.



**Figure 5**

Schematic diagram showing prevention of endurance exercise-induced sinus bradycardia by ACh (acetylcholine)-activated  $K^+$  current ( $I_{K,ACh}$ ) targeting. **Left:** Summary of changes in inward ionic currents (shown in the *green box*) and outward  $I_{K,ACh}$  (shown in the *red box*) in isolated sinus node myocytes from sedentary mice, swim-trained mice, and swim-trained mice lacking  $I_{K,ACh}$ . **Middle:** Corresponding action potentials recorded from isolated sinus node myocytes showing changes in intrinsic pacemaker activity. **Right:** Corresponding electrocardiogram (ECG) recordings showing changes in heart rate in vivo. Data from Bidaud et al.<sup>22</sup> Endurance exercise induces the downregulation (shown by a *red arrow*) of key inward ionic currents underlying diastolic depolarization, thereby creating an imbalance between inward currents and outward  $I_{K,ACh}$ ; consequently,  $I_{K,ACh}$  acts as a brake, slowing pacemaker activity and thereby heart rate.  $I_{K,ACh}$  targeting (genetic ablation) both removes the brake and prevents downregulation of inward ionic currents, thereby preventing the slowing.  $I_{Ca,L}$ , L-type  $Ca^{2+}$  current;  $I_{Ca,T}$ , T-type  $Ca^{2+}$  current;  $I_f$ , funny current.

that miRs play fundamental roles in arrhythmia pathophysiology has gained progressive ground over the last decade.<sup>71</sup> We hypothesized that miRs that repress HCN4 and  $Ca_v1.2$  mRNAs are upregulated in the sinus node after exercise training and might constitute novel targets for pacemaker-selective therapeutic intervention using specific inhibitors—anti-miRs: a screen of 750 miRs in the mouse sinus node identified significant increases in 25 miRs after swim training, and based on extensive *in vitro* investigations, miR-423-5p was determined as a key HCN4 regulator (Figures 4A and 4B).<sup>20</sup> Strikingly, pharmacological inhibition of miR-423-5p with an anti-miR reversed training-induced bradycardia both *in vivo* and in the isolated sinus node via restoration of HCN4 and  $I_f$  (Figures 4B–4E).<sup>20</sup> In recent work, we have determined the therapeutic efficacy of miR targeting in the treatment of swim training-induced AV node dysfunction.<sup>19</sup> In mice, intraperitoneal injection of a combination of 2 anti-miRs designed to restore expression levels of HCN4 and  $Ca_v1.2$  by suppression of miR-432 and miR-211-5p (upregulated by exercise training in both horse and mouse AV nodes) restored the PR interval to pretraining levels (Figures 4F–4I).<sup>19</sup> These studies are the first proof of concept of miR targeting as a therapeutic approach to restore nodal function. miRs have recently emerged as druggable targets for cardiovascular disease,<sup>72</sup> and the first-in-human study repressing miR-132 with antisense oligonucleotides (anti-miRs) in patients with heart failure has been reported.<sup>73</sup>

2. *G-protein-gated inwardly rectifying K<sup>+</sup> channel 4 (GIRK4)*. The vagus nerve acts on the nodes via the release of the neurotransmitter acetylcholine (ACh), which activates the muscarinic M2 receptor, leading to direct activation of GIRK channels underlying the ACh-activated K<sup>+</sup> current ( $I_{K,ACh}$ ). The channel underlying  $I_{K,ACh}$  is made of 2 subunits: GIRK1 and GIRK4 (also known as  $K_{ir3.1}$  and  $K_{ir3.4}$ ). We have shown that  $I_{K,ACh}$  suppression, either by GIRK4 knockout or by pharmacological block of  $I_{K,ACh}$  by tertiapin-Q, rescues bradyarrhythmias in mouse models of congenital channelopathies caused by loss of function of HCN4,  $Ca_v1.3$ , and  $Ca_v3.1$  channels.<sup>74–76</sup> Of relevance here, we have shown that  $I_{K,ACh}$  suppression also rescues swim training-induced sinus bradycardia (in the case of GIRK4 knockout or pharmacological block of  $I_{K,ACh}$  by tertiapin-Q) and prolongation of the PR interval (in the case of GIRK4 knockout; tertiapin-Q not tested) in the mouse.<sup>22</sup> The rescue is presumably, in part, the result of the removal of the tonic “brake” on the nodes by  $I_{K,ACh}$  as in the case of cardioneuroablation (Figure 5). However, there is another factor contributing to the rescue: GIRK4 knockout prevents the swim training-induced downregulation of  $I_f$  (as well as of  $I_{Ca,T}$  and  $I_{Ca,L}$ ) (Figure 5)<sup>22</sup>; GIRK4 appears to be involved in the transcriptional regulation of pacemaker ion channels and thus the long-term regulation of pacemaker activity. GIRK4 inhibition by tertiapine-Q or a related drug is therefore a potential therapeutic strategy for exercise training-induced bradyarrhythmias. GIRK4

knockout blocks the swim training-induced upregulation of a set of miRs, including the HCN4-downregulating miR-423-5p,<sup>22</sup> and this is consistent with the hypothesis that GIRK4 is acting via miRs.

3. *AMP-activated protein kinase (AMPK)*. AMPK is a fuel-sensing enzyme, and it is activated by an increase in the adenosine monophosphate/adenosine triphosphate (AMP/ATP) ratio; once activated, AMPK will restore the AMP/ATP ratio by stimulating energy-generating processes and decreasing energy-consuming processes.<sup>77</sup> A decrease in heart rate is one means of reducing energy consumption, and activation of AMPK (as a result of a gain-of-function mutation in AMPK) results in bradycardia in the human, and in the mouse the same mutation results in a downregulation of HCN4 and  $I_f$ , potentially a downregulation of the  $Ca^{2+}$  clock pacemaker mechanism (as a result of an upregulation of phospholamban), and a slowing of pacemaking and the intrinsic heart rate.<sup>78</sup> Yavari et al<sup>78</sup> showed that in the mouse, exercise training as a result of 10 weeks of voluntary wheel running results not only in a downregulation of  $I_f$  and a slowing of pacemaking and the intrinsic heart rate but also in activation of AMPK and knockout of the  $\gamma 2$  subunit of AMPK prevents the downregulation of  $I_f$  and slowing of pacemaking. This suggests that AMPK is responsible (in part at least) for the exercise training-induced bradycardia and therefore AMPK is a potential therapeutic target. However, although Yavari et al<sup>78</sup> did not comment on the effect of knockout of the  $\gamma 2$  subunit of AMPK on the exercise training-induced prolongation of the PR interval, they did report that activation of AMPK (as a result of a gain-of-function mutation in AMPK) did not affect the PR interval. If and how AMPK works with GIRK4 and miRs is not known.

## Conclusion

With increasing popularity of recreational exercise and competitive athletics, the clinician caring for athletes may be confronted with an increasing number who exhibit exercise training-induced symptomatic bradyarrhythmias. Appreciation of the fundamental biology underlying this phenomenon may help dispel uncertainties in the management of these patients, provide novel insights into the pathophysiology of cardiac conduction system disease that may extend to management of bradyarrhythmias in the general population, and help in the development of novel therapies.

## Appendix

### Supplementary data

Supplementary data associated with this article can be found in the online version at <https://doi.org/10.1016/j.hrthm.2024.02.050>.

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