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Review

Regulation of cardiac rhythm in hibernating mammals

William K. Milsom [a,*], M. Beth Zimmer [a], Michael B. Harris [b]

[a] *Department of Zoology, University of British Columbia, 6270 University Boulevard, Vancouver, BC, Canada V6T 1Z4*
[b] *Department of Medicine, University of Calgary, Calgary, Alta, Canada T2N 4N1*

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Abstract

The dramatic fall in heart rate exhibited by mammals entering hibernation begins before there is any noticeable fall in body temperature. The initial, progressive decrease in heart rate is the result of a cyclic parasympathetic activation that induces skipped beats and regular asystoles as well as slows the even heart beat. As body temperature subsequently falls, the parasympathetic influence is progressively withdrawn and periods of parasympathetic and sympathetic dominance alternate and give rise to regular periods of arrhythmia (tachycardia followed by bradycardia), and occasional long asystoles or periods of highly irregular cardiac activity. Superimposed on this is a vagally-mediated, respiratory sinus arrhythmia that is accentuated in species that breathe episodically. These events give way to a uniform heart rate in deep hibernation at low temperatures where both parasympathetic and sympathetic tone appear absent. The complete absence of tone is not a function of reduced temperature but is reflective of the state of deep, steady state hibernation. The elevation in heart rate that accompanies the onset of arousal is the result of dramatic increases in sympathetic activation that precede any increases in body temperature. As body temperature then rises, sympathetic influence is slowly withdrawn. Arrhythmias are also common during natural arousals or shifts from lower to warmer hibernation temperatures as periods of parasympathetic and sympathetic dominance again alternate *en route* to re-establishing a steady state in euthermia. The mechanism behind, and the biological significance of, cardiac changes mediated through orchestrated arrhythmias remain unknown.

Keywords: Autonomic nervous control; Heart rate; Hibernation; Parasympathetic control; Sympathetic control; Rodents; Vagus nerve

1. Introduction

As mammals enter hibernation, their metabolic rates fall, accompanied by proportionate falls in ventilation and cardiac output [24,30,31,41,50]. The latter is as a result of a dramatic slowing of heart rate. The stroke volume of the heart increases as a result of passive mechanisms arising from the lengthening of diastole and associated increases in venous return [27,41]. Total peripheral resistance rises, in part as a result of a modest, generalized peripheral vasoconstriction, but primarily as a result of the large increase in the viscosity of the cold blood [27,35,36]. While blood pressure falls significantly, the increases in stroke volume and total peripheral resistance result in a slow diastolic run off such that, despite the prolonged diastolic interval and fall in systolic blood pressure, diastolic blood pressure remains relatively high [4,35]. Perfusion of critical organs is maintained as is autoregulation of coronary flow [3,5,7,21]. The hearts of non-hibernating mammals become arrhythmic and/or fibrillate and cease to function between 10 and 15°C but the hearts of hibernating mammals continue to function at temperatures approaching 0°C, regardless of the season [4,8,32].

Many aspects of cardiac function in hibernating mammals have been reviewed previously [6,11,24,32]. In this review, we will focus on the manner in which heart rate changes during entrance into, and arousal from hibernation, as well as on the way in which these changes are produced. This is a fascinating topic that has not received much attention in recent years and for which data is available primarily only for rodent spe-

* Corresponding author. Tel.: +1-604-822-2310; fax: +1-604-822-2416.
E-mail address: milsom@zoology.ubc.ca (W.K. Milsom)

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cies. While the superficial picture is one of a smooth progressive change in heart rate, the data suggest such changes result from unique, non-stochastic shifts in the balance of sympathetic and parasympathetic cardiac motor outflow. The mechanisms underlying the production of these changes and their biological significance are far from clear.

2. Control of heart rate during entrance into hibernation

Entrance into hibernation is a carefully regulated process that involves a shift in the set point for temperature regulation to progressively lower temperatures [20,43]. While metabolism appears to be actively suppressed during entrance [14,18,19], shivering is also employed throughout entrance as a brake to the speed of cooling [45]. Thus a complex interaction between reduced heat production and both heat loss and heat gain mechanisms is employed to maintain body temperature near the ever changing set point [20,43]. The net effect is a relatively slow, progressive fall in metabolism followed by a fall in body temperature [24,30,31,41,50].

In all hibernators, the heart rate slows prior to any decline in body temperature during entrance into hibernation [30,46,50]. The changes in heart rate and cardiac output mirror the changes in metabolic rate and this clearly indicates that this fall is part of the orchestrated events that produce the entrance rather than a consequence of the change in body temperature that results. Indeed, during periods when body temperature falls too quickly, increased heat production and reduced heat loss can be employed to elevate body temperature back towards the set point while heart rate continues to fall [31]. Furthermore, in anesthetized animals made hypothermic by chilling, body temperature falls much faster and heart rate slower such that heart rate is much more rapid at any given body temperature during hypothermia (where heart rate and metabolism follow body temperature) compared to entrance into hibernation (where body temperature follows metabolism and heart rate) [30]. The fall in heart rate is so dramatic in the early stages of entrance that heart rate may decline by over 50% while body temperature falls by less than 1°C [45](Fig. 1). This initial fall in heart rate is the result of parasympathetic activation and vagal slowing of the heart (see Ref. [32] for review).

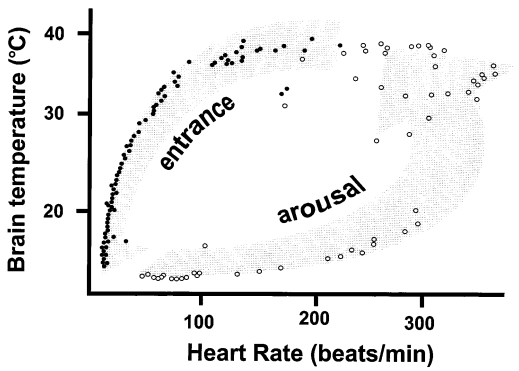

Fig. 1. The relationship between heart rate and body temperature during a consecutive entrance into and arousal from hibernation in a California ground squirrel. (Modified from Strumwasser [45])

Given such a dramatic fall in heart rate and increase in parasympathetic outflow, the possibility arises that the intrinsic autorhythmicity of other elements of the conducting system could break through and become expressed. Interestingly, it has been shown, in bats at least, that there is cholinergic innervation of the ventricle [38,39]. Either stimulation of intramural nerves or administration of exogenous acetylcholine (Ach) caused a decrease in isolated ventricular contractile force at both 37 and 7°C. These responses were blocked by the muscarinic receptor antagonist hyoscine. One possible regulatory role of this cholinergic innervation of the ventricle may be to prevent 'vagal escape' during the powerful parasympathetic inhibition of pacemaker activity in early entrance.

The initial slowing of the heart arises from both a lengthening of the time between even beats and the appearance of skipped beats. The latter is a hallmark signaling the onset of entrance in many species of mammal [10,22,26,28–30,32,34,40,44,46–48](Fig. 2). In species that exhibit a regular pattern of evenly spaced breaths, as body temperature falls the skipped beats change to periods of asystole occurring at regular intervals [31](Fig. 3). The skipped beats and asystoles contribute most significantly to the overall smooth decline in mean heart rate. As animals approach deep hibernation, in most studies heart rate becomes very even (Fig. 3) although isolated, long asystoles may still occur [10,34]. As these periods of asystole progress, respiratory rate increases and a flinch of the body often occurs before the heart resumes beating. These periods of asystole become more frequent and the periods of tachycardia between them become shorter until the animals attain the typical heart rate of deep hibernation [32].

In species that exhibit an episodic pattern of breathing in which periods of almost continuous breathing are interspersed by long periods of apnea, as body temperature falls the skipped beats give rise to two very different types of arrhythmia. The first is a ventilatory sinus arrhythmia in which periods of tachycardia are associated with the breathing episodes. The magnitude of this ventilatory tachycardia decreases with ambient temperature being 108% at 15°C, 32% at 10°C and 11.5% at 5°C in the golden-mantled ground squirrel [17]. The second is a progressive arrhythmia that occurs during the periods of apnea (Fig. 4). Following a breathing episode, heart rate tends to be quite uniform

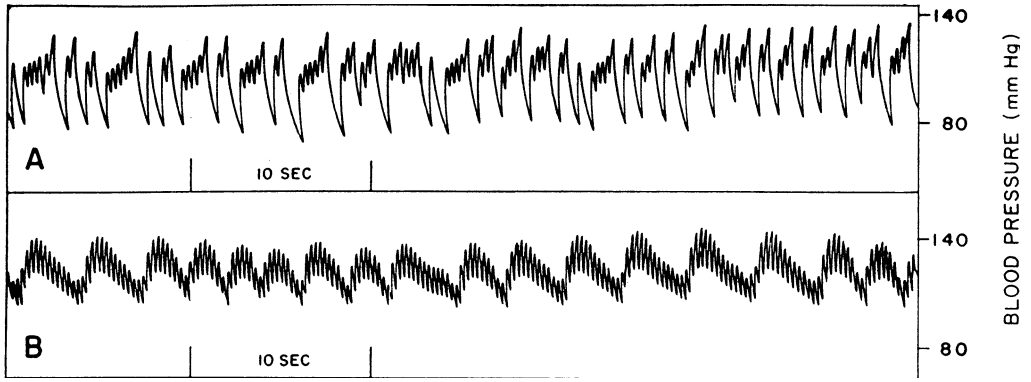

Fig. 2. Blood pressure of a thirteen-lined ground squirrel entering hibernation. (A) Thoracic temperature is 29.5°C, skipped beats are evident. (B) Same animal 10 min after treatment with atropine. Thoracic temperature is 29°C. (From Lyman [32])

and slow. As the apnea progresses short periods of tachycardia followed by bradycardia begin to appear. These become more frequent and often more prolonged as the apnea continues. Finally, the next breathing episode will normally commence during a period of tachycardia and, at higher temperatures, this event is often accompanied by body movements ([37], Zimmer and Milsom, unpublished data). On rare occasion these alternating periods of cardiac acceleration and deceleration occur without the ventilatory sinus arrhythmia. In such cases while the periods of arrhythmia still increase in frequency and duration throughout the apnea, there is no tight correlation between the start of the next breathing episode and the production of the most prolonged period of tachycardia; often the tachycardia significantly lags the onset of breathing [37,48].

Administration of atropine once animals have started to enter hibernation, abolishes skipped beats and asystoles and elevates heart rate overall [35,48]. These observations indicate the heart rate is being modulated and slowed (inducing skipped beats and asystoles, as well as the slowing of the even beats) exclusively by parasympathetic action. Animals that are fully atropinized once entrance has started, however, continue into deep hibernation suggesting that once entrance is initiated, parasympathetic activity and these orchestrated changes in heart rate are not necessary for entrance [32,48]. Animals that have been atropinized before they begin to enter hibernation, however, rarely succeed in entering hibernation suggesting that parasympathetic activation and the initial changes in heart rate that occur before body temperature starts to fall may be necessary for entrance [31].

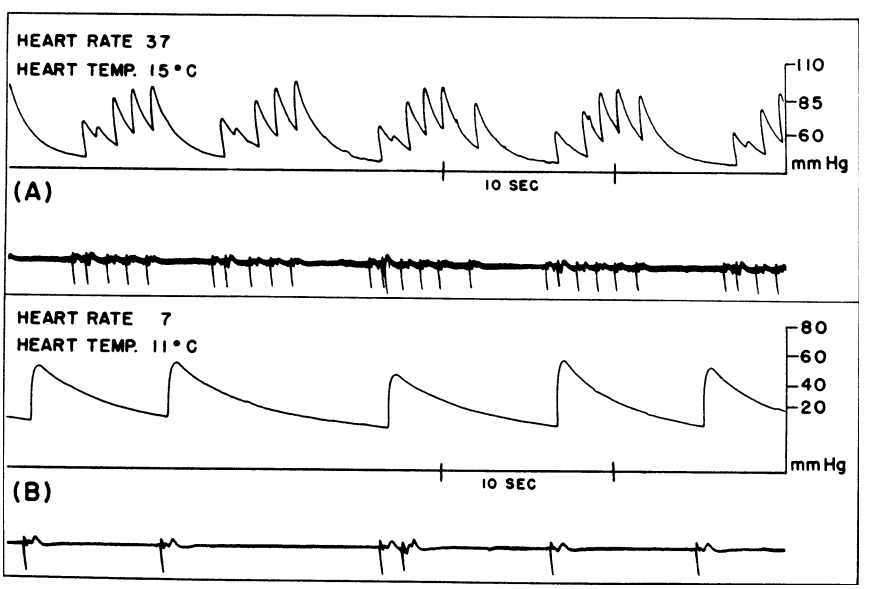

Fig. 3. Blood pressure and electrocardiogram of a thirteen-lined ground squirrel entering hibernation. (A) Thoracic temperature is 15°C, rhythmic asystoles are evident. Also note that at the start of each group of beats following an asystole there is an interpolated premature beat accompanied by little or no pulse pressure. (B) Thoracic temperature is 11°C and heart rate has become uniform but extra systoles with no pulse pressure are still present. (From Lyman [32]).

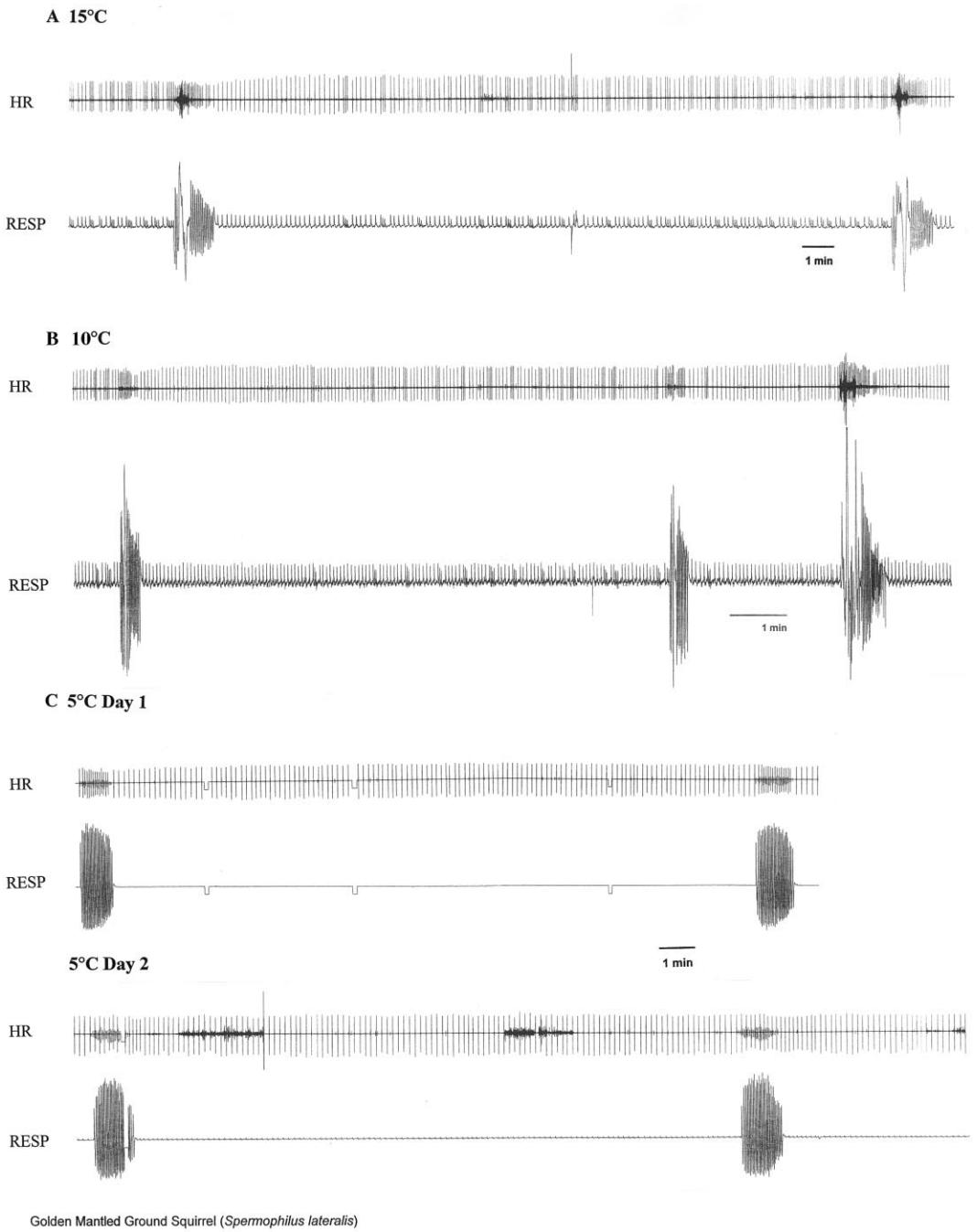

Fig. 4. Electrocardiogram and ventilatory air flow of a golden-mantled ground squirrel hibernating at progressively lower temperatures. At 15°C (A); and 10°C (B), ventilation is accompanied by a tachycardia and periods of arrhythmia consisting of alternating tachycardia and bradycardia occur with increasing regularity throughout the apnea between breathing episodes. Over time at 5°C both the arrhythmias (C, Day 1) and ventilation tachycardia (C, Day 2), disappear. (Note the heart beat is evident in the respiratory trace in A and B).

As with administration of atropine, the effects of vagotomy can only be studied once entrance into hibernation is underway. In euthermic golden mantled ground squirrels vagotomy consistently produces respiratory arrest and death [16]. Once entrance is underway, however, vagotomy can be performed successfully and the animals enter deep hibernation. Vagotomy under these conditions eliminates the ventilation tachycardia, the periods of arrhythmia that occur throughout the periods of apnea and increases the mean heart rate [17,37](Fig. 5). The new heart rate is always intermediate in value between the fastest and slowest rates observed during the arrhythmic periods of acceleration and deceleration that occur during the periods of apnea [37](Fig. 5). In these animals the vagus nerve contains both parasympathetic and sympathetic cardiac fibres

and these results are interpreted to suggest that the periods of tachycardia that occur during the prolonged apneas must involve sympathetic stimulation as well as parasympathetic withdrawal because removal of parasympathetic tone by vagotomy does not elevate heart rate to this extent. The data also suggest that the ensuing bradycardia must be as a result of parasympathetic activation as well as sympathetic withdrawal because removal of sympathetic tone by vagotomy does not reduce heart rate to this extent. Thus the unique arrhythmias that occur throughout the periods of apnea between breathing episodes appear to be the result of alternating periods of sympathetic and parasympathetic dominance.

Administration of exogenous ACh and vagal stimulation continue to reduce heart rate both in intact animals and isolated hearts but this effect is proportionately reduced with temperature throughout entrance [6,35]. Thus the massive increase in parasympathetic tone associated with the initial fall in heart rate before body temperature began to fall, is progressively withdrawn once body temperatures do begin to fall and mean heart rate becomes more a function of the reduced body temperature [32,46].

Following atropine administration long periods of asystole do still occur and it has been suggested that this is the result of withdrawal of sympathetic activity [35]. Indeed, evidence continues to accumulate for a temperature sensitive but continued role of the sympathetic nerves in regulating heart function in hibernators throughout entrance. In hibernating hamsters and ground squirrels the β-adrenergic agonist isoproterenol induced a transient heart rate increase which was blocked by the β-adrenergic antagonist propranolol [32,48]. In isolated hearts, at decreasing temperatures, catecholamines induce a decreased but noticeable positive inotropic and chronotropic effect [25,42]. Similar

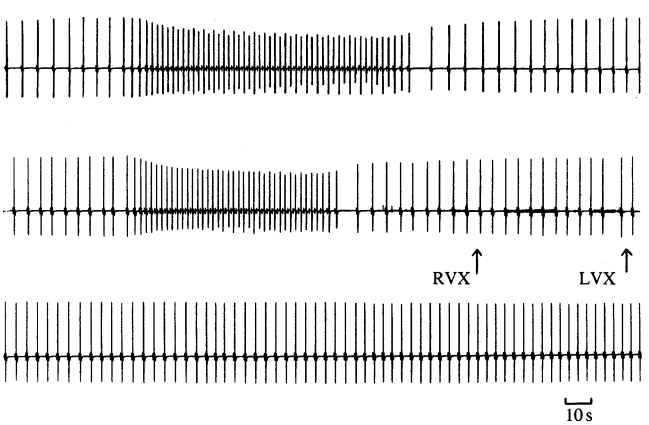

Fig. 5. The effect of bilateral vagotomy on the heart rate of an anesthetized, hibernating golden-mantled ground squirrel exhibiting an oscillating pattern of accelerating and decelerating heart rate. RVX, right vagus cut; LVX, left vagus cut. The traces are continuous. (From Milsom et al., [37])

decreases in temperature in isolated rat hearts led to negative inotropic effects in response to sympathomimetics [42]. This decreased but persistent effect in the hearts of hibernators may be mediated by a decreased affinity and number of receptors in the plasmalemma of cardiac cells [15].

In studies performed on hypothermic animals heart rate slows as a result of a lengthening of the intracardiac interval as temperature falls. There is no appearance of skipped beats, asystoles or arrhythmic cycles of tachycardia and bradycardia once breathing becomes episodic ([23], Zimmer and Milsom, unpublished data). These data suggest that the unique pattern of decreasing heart rate through regulated forms of arrhythmia is not an effect of reduced temperature but is a function of the events associated with hibernation *per se*.

In addition, during entrance, as well as during deep hibernation, sporadic electrical depolarizations of the heart often appear in EKG records with little or no change in arterial pulse pressure [31](Fig. 3). In most instances, these beats are premature. Electrical depolarizations without visible contraction were also observed in cold, isolated hearts from animals that hibernate [33]. The cause of this electrical-mechanical dissociation remains unknown.

3. Control of heart rate in 'deep' hibernation

In all animals in deep hibernation, heart rate appears to be regular and slow. The relative roles of the parasympathetic and sympathetic nervous systems in this state are not yet clear. It is believed by some [32,34,35] that parasympathetic influence is now at a minimum and that the system is predominantly under sympathetic control. There is also evidence, however, to suggest that both sympathetic and parasympathetic tone are reduced in proportion to body temperature with parasympathetic tone remaining dominant and suppressing sympathetic influence [48]. There is also evidence to suggest that both are completely absent [17,37]. The data which give rise to these discrepant views is considered next.

As noted already, many experiments on isolated hearts as well as on intact animals suggest that the resting tone in both sympathetic and parasympathetic nervous systems is progressively reduced as body temperatures fall and animals approach the state of deep hibernation. The sensitivity of the heart to both sympathetic and parasympathetic agonists and antagonists is greatly reduced. In several studies, administration of epinephrine, norepinephrine or isoproterenol at this time, however, will still increase heart rate and these effects are blocked by β-adrenoreceptor antagonists (propranolol) [32,48]. Similar results have been obtained from isolated hearts at these temperatures

[25,42]. Also, drugs that decrease blood pressure and peripheral resistance will give rise to compensating increases in heart rate [34,35].

In many studies, neither atropine, ACh, vagotomy or vagal stimulation appeared to have significant effects on heart rate at this time [32,35] and thus the barostatic reflexes just mentioned were assumed to arise from increased sympathetic tone. From this data it was suggested that parasympathetic influence had been reduced to an absolute minimum in the deeply hibernating state. Variations still occurred in heart rate and these were not as a result of changes in the inherent rhythmicity of the heart. If the pacemaker were the sole determinant of the heart rate in deep hibernation, heart rate and body temperature should be closely correlated and they were not. Furthermore, variations in heart rate were not blocked by the alkaloid veratradine [35] which normally slows the heart by a direct action on the pacemaker. It was suggested therefore, that the variations that remain were the result of changes in sympathetic influence and that this influence further continued to effect physiological reflexes that serve to relate heart function to the rest of the circulatory system in deep hibernation [32].

This conclusion has been challenged by the work of others, however. Twente and Twente [48] maintain the contrary, that the parasympathetic nervous system plays a dominant role in deep hibernation and suppresses sympathetic influence. These researchers found that in two species of ground squirrel and one species of bat, even in steady state deep hibernation when animals had heart rates below 6 beats per min, atropine increased heart rate in the range of 37–117% (from 5.3 to 9.4, 2.5 to 3.5 and 5.2 to 11.3 beats per min in *Citellus lateralis*, *Citellus columbianus* and *Epitescus fuscus*, respectively). Pronounced diastolic arrhythmias continued to be present in their traces in deep hibernation (albeit very infrequently) which were blocked by atropine, indicating that they arose as a result of parasympathetic influence.

While not challenging concepts about the dominance of either the sympathetic or parasympathetic nervous systems in the control of cardiovascular function during deep hibernation, other studies support the conclusion that the parasympathetic system still plays some role in cardiovascular control in hibernating animals [2,17,37,46]. Vagal tone was shown to be low in both euthermic and hibernating golden-mantled ground squirrels and hence vagotomy (or atropine administration) under either condition only led to a rise in heart rate of 6–8% [37]. When heart rates were below 10 beats per min in deep hibernation, this amounted to a change of only 1 beat per min. Similarly, while vagal stimulation had profound effects on heart rate in euthermic animals, when reduced proportionately with temperature and superimposed on the very low heart rates found in hibernation, the net effect was again very small [37]. Where the manifestations of parasympathetic tone were more evident, and potentially of physiological significance, was in the ventilation tachycardia associated with episodic breathing. While this influence was highly temperature dependent, and hence more prevalent in animals hibernating at higher body temperatures, it was present in animals hibernating at low body temperatures as well [17].

Given that both parasympathetic and sympathetic influences are so greatly reduced at low body temperatures, and the heart rates they modulate are so low, it is not surprising that in many studies the effects of parasympathetic and sympathetic agonists and antagonists fail to reach statistical significance (see Ref. [32] for review). This may be more than a consequence of statistical analysis of small changes, however. Many researchers have been careful to distinguish between hibernation at low body temperatures and deep hibernation and this distinction may account for much of the variability in the data. As such, while deep hibernation occurs at low body temperatures, it may be a special state having effects distinct from those that result from reduction in temperature alone. In this context there is a significant amount of data to suggest that animals in this state are unresponsive to sympathetic and parasympathetic influences but can arouse from this state and become responsive.

It has been shown in several studies that vagal stimulation via chronically implanted stimulating electrodes does not produce bradycardia in deep hibernation. High voltage stimulation, however, gives a tachycardia and arousal. Once arousal starts, subsequent stimulation will produce a bradycardia [1,23,32]. Along similar lines, ACh and metacholine administration via indwelling catheters in deep hibernation initially produce tachycardia rather than bradycardia but subsequent injections once cardioacceleration has occurred produce a bradycardia [23,35]. In all of these studies, the observed initial lack of parasympathetic influence in the deeply hibernating animal is not simply an effect of low temperature for a period of cardioacceleration, often without any change in body temperature, is required before normal parasympathetic influence is restored. Lyman and O'Brien [35] observed that it took a shorter period of cardioacceleration before normal parasympathetic influence was restored in ground squirrels that had just entered hibernation than in animals that had hibernated for longer periods. This suggested that changes occurred over the first few days of a bout of hibernation after the animals had reached their stable hibernation temperature. In this regard, we have observed that both the respiratory related sinus arrhythmia and the cyclic arrhythmias occurring during the apneas between breathing episodes in golden-mantled ground squirrels disappear over subsequent days of

hibernation at low (5°C) temperature. As discussed above, the absence of the arrhythmias during the apneic interval implies removal of both sympathetic and parasympathetic tone. Since these changes also occur 1 day or more after body temperature has stabilized, this is not simply a temperature effect.

4. Control of heart rate during arousal from hibernation

It has been proposed that deep hibernation is under autonomic control whereby parasympathetic suppression of sympathetic stimuli maintains hibernation until changes occur in the thresholds of central neurons to sympathetic stimuli (progressive irritability) leading to a sympathetic dominance which allows arousal to ensue [47–49]. Lyman[1] [32] has suggested that some shift in the internal milieu or changes in some component of the heart itself must cause this change in the threshold of sympathetic and parasympathetic responsiveness but what this may be remains an intriguing question. This question is made all the more enigmatic by the fact that it can not be studied in isolated hearts because the procedure required to isolate hearts removes the state effect.

In many instances, arousal may begin slowly with animals continuing to hibernate but at progressively warmer body temperatures. In these instances, the cardiac arrhythmias described earlier reappear [48]. In all instances, however, animals appear to become committed to the arousal process and then, heart rate, ventilation rate and metabolism increase rapidly and simultaneously [9,13,27]. As with entrance into hibernation, changes in heart rate occur prior to any changes in body temperature [45](Fig. 1). The increases in heart rate and cardiac output mirror the changes in metabolic rate again clearly indicating that this rise is part of the orchestrated events that produce the arousal rather than a consequence of the changes in body temperature that result. The initial increase in heart rate is rapid and heart rate may rise from less than 10 to more than 300 beats per min while body temperature rises by less than 3°C [45](Fig. 1). This initial rise in heart rate is exclusively as a result of sympathetic activation because there is virtually no parasympathetic tone to withdraw. Sympathetic stimulation appears necessary for arousal [32]. During arousal, heart rates may peak at over 500 beats per min in several rodent species. Blood pressure reaches its maximum early in the arousal process well before heart rate reaches its maximum suggesting that progressive vasodilation and reopening of vascular beds for rewarming of tissue must be occurring subsequent to this [9,13,27]. Marked arrhythmias occur throughout arousal also although this has received very little attention [12,48]. Heart rates peak in mid to late arousal and this coincides with the peak metabolic rates associated with the demands of shivering and non-shivering thermogenesis. Once body temperature starts to rise sympathetic tone is slowly withdrawn until it is again at normal levels as body temperature attains its euthermic level. Presumably parasympathetic tone remains low but the sensitivity of the heart to sympathetic and parasympathetic agonists will progressively increase with body temperature [6,25,32,42,48].

5. Conclusions

Dramatic changes occur in heart rate as part of the events producing entrance into and arousal from hibernation. On entrance, an initial large increase in parasympathetic tone reduces heart rate by as much as 50% before body temperature falls significantly. This increase in parasympathetic tone is slowly replaced by the Q_{10} effects of temperature such that heart rates of less than 10 beats per min are maintained in deep hibernation at low body temperatures in the apparent absence of any parasympathetic tone. The heart appears to be slowed by cyclic parasympathetic activation inducing skipped beats, asystoles and slowing of the even beats in animals that breathe in a regular fashion. In species that breathe episodically, a vagally mediated ventilatory tachycardia is also present as well as cyclical periods of tachycardia and bradycardia that occur throughout the apneic intervals. The latter are the result of alternating periods of sympathetic and parasympathetic dominance. In deep hibernation, the heart beat is slow and uniform and evidence suggests that cardiac sensitivity to both sympathetic and parasympathetic influences is greatly reduced if not eliminated. On arousal, an initial large increase in sympathetic tone elevates heart rate, often above euthermic levels, before body temperature increases significantly. This increase in sympathetic tone is slowly replaced by the Q_{10} effects of temperature as body temperatures rise and return to euthermic levels.

While there is a large body of literature that describes these events, there is little to explain why the heart is slowed by such carefully orchestrated arrhythmias. There is no evidence to indicate how this is achieved in a mechanistic sense although the data certainly suggest it is of central origin. It also remains unclear why this occurs in a biological sense; what is the physiological

[1] While the roles of the parasympathetic and sympathetic nervous system in controlling cardiac rhythm are undoubtedly linked to the roles of these two branches of the autonomic nervous system in controlling hibernation *per se*, thresholds for the control of these two processes do appear different [48]. Consequently, a continuing role of autonomic control of deep hibernation is not incompatible with an absence of autonomic control of cardiac rhythm in deep hibernation.

significance of producing change in this way. Does it have any adaptive significance? These questions, amongst others, must remain a focus for work to come.

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