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EDITORIAL

Rest Heart Rate and Life Expectancy

HERBERT J. LEVINE, MD, FACC

Boston, Massachusetts

Among mammals, there is an inverse semilogarithmic relation between heart rate and life expectancy. The product of these variables, namely, the number of heart beats/lifetime, should provide a mathematical expression that defines for each species a predetermined number of heart beats in a lifetime. Plots of the calculated number of heart beats/lifetime among mammals against life expectancy and body weight (allometric scale of 0.5×10^6) are, within an order of magnitude, remarkably constant and average $7.3 \pm 5.6 \times 10^8$ heart beats/lifetime. A study of universal biologic scaling and mortality suggests that the basal energy consumption/body atom per heart beat is the same in all animals ($\sim 10^{-8}$ O_2 molecules/heart beat). These data yield a mean value of 10×10^8 heart beats/lifetime and suggest that life span is predetermined by basic energetics of living cells and that the apparent inverse relation between life span and heart rate reflects an epiphenomenon in which heart rate is a marker of metabolic rate. Thus, the question of whether human life can be extended by cardiac slowing remains moot and most likely will only be resolved by retrospective analyses of large populations, future animal studies and clinical trials using bradycardic therapy.

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> . . . the fundamental object of contention in the life struggle, in the evolution of the organic world, is available energy.
>
> Ludwig Boltzmann (1886)

It is common knowledge that smaller mammals have higher heart rates and shorter life spans than larger members of their class. The explanation of the former is a biophysical imperative in which the ratio of heat loss (a function of body surface area) to heat production (a function of body mass) increases as body size is reduced. Prevention of a fall in body temperature in homeotherms necessitates an increased metabolic rate, which in turn is correlated with, and is perhaps responsible for, an increased heart rate. Indeed, regression analysis on logarithmic coordinates between body mass and metabolic rate among mammals yields a straight line that has exactly the same slope as a plot between body mass and heart rate (1). In addition to the role of metabolic rate, other allometric biophysical principles may be operative in determining the optimal heart rate in animals of differing size (2). The explanation of a shorter life span in smaller mammals, however, is less apparent.

According to Sohal and Weindruch (3), there are only three regimens that reliably extend the maximal life span of animals: 1) lowered ambient temperature in cold-blooded animals and hibernating mammals; 2) a decrease in physical activity in cold-blooded animals; and 3) caloric restriction. Although associated decreases in heart rate generally accompany all three of these regimens, a primary reduction in heart rate has not been established as etiologic in extending life span. The following represents an effort to examine the variations in life span in mammals, with particular reference to their relation to heart rate.

Among mammals, with the exception of the human species, there is a linear, inverse semilogarithmic relation between heart rate and life expectancy. As illustrated in Figure 1, this relation, excluding humans, spans a 35-fold difference in heart rate and a 20-fold difference in the life span of these mammals. Although some minor differences exist among the four major orders of mammals (Life span/unit weight of primates > Carnivores = Rodents > Ungulates) (7), this overall inverse relation between heart rate and life span appears valid. The one conspicuous exception to this observation is humans. One might speculate as to the reasons why, or more specifically how, modern humans have stretched the boundaries of biology to achieve a life expectancy of 80 years. Perhaps the most obvious explanations would credit advances in science, medicine and sociology. Although there are moments and events in our present civilization that seem to threaten this achievement, it is clear that at least for now the human species is, among mammals, the front runner in life expectancy.

If we accept the observation that there is indeed an inverse relation between heart rate and life span, then the product of these variables, namely, the number of heart beats/lifetime, should provide a mathematical expression that defines for each species a predetermined number of heart beats in a lifetime.

In Figure 2A, the calculated number of heart beats/lifetime among mammals is plotted against life expectancy. It will be seen that despite a 40-fold difference in life expectancy, the number of heart beats/lifetime is, within an order of magnitude, remarkably constant. When the calculated number of heart beats/lifetime of mammals is plotted against body mass (Fig. 2B), the constancy of heart beats/lifetime is even more

From the Department of Medicine, Division of Cardiology, Tufts University School of Medicine and New England Medical Center, Boston, Massachusetts.

Address for correspondence: Dr. Herbert J. Levine, New England Medical Center, 750 Washington Street, Box 315, Boston, Massachusetts 02111. E-mail: herbert.levine@es.nemc.org.

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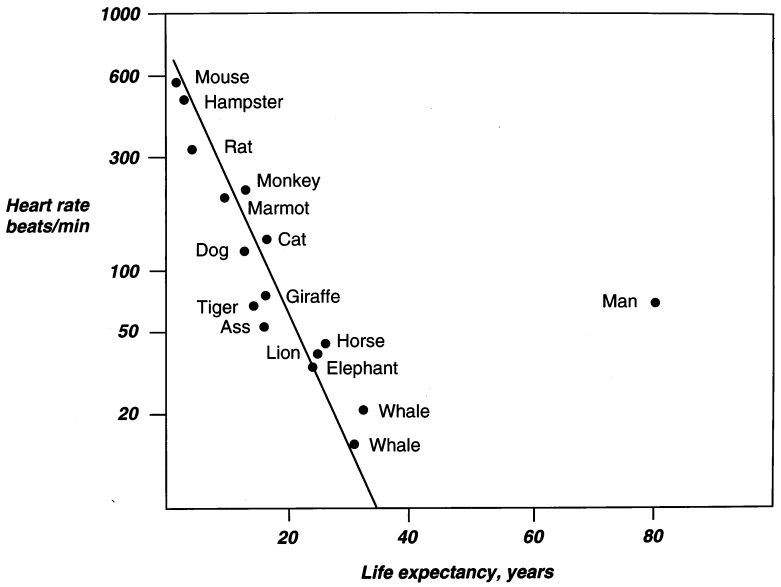

Figure 1. Semilogarithmic relation between rest heart rate and life expectancy in mammals. Most coordinates represent average values (4–6).

striking, particularly when it is appreciated that the allometric range spans almost 0.5 million-fold in body weight (from hamster to whale). Because heart weight and body weight are almost linearly related in large and small mammals (8) (heart weight is 0.5% to 0.6% of body weight), this allometric relation would be the same between heart weight and heart beats/lifetime.

These observations suggest that despite wide variations in body size and heart rate, the total number of heart beats/lifetime among mammals is remarkably constant. Although this analysis has not been examined among nonmammalian vertebrates, there is reason to believe that the relative constancy of heart beats/lifetime is widely distributed in the animal kingdom. For example, a Galapagos tortoise with a life expectancy of 177 years and a heart rate of 6 beats/min (4) has 5.6×10^8 beats/lifetime, quite similar to the mean value of 7.3×10^8 calculated from the mammals shown in Figure 2. Among fish, the average number of heart beats/lifetime tends to be an order of magnitude less than that in mammals (i.e., 3.5×10^7 for haddock and 6.7×10^7 for brown trout), whereas the tiny arthropod *Daphnia* uses up to 1.3×10^7 heart beats (at 25°C) in a brief life span of 30 days (9).

However, it does appear clear that there is little variation in the total number of heart beats/lifetime among mammals, and perhaps this observation can be extended to many species of animals. This finding suggests that a basic characteristic of the energetics of living matter drives this phenomenon. Some insight into this mechanism is provided by the intriguing report by Azbel (10) on universal biologic scaling and mortality. Drawing from a wide allometric scale of 10^{20}-fold among living organisms, Azbel concludes that the energy consumption/body atom per heart beat is the same (within an order of magnitude) in all animals. Indeed, he calculates that the basal O_2 consumption/body atom of all animals is ~ 10 O_2 molecules/lifetime and in those animals with a heart, $\sim 10^{-8}$ O_2 molecules/heart beat. It is therefore not surprising that the number of heart beats/lifetime calculated from these data (10×10^8) is strikingly similar to the mean value observed among the mammals shown in Figure 2 (7.3×10^8). That Azbel extends his analysis to include protozoa and bacteria with oxygen metabolism (unit time replacing a heart beat) further suggests that life span is predetermined by basic energetics of living cells and that the apparent inverse relation between life span and heart rate reflects an epiphenomenon in which heart rate is a marker of metabolic rate.

These considerations do not exclude the possibility that rest heart rate may prove to be a determinant of life span, and perhaps the obvious extension of these observations is to ask whether there is the potential to prolong life by measures that reduce average heart rate. If humans are predetermined to have ~3 billion heart beats/lifetime, would a reduction in average heart rate extend life? If so, one might estimate that a reduction in mean heart rate from 70 to 60 beats/min throughout life would increase life span from 80 to 93.3 years. Although this experiment has never been performed in humans, Coburn et al. (11) have made an effort to examine this question in an animal study. Several hundred A/J mice, on weaning, were fed normal feed or feed containing ~0.05 mg digoxin/day. Although equivalent doses of digoxin would promptly kill a human (>100 mg/day), the treated mice lived longer than control mice (50% survival of 850 vs. 700 days, $p < 0.001$) and had slower heart rates (266 vs. 563 beats/min, $p < 0.001$). However, the conclusion that prolongation of life in these mice was the consequence of a slower heart rate was seriously confounded by the fact that the mice treated with digoxin had a lower body weight than control mice, and starvation has been shown to extend the life of rodents (3). Interestingly, the digoxin-treated mice were found to have caloric intake comparable to the control mice, and therefore the explanation for weight loss in the treated mice is unex-

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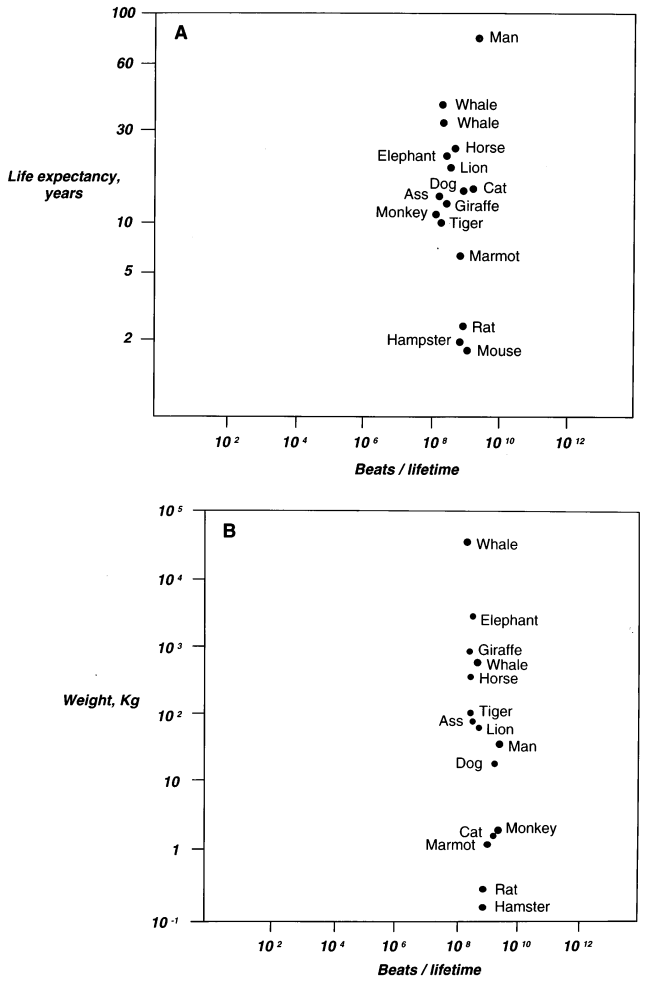

Figure 2. Relation between life expectancy and total heart beats/lifetime (**A**) and allometry of total heart beats/lifetime (**B**) among mammals (see text).

plained. Thus, a specific role for cardiac slowing in the prolongation of life in digoxin-treated A/J mice remains at best uncertain.

Together, the above observations suggest that a primary reduction in myocardial metabolic rate, with associated cardiac slowing, may have the potential to prolong human life. However, because myocardial O_2 consumption/unit weight is the same in normal, hypertrophied and failing human hearts (12), the demonstration that a primary reduction in heart rate prolongs life would have to invoke a mechanism other than a reduction in myocardial metabolic rate. Nonetheless, clinical studies abound with the suggestion that cardiac slowing may improve survival. Beta-adrenergic blockade improves survival in patients after myocardial infarction (13) and possibly in patients with dilated cardiomyopathy (14,15), and the bradycardic effects of regular exercise are considered by many to extend life in those with or at risk for coronary disease. Although it is acknowledged that the malefic effects of sustained beta-adrenergic stimulation in cardiac disease are far greater than that of positive chronotropism, the provocative observation that heart rate and life expectancy among mammals are inversely related and that their product is a near constant begs the question, "Can human life be extended by cardiac slowing?"

Thus, although there are considerable constraints on the likelihood of demonstrating a life-prolonging effect of cardiac slowing in humans, efforts to do so should not be discouraged. Perhaps a first attempt in this direction would be an actuarial analysis of life insurance data because a purely bradycardic agent for use in animal studies and clinical trials is not yet available to us.

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