The Origin of Disease and Health, Heart Waves: The Single Solution to Heart Rate Variability and Ischemic Preconditioning

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In the world of medicine are two extraordinary experimental mysteries that intuition at first suggests are totally unrelated. The first mystery, from the field of cardiology, is: Why does a decrease in heart rate variability (HRV) emerge as a single common risk factor for virtually all chronic disease patients at all ages? The second puzzle, from the field of cardiovascular surgery, is: Why should the process of cyclically clamping and declamping the coronary arteries—called ischemic preconditioning—just prior to clamping them for a prolonged period during coronary surgery protect the myocardium from cellular death?

The first mystery is associated with disease and death; the second with survival and life. These associations may be counterintuitive: a decrease in HRV should imply stability and life, not mortality; ischemic preconditioning should imply instability and death, not well being. Moreover, these mysteries are interrelated. Although researchers in molecular biology are looking for two different answers for these mysteries, I am suggesting one, albeit counterintuitive, answer.

As a vascular surgeon dealing with patients in crisis, and as founding chairman of the United States Olympic Sports Medicine Council dealing with athletes in their prime, I had the unique opportunity to view the heart in both the worst case circumstances in the operating room and in the best case on the playing field. From these combined perspectives, I have developed a new understanding of heart behavior called heart waves, which also suggests the way waves behave in nature.

This new understanding of wave behavior explains how the seemingly complex, disparate information of the body's behaviors, molecular biology, and genes is organized into a single coherent picture. I call this the wave theory.[1]

The theory has wide implications. It not only suggests an explanation for the two mysteries but also explains the underlying origin of chronic disease; at the same time, it provides the means for prevention and reversal of those diseases and the means for optimizing health, performance, and longevity. This paper presents the wave theory, previously described in the context of universal law,[2] as it relates to the function of the human heart in biology and medicine.

Why is Decreased Heart Rate Variability (HRV) Associated With So Many Health and Behavior Disorders?

HRV is a simple measure of the beat-to-beat evenness of consecutive heartbeats. A decrease in HRV corresponds to consistent interbeat intervals (IBI). The more metronome-like the heart rate, the lower the HRV. Conversely, the more uneven the IBI, the greater the HRV.

HRV is easily calculated by measuring the time between successive R-R intervals of QRS complexes as recorded on an electrocardiographic strip (Figure 1a, b). To measure HRV and heart rates over linear time, each heart-beat cycle of systole and diastole is treated as a dimensionless point. Medicine ignores nature's cycles of systole and diastole in favor of idealizing the cycles as serial points in a straight line to calculate beat-to-beat heart rate variability. The patterns of natural heart beats are converted into points, lines, and numbers (as if there were gaps from point to point). In this dematerialization of the cyclic heart pattern into abstractions the natural continuum of the heart wave is lost (see Figure 1c, d).

Over the last thirty years a decrease in HRV has received increasing attention as a prognostic indicator of risk associated with a variety of

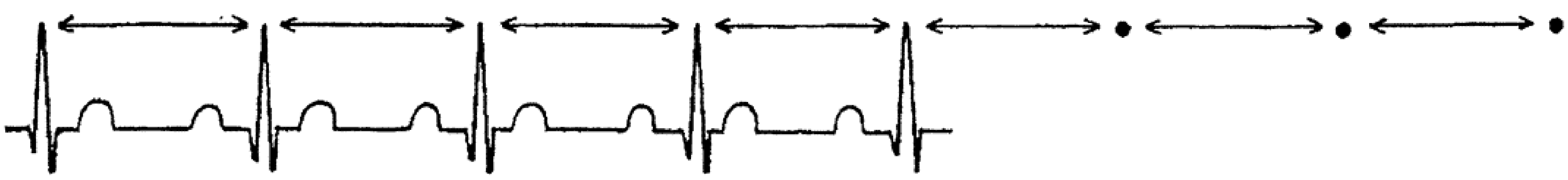

Figure 1a. Decreased HRV on an ECG.

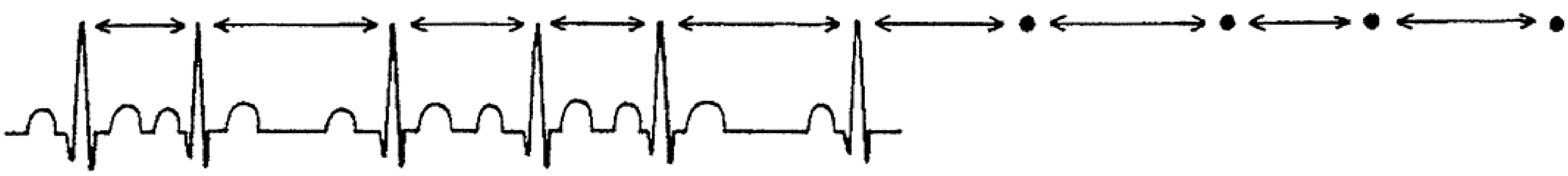

Figure 1b. Increased HRV on an ECG.

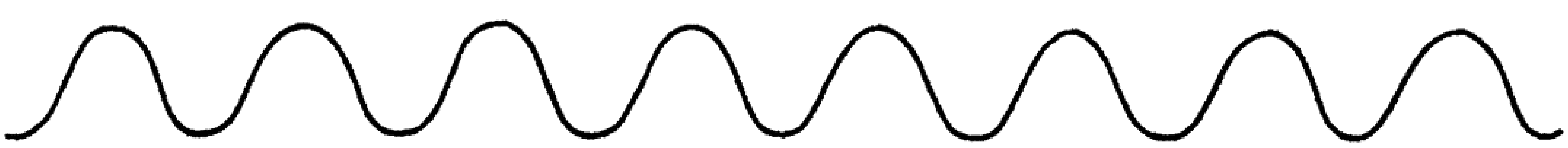

Figure 1c. Decreased variability of systole/diastole.

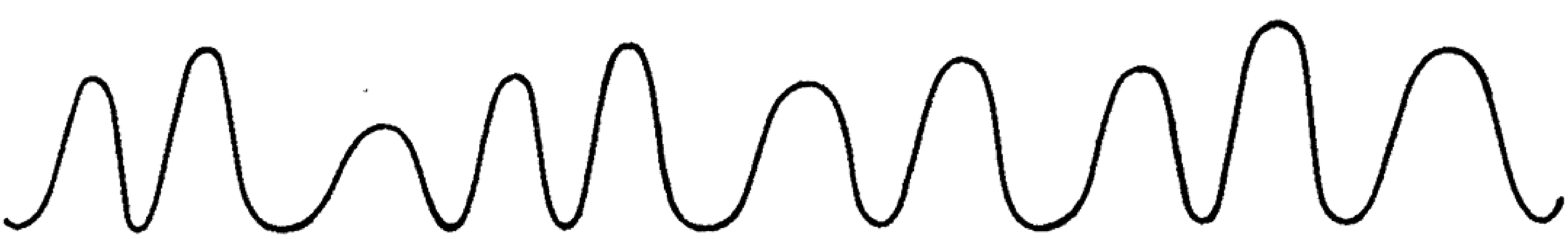

Figure 1d. Increased variability of systole/diastole.

chronic diseases, behavioral disorders, mortality, and even aging. The finding of one single risk factor for such a wide variety of problems is unexpected. Historically medicine has searched for a single causal agent—such as a molecular abnormality, a virus, or a genetic mutation—as the etiology of any particular disease. Similarly we tend to think of a specific risk factor as being associated with a particular disease. Consequently the discovery of a single risk factor associated with the widest spectrum of disorders is strong evidence of some underlying connecting phenomenon of disease and health that we have not yet understood.

Decreased HRV in Health and Behavioral Disorders

A review of the literature shows the magnitude of decreased HRV as one single risk factor involving a surprisingly wide spectrum of disorders—from *in utero* and infant mortality to geriatric mortality; from cancer and cardiovascular disease to autoimmune and behavioral disorders; from HIV/AIDS infection to drug addiction and juvenile delinquency. No other single risk factor has been implicated so convincingly and in such a wide range of conditions.

The first description of a decrease in HRV as a risk factor for disease was published in 1965 by E. H. Hon and S. T. Lee when they observed its association with infant mortality.[3] Schechtman, et al., found decreased HRV in Sudden Infant Death Syndrome.[4] Intriguingly a more recent

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study on SIDS by Harper reported a low variability in the intervals between breaths in SIDS babies.[5] As part of the Framingham Heart Study, H. Tsuji, et al., reported that in an elderly cohort with a mean age of 72 ±6 years reduced HRV was found to predict mortality from all causes, in particular cancer and cardiovascular disease.[6] They concluded that ambulatory ECG monitoring of HRV offers prognostic information that can supplement that provided by the evaluation of traditional risk factors. Clearly, this has important implications for all of medicine and science.

A current Framingham Heart Study describes the impact of reduced HRV on risk for cardiac events.[7] This was the first prospective study to suggest an association between reduced HRV and heart disease risk in a community-based population. Hayano, et al., reported a positive correlation between decreasing HRV and the progression of coronary artery disease.[8] Temoshok, et al., showed that patients with HIV infection and AIDS who displayed increased heart rate reactivity and "physiological toughness" survived significantly longer than those with decreased HRV.[9] Neubauer, et al., found in patients with multiple sclerosis reduced long term and short term HRV marked by "an abnormally great regularity, broken now and then by peculiar bursts of changes in heart rate."[10] In another autoimmune disease study, Murry, et al., correlated decreased HRV with insulin dependence in diabetic males.[11] Gunderson, et al., saw a similar HRV pattern in juvenile diabetics.[12]

Hirsh, et al., found that HRV decreased in subjects with weight maintenance at higher than "usual" levels but increased with low-calorie feeding or with weight maintenance at lower than "usual" levels.[13] Garfinkel, et al., found reduced HRV among cocaine users.[14] Raine, et al., found correlations between HRV and juvenile delinquency and adult criminal behavior.[15] The significance of the finding of decreased autonomic arousal associated with a low heart rate has been confirmed through additional research by Adrian Raine in Mauritius. He studied 1,795 children between the ages of 3 and 11 and found a statistically significant correlation between the incidence of aggression and those turning to juvenile crime with a decrease in autonomic arousal and heart rate.[16] Lowensohn found low HRV among patients with severe brain damage.[17]

In 1994, an International Task Force representing the European Society of Cardiology and the North American Society for Pacing and Electrophysiology was established to study HRV. The task force identified changes in HRV that may be early manifestations of neurological disorders including Parkinson's disease, multiple sclerosis, and Guillain-Barre syndrome. The Task Force also suggested that HRV may contribute to our understanding of the effects of space flight.[18] Goldberger, et al., saw evidence that bed-rest reduces HRV.[19] Waddington, et al., showed that HRV declines linearly with age.[20] O'Brien, et al., found a similar decline of HRV using a computerized method of measurement of R-R interval variation.[21]

Though aging is not a chronic disease per se, a decrease in HRV associated with aging is significant for two reasons: (1) the general incidence of chronic disease increases with increasing age and (2) both a decreased maximum heart rate and a decrease in HRV are found to be associated with increasing age.

The HRV International Task Force

The above studies all point to the fact that HRV stands alone as a single risk factor of virtually all chronic diseases and behavioral disorders at all ages. However, despite HRV being easy to quantify, without a definitive understanding of what HRV truly represents, it has remained a complex issue for medical science. This was emphasized by the HRV International Task Force of mathematicians, engineers, physiologists, and physicians.

The Task Force's objective was to study the many ramifications of HRV including the significance and meaning of its many different measures.

The goals of the Task Force are: to standardize the nomenclature and specify standard methods of measurement, to define physiological and pathophysiological correlates, to describe appropriate clinical applications, and to identify future areas of research.[22]

HRV, Maximum Heart Rate, and Heart Waves

The solution to the HRV mystery requires a new understanding of how

HRV is connected to maximum heart rate and to what I call heart waves.

Maximum Heart Rate

Exercise physiologists and fitness buffs use a different kind of heart rate measurement that, unlike HRV, is well known to the general public: maximum heart rate. Maximum heart rate has been routinely used to assess one's target heart rate zone for linear aerobic exercise. The rough rule of thumb to determine one's maximum heart rate is to subtract your age from 220. The key point of this fitness formula is simple, yet compelling: as one gets older, the maximum heart rate drops (Figure 2).

This lowering of maximum heart rate with increasing age is accepted as a given because of the perceptions that (1) it is just the way nature works and (2) there is nothing one can do about it. Indeed, exercise physiologists do not consider raising the maximum heart-rate level as a way to increase longevity because training to a maximum heart rate is itself considered a risk factor for a heart attack.

Heart Rates and Heart Waves

As a matter of course, medicine and science plot heart-rate changes (maximum heart rate, resting heart rate, target heart rate, and HRV) on linear electrocardiographic strips. The assumption is that both the heart beat itself and heart beats averaged over time as a heart rate are linear in nature. We are so accustomed to seeing and using linear electrocardiograms and averaging heart rates over linear time that it seems to make sense that that's the way it works in nature. The inference is that a heart beat can be treated as an abstract mathematical point moving step-by-step in a line to be averaged out into a heart rate (beats per minute).

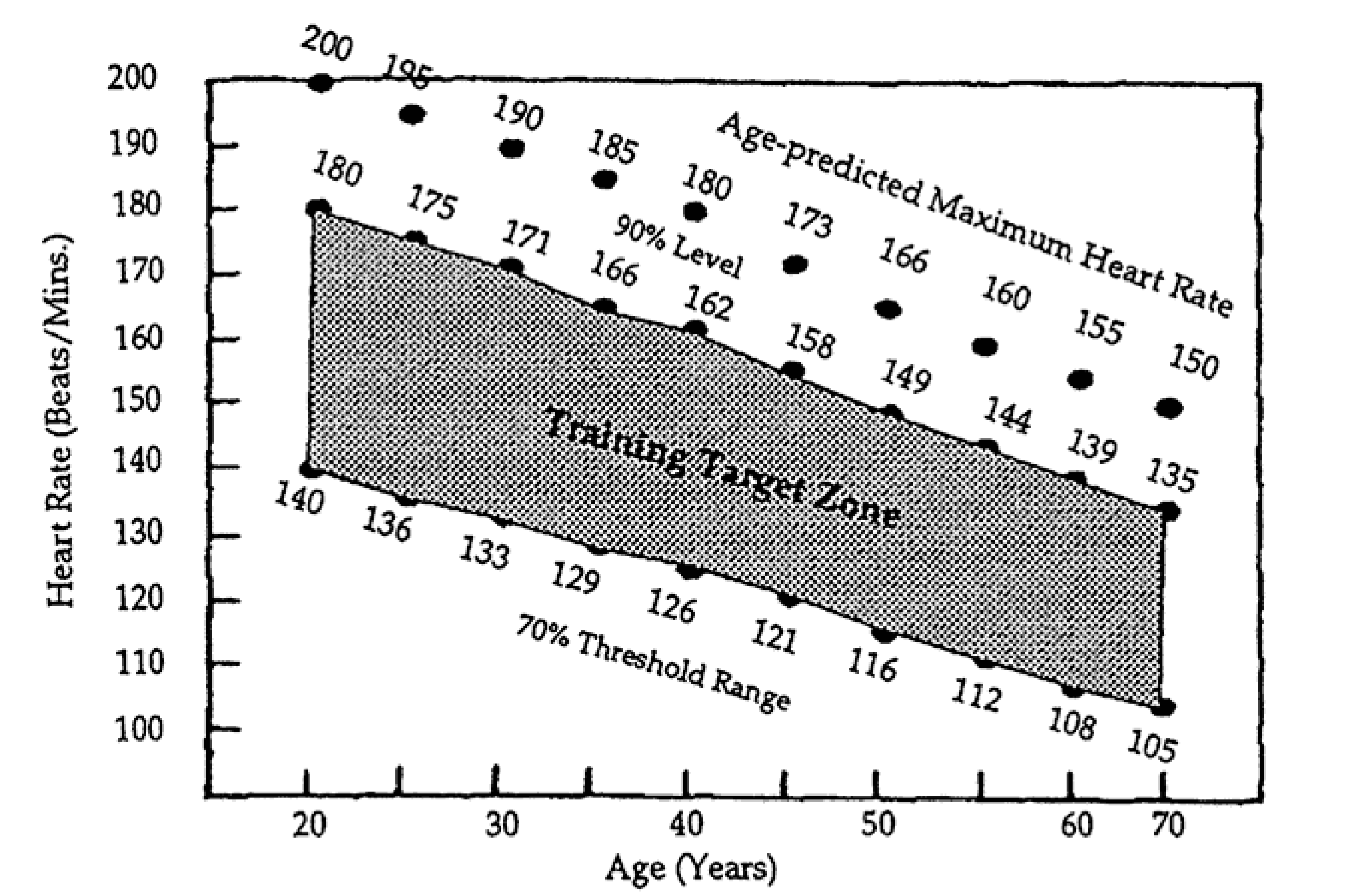

Figure 2. Typical minimum heart rates.

The following three steps show that, though the linear analyses of maximum heart rate and HRV are useful from a measurement perspective, they do not reflect the way the heart behaves in nature. In the three steps that follow I will explain:

1. The way the heart beat is a wave.
2. The way the heart rate is a wave.
3. The way the heart beat as a wave and the heart rate as a wave simultaneously wave within one another in what I call the heart wave.

Step 1:The Heart Beat as a Wave

Currently, medicine analyzes HRV by treating each heart beat as if it were a dimensionless point on an electrocardiogram. Instead, I view the heart beat as it actually exists in nature: a cycle of systolic contraction (work) and diastolic relaxation (recovery). The heart beat itself is an inherent wave continuum of energy expenditure and energy recovery (see Figure 3a).

Step 2: Maximum Heart Rate as a Wave

Maximum heart rate, as achieved by intensive exercise, is currently viewed as an isolated, linear measurement averaged out over time (heart beats per minute). However, in nature as with HRV, the maximum heart rate is a wave continuum. Beginning with one's resting heart rate, exercise increases metabolic activity until the maximum heart rate is reached. As one recovers, metabolic activity decreases and the heart rate slows toward the resting heart rate. Therefore, in nature, "maximum heart rate" and "resting heart" are not separate entities. Like systole and diastole, maximum heart rate (as achieved through the process of exercise) and resting heart rate (as achieved through the

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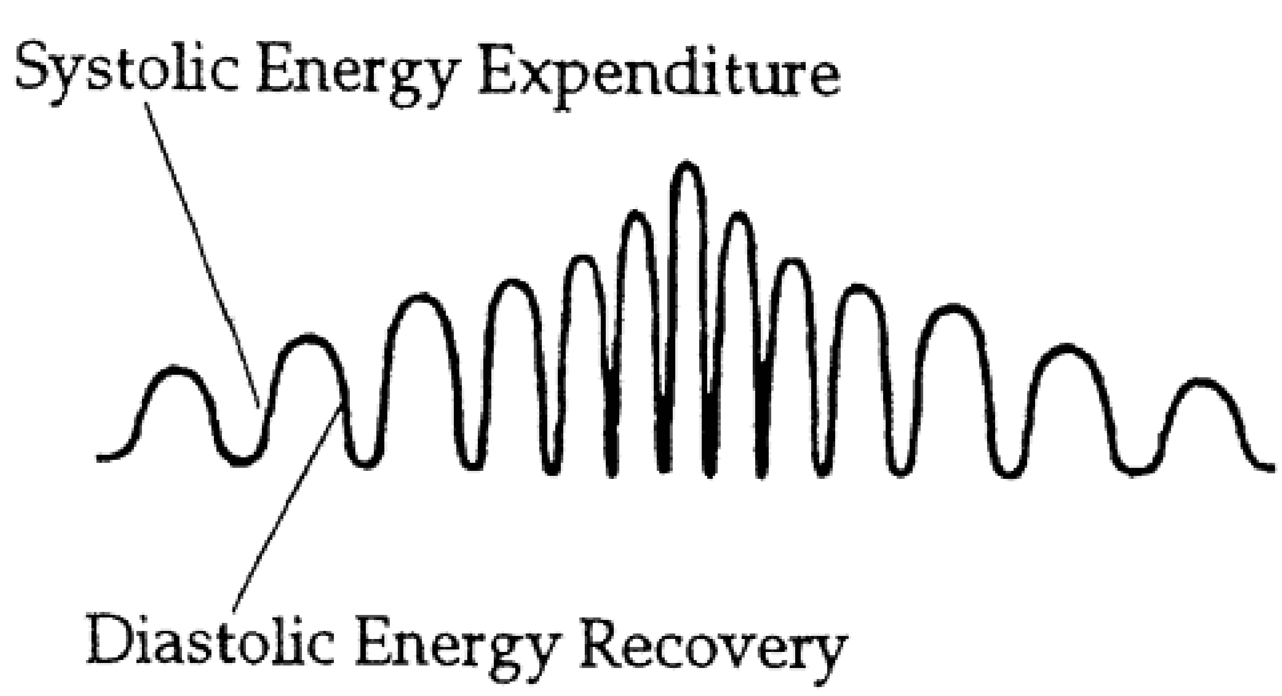

Figure 3a. *Cycles of systolic expenditure and diastolic recovery.*

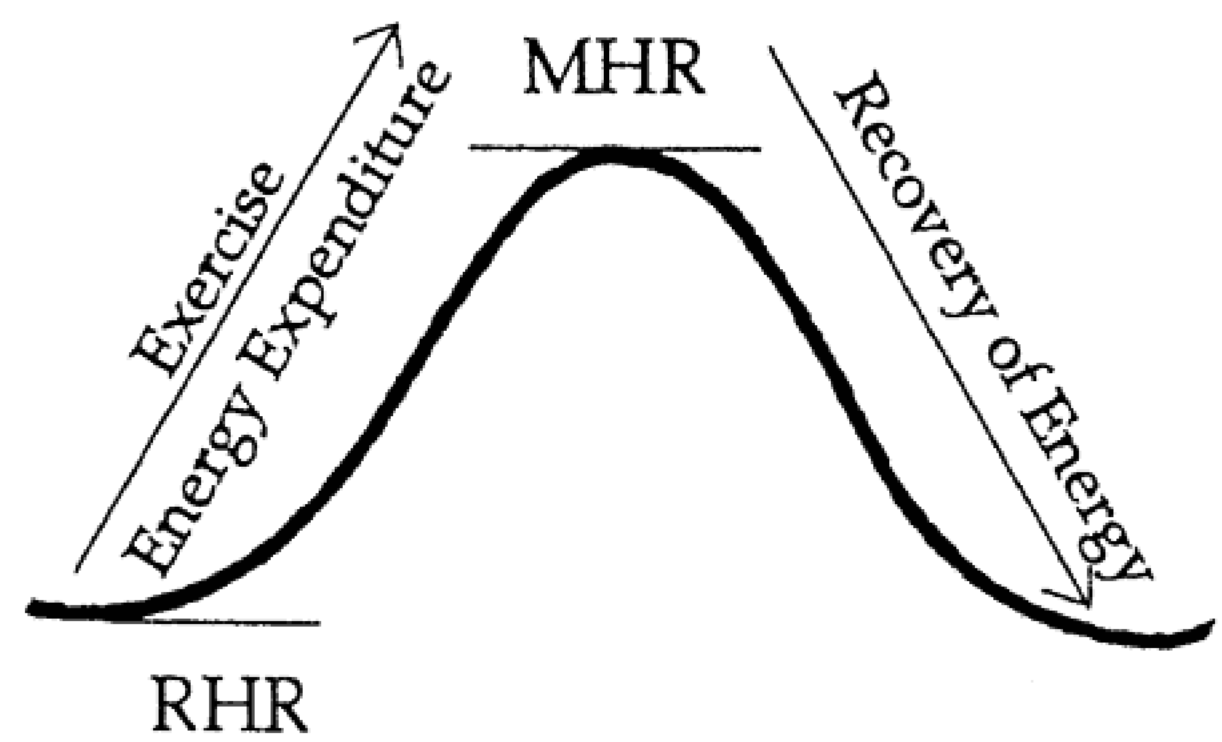

Figure 3b. *The wave continuum of resting heart rate and maximum heart rate.*

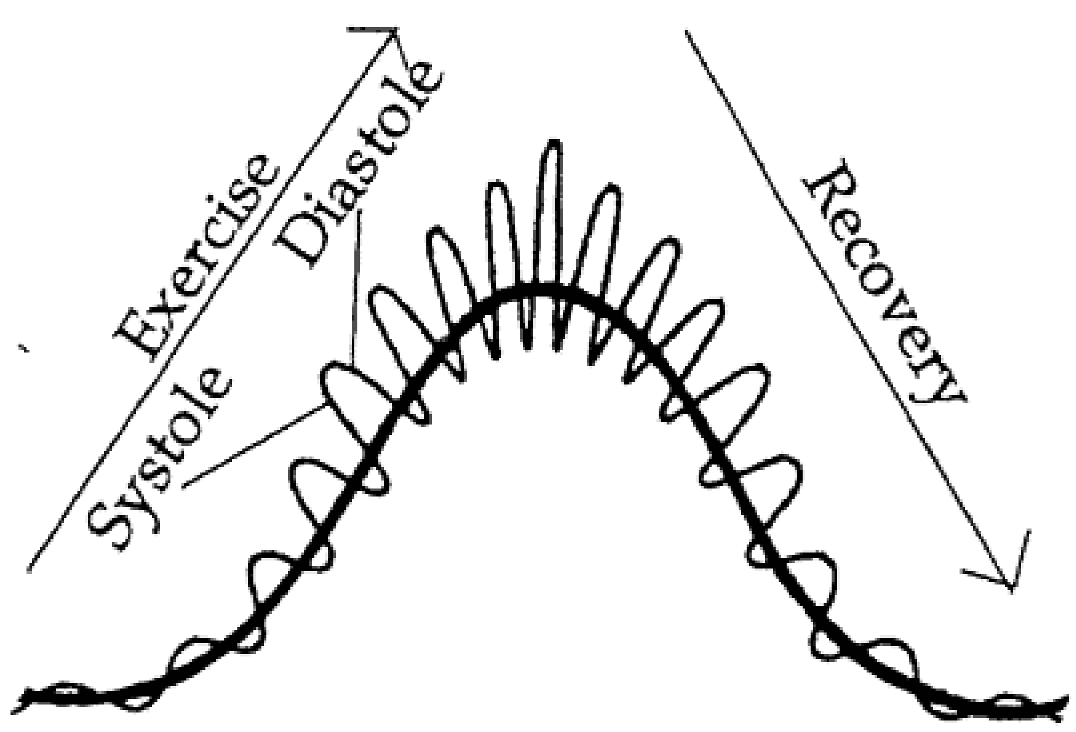

Figure 3c. *The heart wave.*

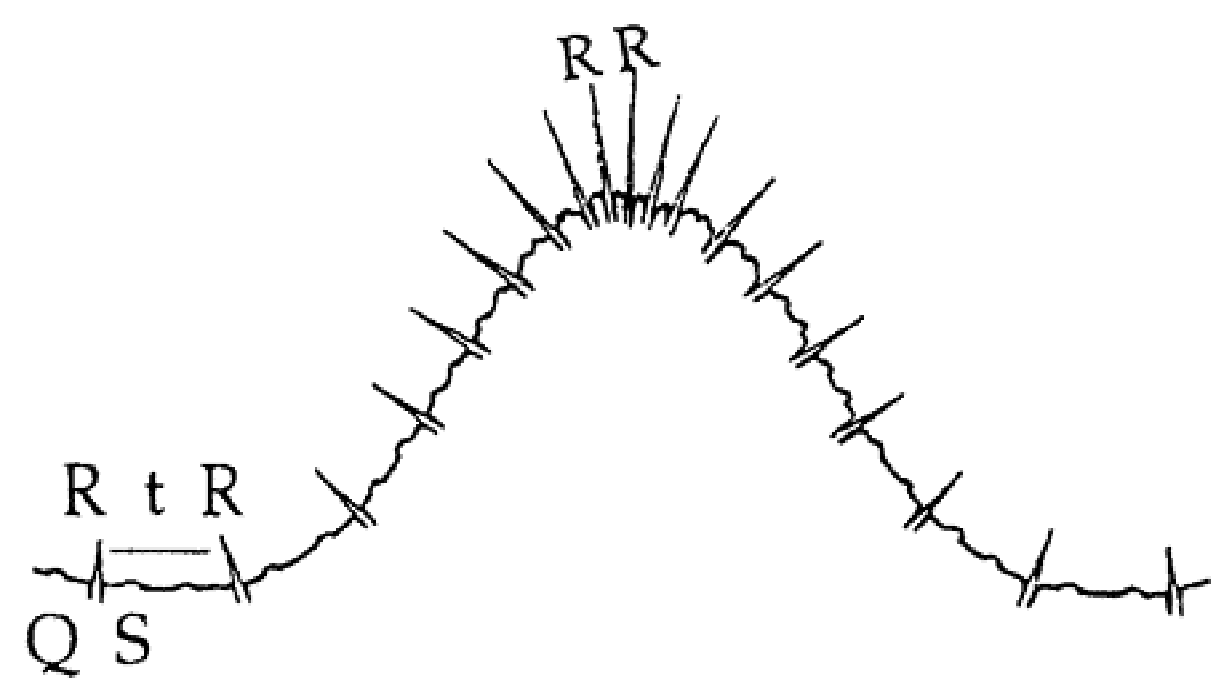

Figure 3d. *Increasing and decreasing frequency and amplitude of the QRS complex.*

process of recovery) is an inherent wave continuum of energy expenditure and energy recovery (Figure 3b).

From this same understanding of waves, it follows that the two so-called "components" of the autonomic nervous system—the sympathetic nervous system, which expends energy, and the parasympathetic nervous system, which recovers (conserves) energy—are not two separate components "in balance" or dynamically interacting but are, in reality, a wave continuum.

Step 3: Waves Waving Within Waves

The measurement of beat-to-beat intervals (HRV) is, in reality, the combination of steps 1 and 2: The heart beats as a continuum of waves (systole/diastole, systole/diastole, etc.) that climb up and down the body's behavioral waves of exercise and recovery. Expressed another way, successive systolic/diastolic waves of energy expenditure and energy recovery accelerate and decelerate within the body's exercise/recovery waves of energy expenditure and energy recovery. Thus, in nature, HRV is a wave within a wave: the Heart Wave (Figure 3c). This new understanding means that, in reality, the QRS complexes of an electrocardiogram do not evolve in a linear fashion but ride up and down behavioral heart waves (Figure 3d).

The idea of perceiving the heart wave as a heart rate began with the first modern medical experiments when William Harvey (1578-1657) discovered that the heart beats cyclically as a pump..."The auricle throws the blood into the ventricle [and] the ventricle projects the moving blood into the aorta."[23] Harvey's experiments led to our present day thinking that blood constantly moves through the body in a cardiovascular system of tubes — arteries and veins.

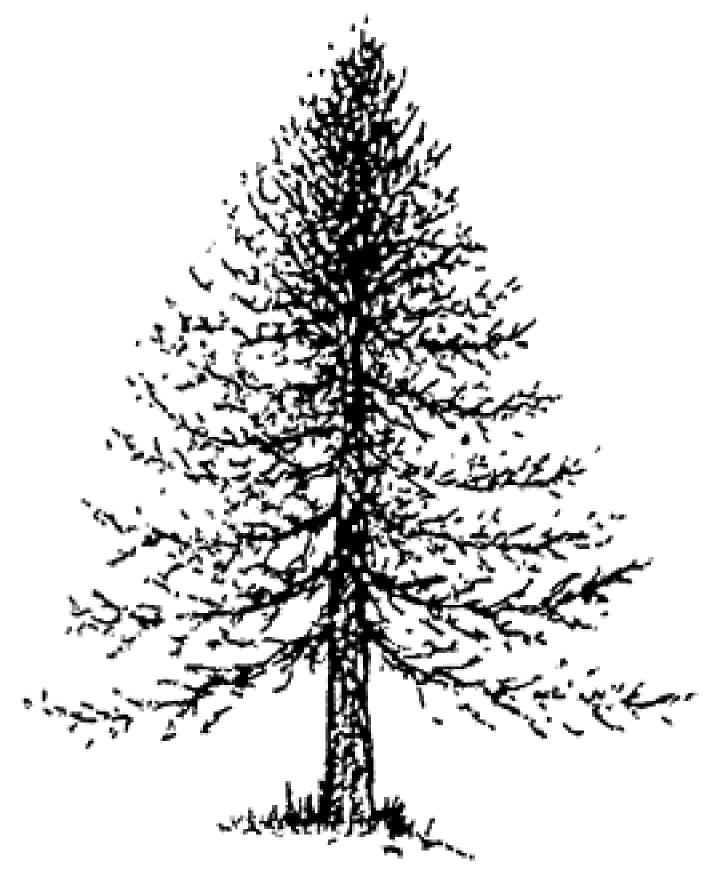

Figure 4a. Increasing frequency of tree branches.

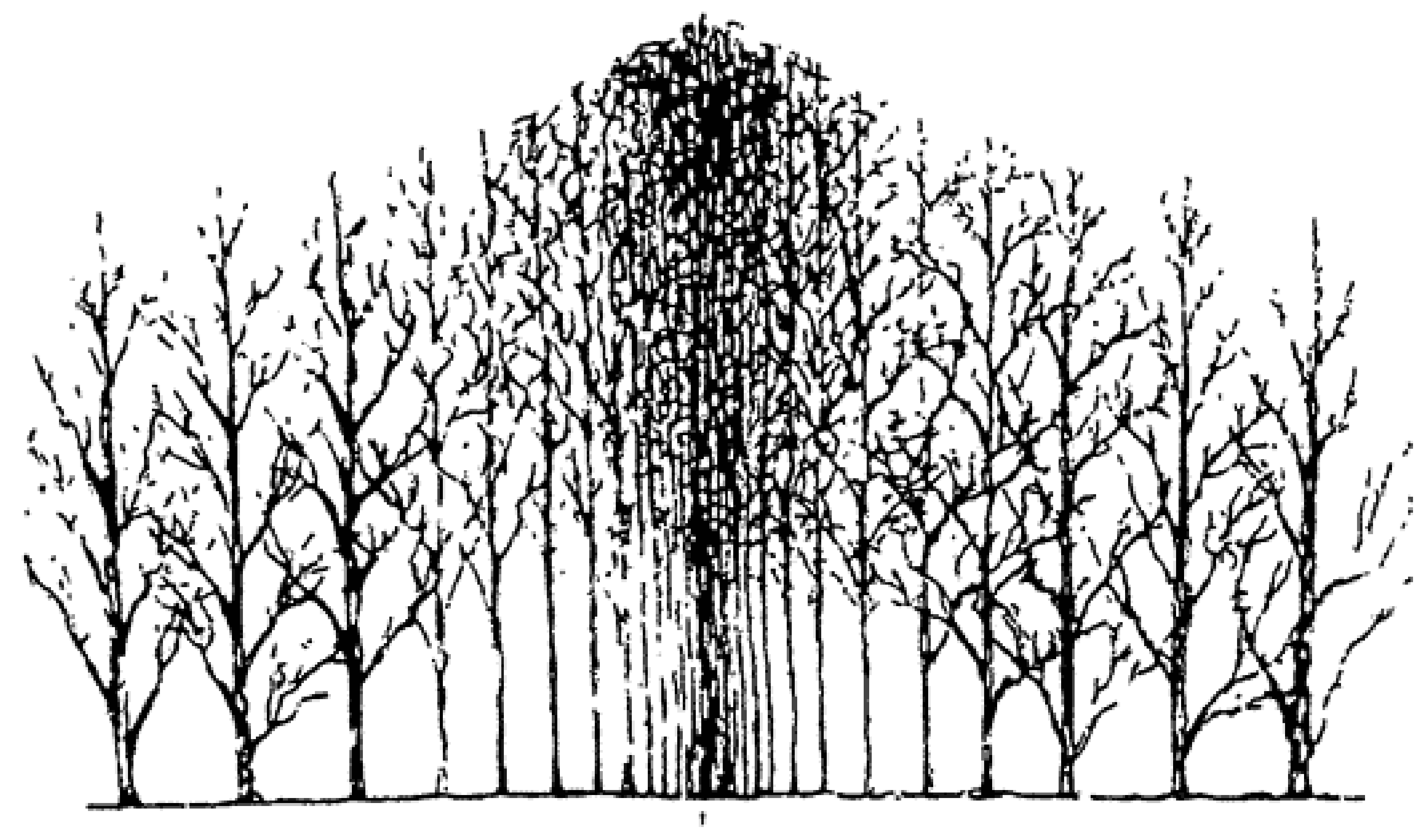

Figure 4b. Tree branches on a linear axis.

In essence an animal's natural heart wave is idealized as a heart rate whose trajectory is on a straight line axis of time with the blood being propelled on a linear axis through space. Therefore, from the very beginnings of modern medicine the wave motion of the heart and circulation was treated as if it moved on straight lines in time and space which ultimately came to be measured as the heart rate on an electrocardiogram (ECG).

The conformation of a tree is a wonderful model of what ECG heart waves would look like in nature if we could see the reality represented by the graphic tracings. The natural pattern of a tree is shaped as a wave (Figure 4a). As the branches rise to the peak, they get thinner, closer together (increased frequency), more dense.

If we were to graph this tree as an ECG graphs a heart wave, it would look like Figure 4b. Each vertical "branch" represents the distance from its tip to the base of the trunk. Consequently, the peak shows the thinner, denser pattern of the topmost branches as taller (increased peak-to-trough amplitude).

If Figure 4b became known as "tree" the same way an ECG tracing has become known as "heart" (the way the heart really works), we would now accept that a tree is something flat on a linear axis. However, we all know what a tree truly looks like in nature; the graphed branches, lined up horizontally, look awkward and unreal. We understand that the representation of the "tree" graph is artificial, the graph is not the real thing it seeks to describe.

With heart waves, we have the opposite case. We straighten out the spiraling electrical signals onto the linear axis of an electrocardiogram and assume that this abstraction is how electrical heart waves exist in nature. Reliance on the ECG as a means to understand the patterns of the heart is as limiting to our greater understanding as claiming that the flat tree graph with lined-up tree branches is an accurate representation of the nature of a tree. In the real world, nature is not linear, printed graphs; it is waves within waves.

What is extraordinary about a heart wave is that it is an inherent wave continuum connecting two different hierarchical levels of structure: the heart and the whole organism. In stark contrast, medicine and science currently treat the heart and the whole organism as two separate "parallel" levels of structure. This simple yet previously unappreciated phenomenon of waves waving within waves is the single continuum connecting all hierarchical levels in nature which I have previously described.[24]

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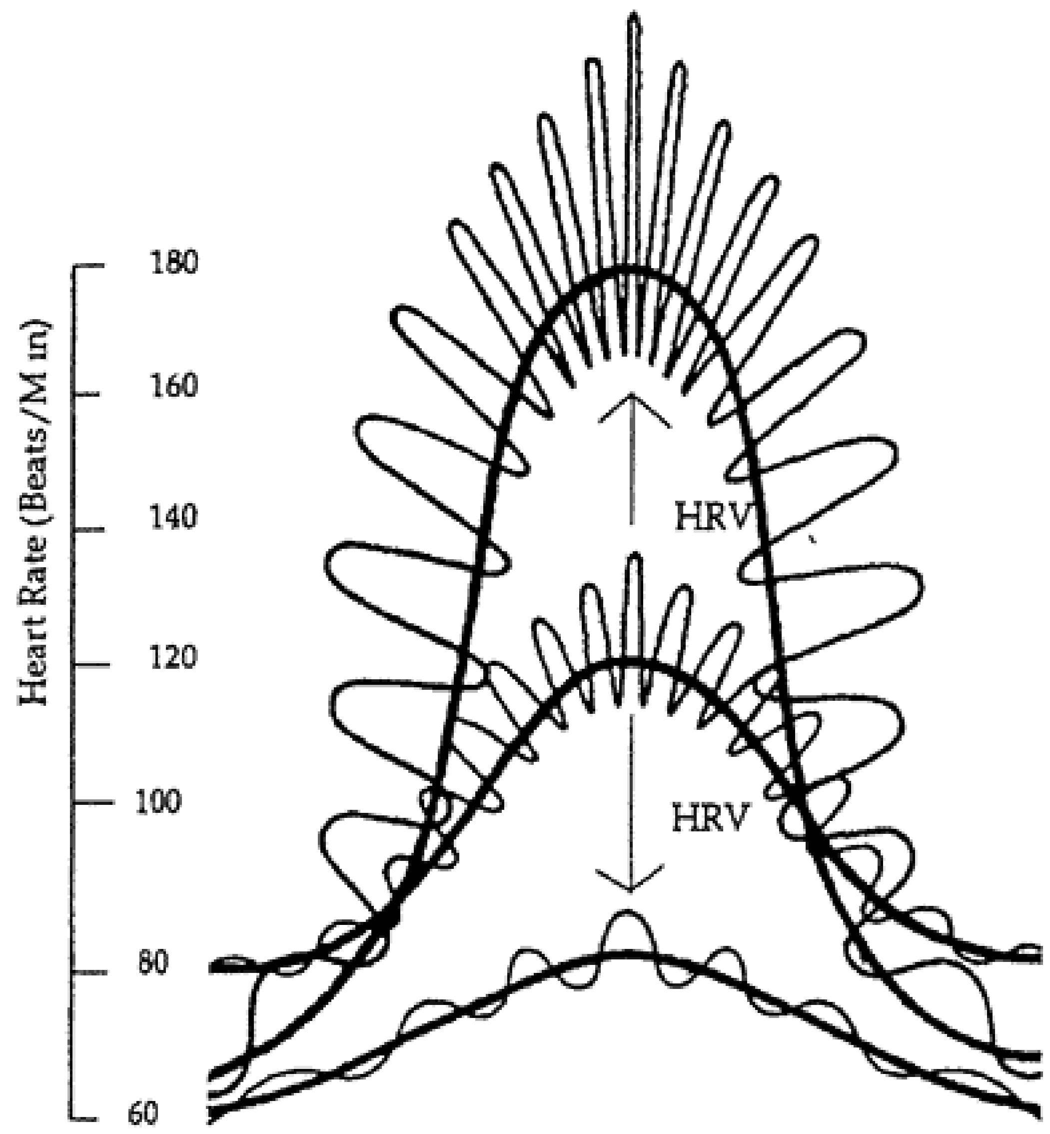

Figure 5. Heart waves of health and disease.

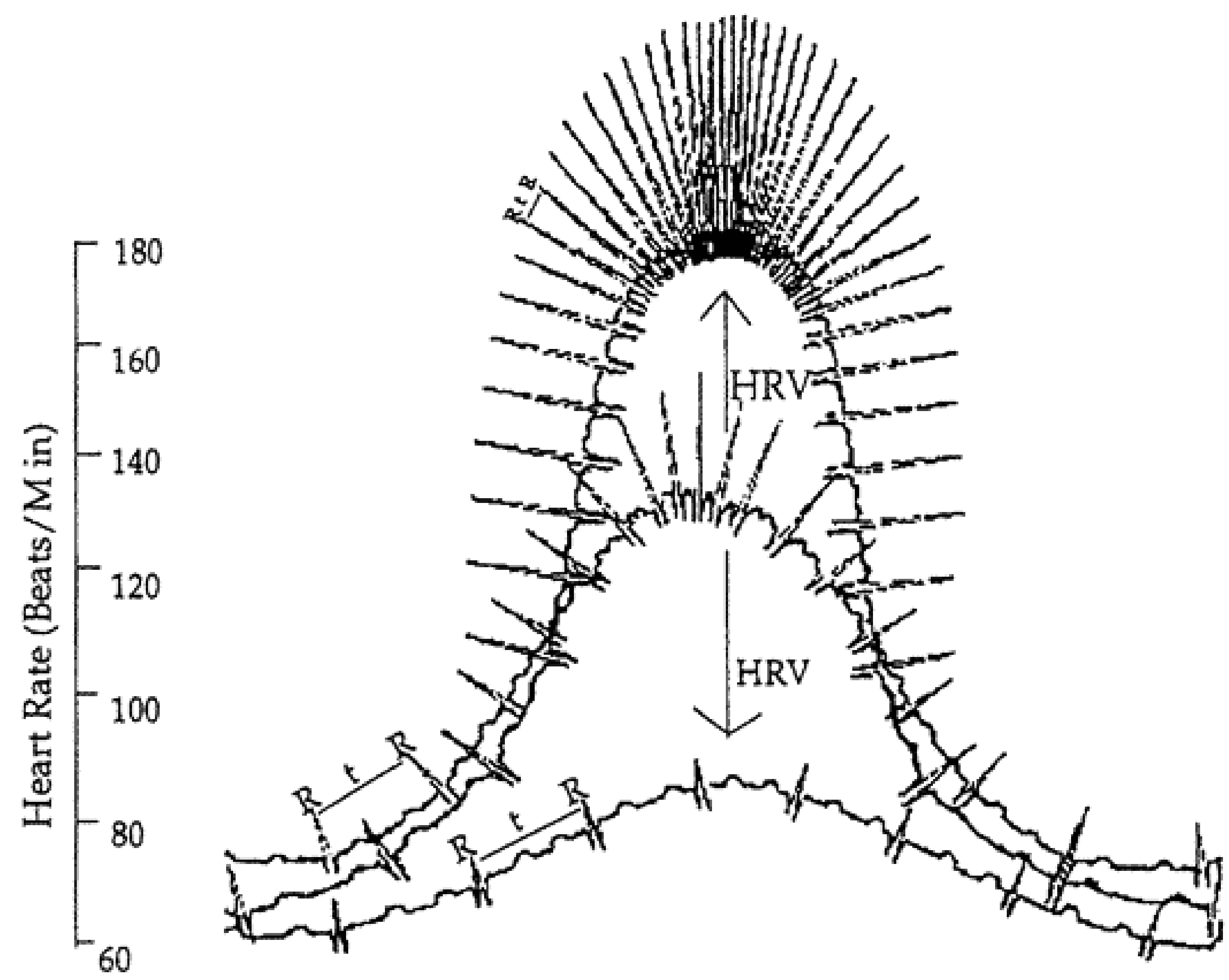

Figure 6. Variable ECG wave vs. HRV.

Heart Waves:The Connection Between HRV, Maximum Heart Rate, and Aging

Because the heart wave is the combination of heart beats as waves inside of behavioral waves of exercise/recovery, any decrease in maximum heart wave range necessarily results in decreased HRV. The narrower the heart wave range, the greater the decrease in HRV. Conversely, an increase in heart wave range results in an increase in HRV (Figures 5 and 6).

The higher the heart wave range, the greater the capacity of the heart rate to vary responsively within its range. From this understanding, one can see that both HRV and maximum heart rate are aspects of the heart wave. Thus, a decrease in range of the heart wave—a decrease in HRV and a decrease in maximum heart rate—is associated with decreasing longevity. Conversely, an increase in heart wave range—an increase in HRV and an increase in maximum heart rate—is associated with increasing longevity.

Heart Waves:The Master Wave of All Behavioral Waves

All of our behaviors, not just exercise and recovery, have a common underlying language of waves. Anxiety and relaxation, eating and not eating, being awake and asleep—all are waves of energy expenditure and energy recovery. In this way waves explain the connection between mind and body. Physiological relaxation from emotional stress is the same as the physiological recovery from exercise stress.[25]

The mind's "relaxation response" is a generalized metabolic slow-down: the heart rate and breathing slow down, blood pressure lowers, muscles relax, oxygen consumption decreases, and stress hormones drop. This mental relaxation response is the same as the physiological response that occurs during recovery from physical exercise; however, in the case of physical exercise, the recovery side of the wave starts from a higher level.

On the other side of the wave, both mental arousal and physical exercise are identical physiological stress responses (the survival-oriented fight/flight, or adrenergic response). Heart rate, breathing, blood pressure, muscle tension, oxygen consumption, and stress hormones increase in both mental arousal and exercise.

Though they seem different in our experience, mental anxiety/relaxation and physical exercise/recovery are identical; they are an inherent wave continuum, except that recovery from exercise begins from a higher wave range. This single underlying language of waves is the long sought-after mind/body connection.

All our behaviors (not just mind/

body) are an indissoluble wave continuum that happens simultaneously. Behavior is the external manifestation of waves. Though our behaviors appear different from one another, at root, they are actually the same; they have the common underlying language of waves. Therefore, they are connected and continuously communicating with one another. For example, if one is afraid and takes off running, the heart wave range will be much higher than if the two behaviors occur at different times. Thus, the heart wave is the "master wave" that represents the collective simultaneity of all the behavioral waves waving within one another.

Heart Waves, Chronic Disease, and Health

The most obvious characteristic of a wave is that it repeats itself over and over. In this sense, a wave is memory just as memory is waves. Rather than defining memory in terms of underlying molecular biological or physiological time-keeping mechanisms, the wave itself is memory. This simple yet astonishing new way of seeing waves explains the characteristic repetitive patterns of all our behaviors as well as the underlying intractability of chronic disease.

Wave memory is extremely important to understand. For example, waking up and going to sleep repetitively throughout a lifetime is a wave memory. The shape of the wake/sleep wave can be changed by going to sleep earlier or later, but one way or another it will repeat itself throughout life. The same is true with all chronic disorders, all of which exhibit cyclic patterns of behavior. Thus, manic depression is a powerful wave of energy expenditure and energy recovery with a long wavelength that repeats itself as a memory over and over throughout the years.

In this same way, autoimmune diseases such as multiple sclerosis, arthritis, asthma, or ileitis are wave disorders. That is, the immune system cyclically becomes "manic"; it goes on the attack of "self" as it moves towards its peak amplitude of energy expenditure, then recedes into the recovery or remission phase where energy is conserved. Both manic/depression and manic immune arousal/remission are the same waves of energy expenditure and recovery that repeat themselves cyclically.

Another example of a powerful wave memory is drug addiction, such as to cocaine or crack, with its characteristic cycles of enormous energy expenditure initiated by the drug (the high), followed by a sharp withdrawal and energy recovery (the crash). From that point on, this powerful wave inherently repeats itself. Therefore, the drug itself is not the addiction - the wave is the addiction. This wave addiction requires the drug to be taken periodically in order to fulfill its cyclic memory pattern. What is being demanded physiologically is the making of the wave - that is the addiction. The drug is just the means by which the wave is initiated. The demand for the drug is secondary to fulfilling the primacy of the addictive wave memory. The significance of this new understanding can not be overstated. It is the wave that is the addiction. If the wave pendulum swings too far in the direction of recovery, and the physiology is unable to "pull out of the dive" the resulting "crash" may lead to coma and even death.

This same pattern of cyclic wave behavior, with its highs and lows, explains such mysterious behavioral phenomena as the serial (wave) killer, post-trauma multiple organ system syndrome, post-traumatic stress disorders, and post-war syndromes which have been associated with armed conflicts at least since the U.S. Civil War, the latest example of which is the Gulf War Syndrome.[26] Military personnel who participated in the Persian Gulf War experienced an enormous metabolic wave of energy expenditure from the combination of emotional and physical stress, lack of sleep, high ambient temperatures, etc. Their immune systems became highly aroused in preparation for action over an extended period of time. This is consistent with recent research that demonstrates that the primary action of the immune system is to respond to danger and not "self."[27] Following their return home, many veterans suffered a major metabolic downward swing on the recovery side of the energy wave with variable degrees of immunological compromise (the crash). Those veterans unable to "pull out of the dive" to reestablish normal, healthy wave patterns are experiencing diverse nonspecific symptoms similar to chronic fatigue syndrome. As has been found with other chronic disorders, HRV and the heart wave range will be decreased in these indi-

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viduals. Therefore the Gulf War Syndrome can be reversed by increasing their heart wave ranges.

Though the term "addiction" has a negative connotation, it is, in reality, the underlying phenomenon responsible for all our behaviors. In this way, all our behaviors are wave memories with characteristic cyclic patterns of varying power and impact. Fundamentally, all behaviors and chronic disorders are wave addictions with the same underlying language of waves that differ only in shape, patterns of communication, longevity, and stability.

In addition to having the memory of the full and correct musical score, one needs the full range of the body's biochemical symphony to achieve optimal health. A decrease in heart wave range is equivalent to a pianist trying to play a piano concerto using only one octave of a piano's full range. Just as a decrease in the heart wave range (decreased HRV) leads to decreased longevity and chronic disease, expanding the heart wave range (increased HRV) leads to increased longevity and health.

In this regard, the implications for fitness training on earth and for space travel are significant. When we speak of fitness, we infer a positive relationship between fitness and health; fitness should cause good health. However, this is not always the case. In fact, there are reports that suggest an association between continuous, long duration exercise with infectious diseases including polio, echoviral meningitis, respiratory and gastrointestinal infections[28] as well as with cancer, cardio-vascular disease, and multiple sclerosis.[29]

This association between fitness training and chronic disorders can now be explained by recognizing that prolonged continuous training in a narrow target heart rate zone, through aerobic exercise or any other form of linear stress, actually will train HRV to decrease. The same would apply to any behavior done in a continuous fashion. By teaching HRV to become more linear, more even—in other words, flattening the heart waves—the individual is actually training to become more susceptible to chronic disease and all-cause mortality.

Instead of linear aerobic fitness, which is designed to push the limits of oxygen consumption (Vo2max) but ignores oxygen recovery, we should be training the heart wave range to expand. In fact, physical fitness (like energy) generally is defined as "the ability to do work." What this definition does not take into account is "the ability not to do work"; i.e., recovery. In contrast to linear fitness, *Wave Fitness*™, a new program designed to expand the heart wave range, incorporates both work and recovery as a wave.

From this new wave perspective, Vo2max is a partial linear measurement that reflects increasing oxidation (energy expenditure), which is only one "side" of the wave. The other "side" of the wave is a decrease in oxygen consumption that reflects antioxidation (energy recovery). Therefore, oxidation and antioxidation are inherently continuous waves.

The mystery of HRV is solved, and the groundwork is laid for a whole new approach to preventing and reversing chronic disease as well as optimizing health, performance, and longevity by expanding the heart wave range (Figures 5 and 6).

Mystery No. 2: Why Does Ischemic Preconditioning Protect the Heart?

The wave principle explains HRV by connecting two hierarchical levels: the heart and the whole organism. In the same way, the wave principle explains ischemic preconditioning by connecting two hierarchical levels: the heart and molecular biology/chemistry.

The experiment, which came to be called "ischemic preconditioning," was designed to measure what was believed to be cumulative damage to cardiac muscle from repeated episodes of coronary angina. To test this hypothesis, Murry et al., simulated heart attacks in a group of dogs by clamping the coronaries for 40 minutes to measure the mass of cardiac necrosis.[30] Then, to determine how much more damage would be created by anginal type ischemic episodes, they simulated repeated anginal episodes in another group of dogs: four cycles of clamping the coronary for five minutes was followed by five minutes of declamping with resumption of blood flow. After these cycles, the coronaries were again clamped for 40 minutes.

The results were not as expected, as an editorial in The Lancet pointed out:

> Several years ago it would have been incomprehensible for a rational physician or scientist to conclude that myocardial ischaemia might somehow act to protect the heart from necrosis. Then Murry et al. reported their improbable observations that an isolated 40-min. occlusion in dogs resulted in an infarct whose mass could be decreased by 75% if the animals were pretreated with four cycles of 5-min. coronary occlusion plus 5-min. of reflow...Recognition of the benefits of ischemic preconditioning has unleashed efforts to define its characteristics, study its mechanism, and apply the principles clinically.[31]

Since that first animal experiment, the same surprising finding has been shown to occur in humans as well. At the University College Hospital in London, cyclic ischemic preconditioning was performed on ten patients, after which the coronaries were clamped for approximately 12 minutes while coronary bypass surgery was performed. Cardiac muscle was biopsied to measure the concentration of adenosine triphosphate (ATP). The muscle of patients who underwent the preconditioning contained 30% more ATP than the ten control patients without preconditioning. According to Derek Yellon, who headed the cardiovascular surgical team: "This could reduce cell damage by 50%-70%."[32]

Similar to the approach used by research teams trying to understand heart-rate variability, research into the mechanisms behind ischemic preconditioning has focused on molecular biological phenomena, such as adenosine receptors, ATP, and heat-shock proteins. The following quotes describe this approach:

> A brief period of ischemia followed by reperfusion renders the heart very resistant to infarction from a subsequent ischemic insult... The mechanism for preconditioning is unknown... We propose that the preconditioning phenomenon is mediated by the buildup of adenosine during the preconditioning occlusion, which in turn stimulates cardiac A1 receptors . . . which leaves the heart protected against infarction even after the adenosine has been withdrawn.[33]

> One of the novel findings of this research is the mechanism of the memory. We believe that the heart 'remembers' that it has been preconditioned through a translocation of PKC from the cytosol into the cell membranes. How might one design a pharmacological approach to confer preconditioning's anti-infarct effect to patients? . . Putting preconditioning in a bottle remains a pharmacological challenge.[34]

The Solution to the Mystery of Ischemic Preconditioning

Clamping and declamping the coronary artery are not two discrete phenomena but rather constitute a powerful wave continuum of energy expenditure and energy recovery. The underlying wave principle is the same here as it is for systole and diastole, exercise and recovery, oxidation and antioxidation, all behaviors, chronic diseases, and the autonomic nervous system. Prior to cyclic coronary clamping and declamping, the oscillatory myocardial chemistry cycles up and down; it increases in frequency, amplitude, and concentration with systole, then reverses with diastole.

When the coronary arteries are clamped, there is a dramatic increase in a survival-oriented metabolic expenditure of energy. This can be likened to an exaggerated systolic contraction but without the physical work of the muscle contracting. Without the declamping phase, the myocardial biochemical oscillations rapidly dampen, leading to myocardial necrosis (Figure 7a).

When the coronary arteries are declamped, there is a dramatic recovery of energy metabolism, which can be likened to diastolic relaxation. By creating several powerful waves through successive clamping and declamping, the complex biochemical oscillations within the myocardium swing up and down cyclically, resulting in increased biochemical variability (Figure 7b).

On the other hand, if an artery is clamped for too long and then declamped (i.e., the revascularization of

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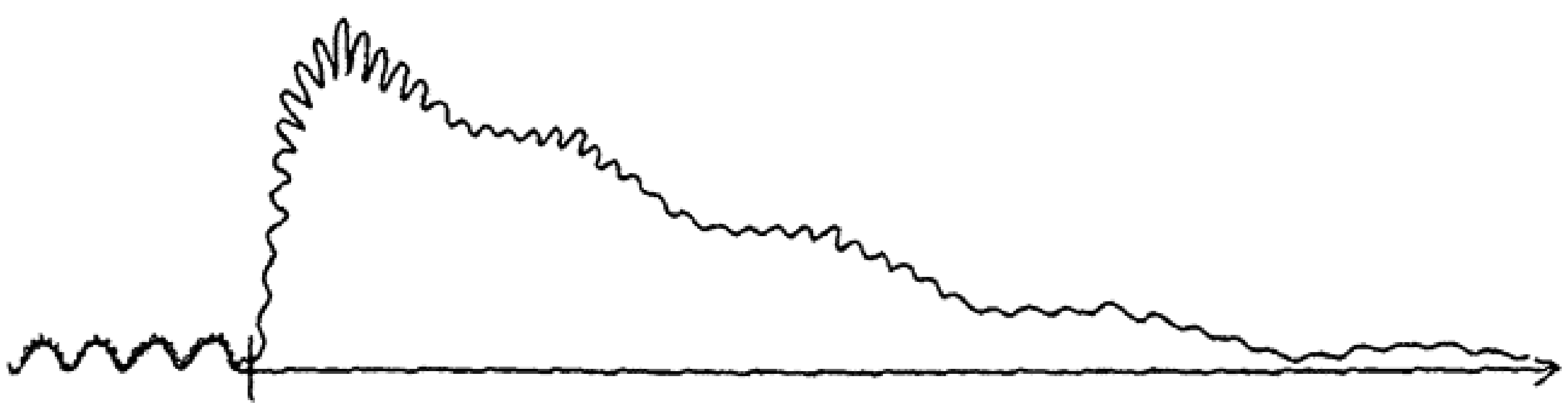

Figure 7a. Continuous coronary clamping leads to decreased biochemical variability.

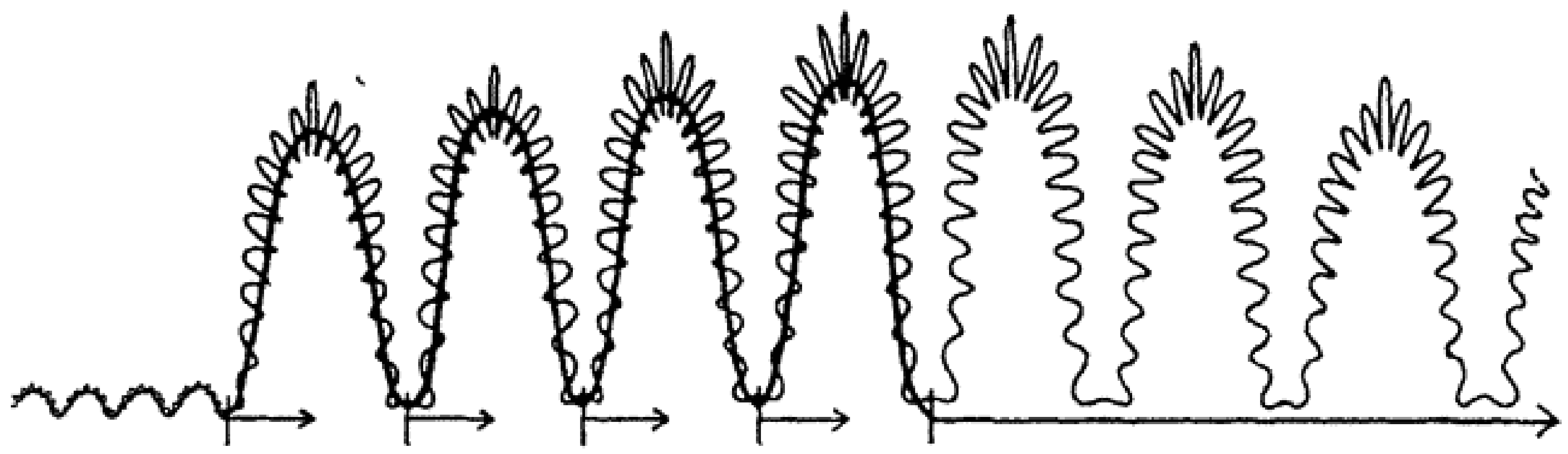

Figure 7b. Successive coronary clamping and declamping leads to increased biochemical variability.

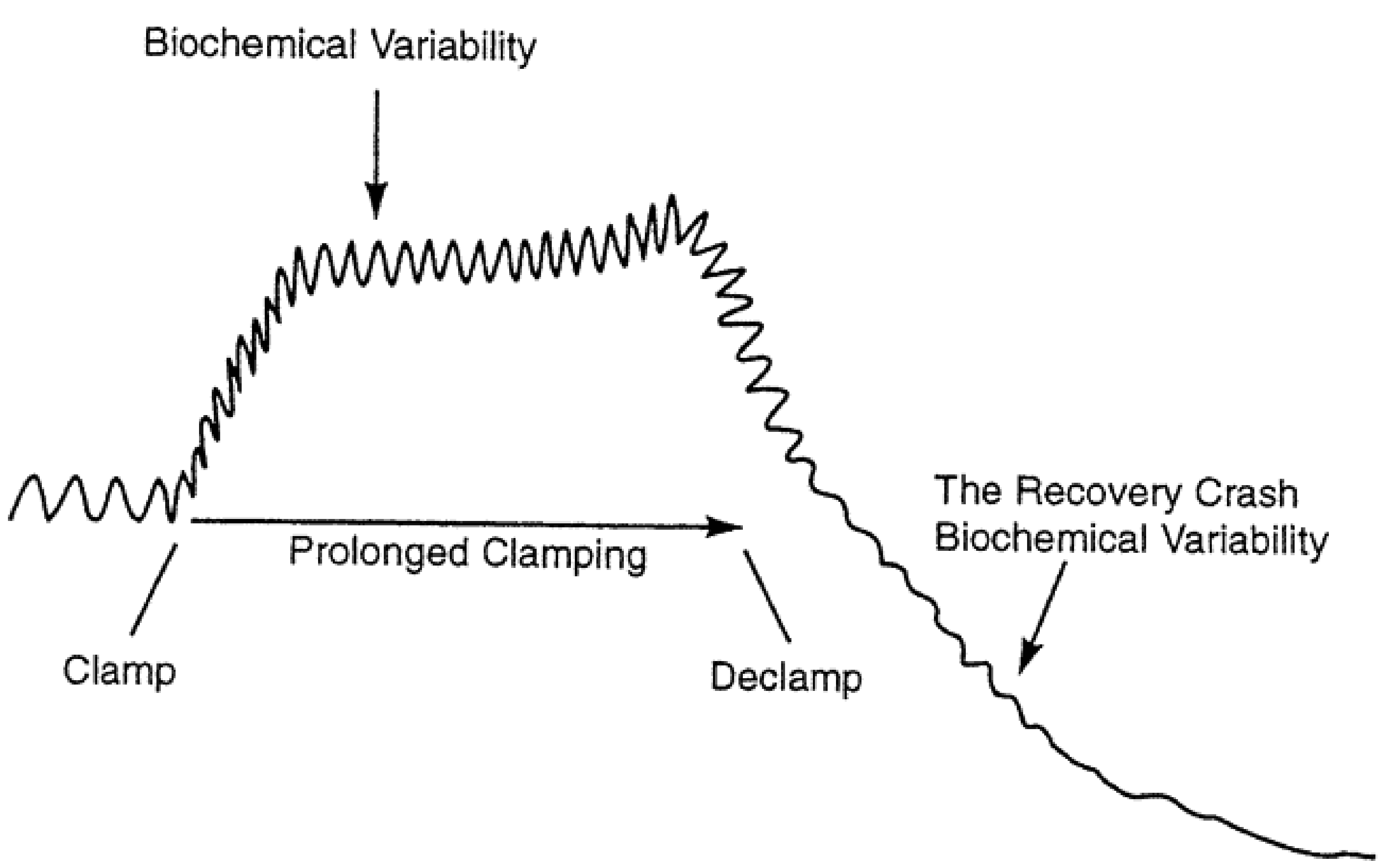

Figure 7c. Prolonged clamping followed by declamping results in decreased biochemical variability and muscle necrosis.

an acutely ischemic limb) the recovery side of the wave will swing down too far and will not "pull out of the dive." The resultant crash, known as "skeletal muscle reperfusion injury,"[35] will lead to decreased biochemical variability and extensive muscle necrosis (Figure 7c). The same wave pattern of a high followed by a crash can be seen in many other medical disorders such as drug addiction, chronic fatigue syndrome, Gulf War syndrome, post-traumatic multiple organ failure syndrome, and sudden death during the recovery period after prolonged, intensive exercise. The same pendulum crash phenomenon as seen here ischemic preconditioning was described in decreased HRV. The common denominator between the two mysteries is heart waves.

From the new understanding of waves waving, biochemical variability is the same as HRV except that it occurs in a different "hierarchical level." During the upward exercise-like swing of the wave, the oscillatory myocardial chemistry (including the energy cycling of ATP, GTP, etc.) rapidly increases in frequency, amplitude, and clustering, which then reverses during the declamping phase. After several cycles of clamping and declamping, the coronary artery is clamped for a prolonged period of time. However, despite this linear prolonged period of coronary clamping, the myocardial oscillatory chemistry continues to swing up and down within its amplified, preconditioned memory wave (Figure 7b).

The preconditioning waves organize the chemical oscillations into an expanded heart wave. Just as an expanded heart wave increases HRV, so too does the expansive coronary preconditioning heart wave increase biochemical oscillatory variability. The result is that the myocardium is substantially protected because of the heightened biochemical communica-

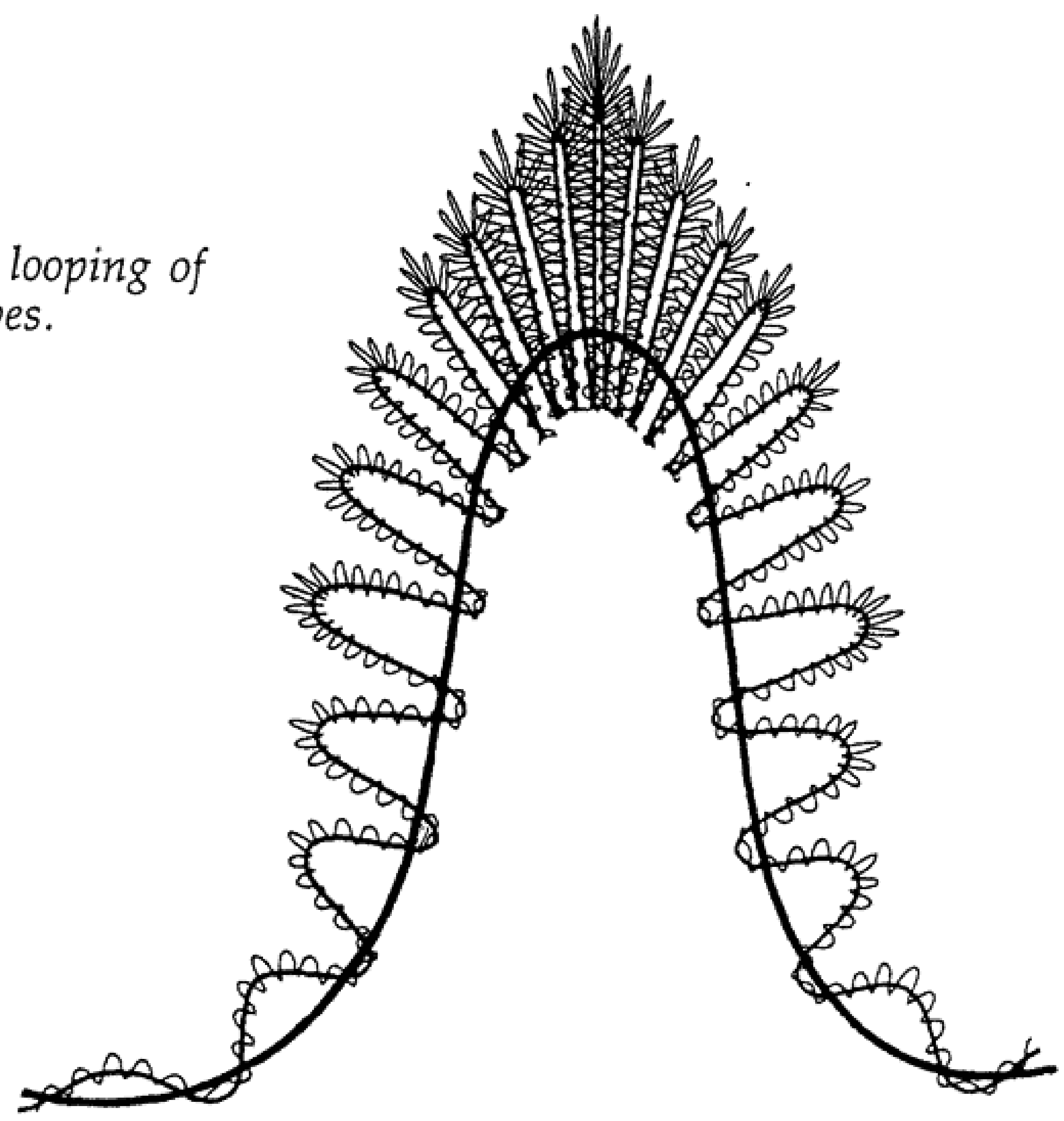

Figure 8. Super looping of biochemical waves.

tion, organization, and coherence—solving the mystery of ischemic preconditioning.

Of interest is the terminology, "ischemic preconditioning," used to describe the clamping and declamping procedure. The word "ischemia" refers only to the lack of blood flow during the clamping phase; the declamping phase is ignored as if it were a passive phenomenon. In the same way, the term "exercise physiology" ignores recovery. Appropriate terminology should describe both sides of the wave.

Preconditioning Resembles a Far-From-Equilibrium Wave Fluctuation

The wave principle also solves Ilya Prigogine's enigmatic concept of far-from-equilibrium and close-to-equilibrium fluctuations. The cycles of coronary clamping and declamping create a high-amplitude wave, which is analogous to Prigogine's far-from-equilibrium fluctuations.[36] Clamping the coronary without prior cycles of clamping and declamping dampens the biochemical oscillations, which is analogous to close-to-equilibrium physiological fluctuations.

The concepts of far-from-equilibrium and close-to-equilibrium fluctuations are not separate entities. Like systole and diastole or clamping and declamping, they are a continuum of waves within waves. The cycles of clamping and declamping in ischemic preconditioning is a high-amplitude (far-from-equilibrium) heart wave, which creates amplified biochemical oscillations. Prolonged clamping of the artery without preconditioning creates a flattened (close-to-equilibrium) heart wave, within which biochemical oscillations are dampened. Consequently, cyclic coronary clamping causes the preservation and health of the myocardium, whereas prolonged clamping causes myocardial necrosis.

This is the same underlying phenomenon as increasing or decreasing heart wave range.

Connecting HRV and Ischemic Preconditioning With the Heart Wave

As with HRV, which connects different hierarchical levels—the whole organism and the heart—ischemic preconditioning also connects different hierarchical levels—the heart and the chemistry. All three levels—the whole organism, the heart, and the chemistry—are a continuum of waves within waves, which I call "superlooping" (Figure 8).

No matter how different and discontinuous hierarchical levels of structure appear to be on the surface, the deep regularity of waves is continuous, simultaneous, but always changing. Decreasing behavioral wave amplitudes from the top down means a simultaneous decrease in heart wave amplitude, which simultaneously decreases biochemical and gene-wave amplitudes, and vice versa, if you start from the bottom up. There is no separation between hierarchical levels; all is waves.

The fundamentality of waves explains the ubiquitous finding of fractal scaling in nature that has so intrigued and yet perplexed science and medicine. The following quotes describe the fractal character of nature and its potential for playing a significant role in medicine:

> Compared with a smooth, classical geometric form, a fractal curve appears wrinkly. Furthermore, if the wrinkles on a fractal are examined at