Thermodynamics of Skeletal Muscle Fiber: Do We Need to Redefine "Active" and "Resting" States?

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Abstract

Aside from patient selection and surgical techniques, functional performance of the latissimus dorsi skeletal muscle has been considered the most important variable influencing long-term survival of those who undergo dynamic cardiomyoplasty. The mechanical, electrical, and metabolic changes of the stimulated muscle cycle are traditionally studied to determine its adequacy. In addition to these events, however, we also need to examine the thermodynamic phenomena, specific changes in heat production and entropy. The major conceptual conflict between mechanical and thermodynamic definitions of muscle function lies in the identification of "resting" and "active" states. If during its stimulated cycle the skeletal muscle behaves as a dissipative thermodynamic structure, then the entropy would be greatest at peak contraction when the system is furthest removed from its normal thermodynamic nonequilibrium state. It would be reduced again during relaxation when the system regains nonequilibrium with restoration of maximal excitability. Hence, thermodynamically, the true physicochemical driving force of muscle contraction, is the downhill tendency toward a state in which the entropy of the system is maximized. Thus, the traditional mechanical approach that muscle alternates from a biological "active" state during contraction to a biological "resting" state during relaxation deserves critical appraisal. In reality, the muscle is thermodynamically active during mechanical relaxation and thermodynamically passive during mechanical contraction. This is an idea whose time has come as interest in muscle cardiac assistance is on the rise.

Key words: stimulated muscle cycle, thermodynamics, entropy, muscle cardiac assistance.

BAM 6 (3): 199-202, 1996

"*Truth can be pursued by many means, and if we are right in belief that reasonable, consistent view of the world is possible, even though we ourselves may never conceive it, then there can be no ultimate conflict between those who pursue the truth from whatever aspect, critically and carefully, without prejudice and with sufficient patience, reverence, and imagination.*"

Archibald Vivian Hill [7]

Since the advent of dynamic cardiomyoplasty a decade ago, there has been a reawakening of interest to describe skeletal muscle fiber in basic mechanical terms, i.e., fast vs. slow. The first physiological function of skeletal muscle studied was its control of the skeletal movement with emphasis on locomotion. The continuous switching from mechanical contraction to relaxation and vice versa has long provided the framework for physiologic and clinical descriptions of normal and abnormal function.

However, we believe that the appropriateness of the terminology that describes the events of muscle contraction, terminology that is derived from purely mechanical considerations, should now be reexamined. The mechanical component of contraction is only one part of a highly integrated mechanochemical process. In fact, the mechanical component of the process is in all respects dependent on another subsystem, the energy-liberating "chemical reactor" that provides the source of energy for such contraction.

Traditional physiologic studies of skeletal muscle distinguish three qualitatively different processes in each stimulated muscle cycle: mechanical, electrical, and metabolic. A fourth process should be added: the thermodynamic

phenomena of heat production and entropy changes that occur in each stimulated muscle cycle.

Based on pioneer investigations by A. V. Hill and others [8] into muscular mechanics, Cesarman et al [3, 4] have been proposing for nearly 20 years that the thermodynamic phenomena is a way to better understand the essence of the rhythmic and cyclic contractility of the heart. In 1989, Brutsaert and Sys [1] considered this concept to be correct from a physiological point of view. More recently, Salthe [10] used this theory to explain some fundamental aspects of the complexities of biological evolution.

It has been 10 years since Carpentier [2] and Magovern [9] first utilized a continuously electrostimulated pedicled flap of latissimus dorsi muscle to assist the failing mechanical function of a compromised left ventricle. At the First Purdue Conference on Cardiac Assistance with Skeletal Muscle in 1988 [5], we proposed that thermodynamic laws should be applied to the study of continuously electrostimulated skeletal muscle to better understand long-term outcome. When thermodynamics are incorporated into the study of muscular activity (Christlieb IY, Cesarman E: unpublished data), it is possible to formulate a theory that utilizes some of the basic behavior of the myofibril, to obtain vital information on skeletal muscle subject to this new functional modality.

In 1865, Clausius [6] introduced the concept of modern thermodynamics as a new discipline and defined entropy, which has since proven to be one of the most important concepts in physics. The laws he described dealt with heat, energy, and their interconversion, and have been further refined by others working in the new conceptual field. These laws were soon to prove essential to the development of the engines of the machine age.

The laws that embody the principle of the conservation of energy and define the concept of entropy were originally described for closed systems in which chemical or mechanical reactions may approach or attain equilibrium. Although the body and its organs may be considered as open thermodynamic systems with steady-state characteristics, it soon became evident that the thermodynamic laws are universally applicable and no less valid for living biological systems. The living cell, the function and viability of which are totally dependent on the transformation of energy, is a most appropriate model for the application of these principles. Thermodynamic concepts offer a unique vantage point for consideration of the actual physicochemical state of internal systems and of physiologic, pharmacologic, pathologic, and clinical aspects of skeletal muscle function.

A major conceptual conflict between mechanical and thermodynamic definitions of muscle function lies in the identification of the "resting" and "active" states. A thermodynamic evaluation requires a revision of many of our concepts of mechanistic muscle physiology. Thus, skeletal muscle may be shown to be thermodynamically active (Figure 1, step 1) during mechanical relaxation (the "resting" state), and thermodynamically passive (Figure 1, steps 4,5) during mechanical contraction (the "active" state).

The term "resting" state was derived from observations of cells considered to be at rest during times of mechanical relaxation. Such a definition ignores what actually is a complex relationship of physical and chemical energetic events. When examined as real cellular phenomena, distinctions between "active" and "resting" states blur. Thermodynamically, the phase of the complete cycle of muscle activity that corresponds to mechanical relaxation is actually the most active bioenergetic state of the myofiber (Figure 1, step 2).

Entropy is defined by the second law of thermodynamics, which was initially formulated to establish that heat cannot be transferred from a cold system to a warm system without the expenditure of work. Entropy deals with the spontaneous movement of energy towards the random distribution of matter and heat. It is not a hazy or ill-defined concept, but rather deals with measurable physical quantity and describes a quantum of the total energy of a system that is not available for meaningful work. Entropy is defined mathematically, expressed in units that utilize the values of calories per mole per degree, and is considered a measure of the degree of randomness or disorder that exists within a system. Indeed, it has been shown that the true driving force of all physical and chemical reactions is the tendency toward that state in which entropy of the system plus its surroundings is maximized (Figure 1, step 6).

During mechanical contraction, the muscle cell calls upon stores of high-energy phosphates to fuel external work. There is a fall in free energy, with most of the utilized energy degraded to heat and randomized to its surroundings. Sodium and potassium ions move passively across the plasma membrane to establish osmotic equilibrium between the intracellular and extracellular compartments. A transmembrane action potential is recorded that demonstrates a sudden decrease in cellular negativity.

In thermodynamic terms, the cell has lost a marked degree of differentiation, integrity, internal structure, and energy at this point and has simultaneously increased its degree of randomness and become more stable as it approaches the state of equilibrium. The stability of the cell is evident by a relative degree of refractoriness to stimulation and by the greater approximation toward equilibrium of its transmembrane gradient. By the end of the contraction, the entropy of the myocell approaches maximal, and it is statistically improbable that the muscle of which that cell is a part will contract again with the same force for the same duration without restructuring of its internal milieu. Unlike the myocardium, the contractile mechanism of skeletal muscle does not have a true refractory period. Repeated stimulation before relaxation produces additional activation of the contractile elements and a response is added to the contraction already present. For this to happen, an active bioenergetic metabolic process must be present throughout the duration of the stimulus at work.

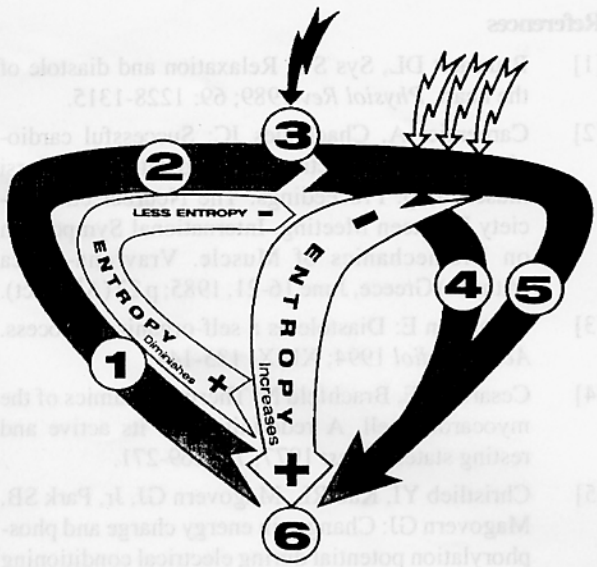

Figure 1. Thermodynamics of functional muscle cycle explained in terms of a "time explosive device." 1. Active relaxation, *organization begins (or resumes), entropy diminishes (load being charged). 2.* "Resting" relaxation, *order is maximized, entropy is least, (timer ON, device is ACTIVE). 3. Stimulus triggers* action potential *(timer goes OFF). 4.* Single stimulus passive contraction *(device explodes, work is produced; the collapsing building has to come down, heat, chaos, ENTROPY are generated). 5.* Multiple stimuli passive contraction *("burst" multiplies all events in stage 4). 6.* Peak contraction is achieved, *entropy reaches its peak, (system at its maximum equilibrium point, all affected matter is at a stand-still, disorder and chaos are proportional to the power of explosion).*

During mechanical relaxation (the so-called "resting" state), consumption of energy is devoted to the work of internal maintenance, on which the integrity and differentiation of the cell as a system depends. Energy is utilized for the restoration of excitability, the transmembrane action potential will be restored by activity of the sodium potassium adenosine-triphosphate pump, and intracellular negativity is re-established. In effect, the transduction of energy from adenosine triphosphate to an osmotic pump approaches a thermodynamic efficiency level of 100%, with little heat produced and randomized into the environment. Energy that is utilized for the metabolic requirements of glycolysis and oxidative phosphorylation permits the replenishment of stores of high-energy phosphates in the cell. Other cellular housekeeping functions are also performed during this period. There is a re-synthesis of contractile and structural proteins and nucleoproteins, glycogen, enzymes, lipids, and other macromolecules. Substrate is modified and chemically transformed to either a new usable form or a storage form. The general work of maintaining cellular structure and membrane integrity occurs, provided enough time elapses before the cycle starts again.

In contrast to the above, a thermodynamic description of the myofiber during mechanical relaxation would indicate that the cell is furthest removed from equilibrium, has approached maximal differentiation and order, replenished its energy stores, reduced its degree of randomness, totally restored its excitability, and enhanced its thermodynamic instability. The cell retains its maximal capability to perform work when stimulated or, in cells possessing automaticity, to discharge spontaneously. In effect, the entropy of the cell has been reduced to a minimum. It is the chemical reactor that produces an increment in free energy, a quantity which can be measured by the consumption of substrate and oxygen, production of enthalpy, dynamic factors, and efficiency. In thermodynamic terms, it is a misnomer to describe muscular relaxation, the moment of maximal excitability and instability, as the "resting" state.

Mechanical relaxation of the skeletal muscle cell and its simultaneous "resting" membrane potential correspond to an active, uphill, thermodynamic process, during which entropy decreases and order increases. Conversely, mechanical contraction of the cell and its accompanying "active" membrane potential reflect a passive, downhill, thermodynamic state, during which entropy and the disorder of the cell approach their maximum. During relaxation and contraction, there is a constant alternation between states of decreasing and increasing entropy. The muscle cell phenomena, hitherto considered "resting" due to their temporal coincidence with mechanical relaxation, in fact constitute the most active thermodynamic state of skeletal muscle fiber. The functional implications of this principle on the long-term performance of the unceasingly electrostimulated to tetanic contraction "conditioned" skeletal muscle, for the purpose of biomechanical circulatory assistance, are greater than generally recognized.

The idea of cell entropy provides a conceptual framework within which we can consider the ideas of excitability, conductivity, contractility, rhythmicity, and membrane permeability. We can also evaluate both diverse pathologic states and the pharmacological actions of various therapeutic agents. In the functional evaluation of dynamic cardiomyoplasty, estimates of muscle cell entropy approach the importance enjoyed by some sophisticated and more easily measured hemodynamic variables.

Entropy of the myocell increases when the cell becomes ischemic, hypoxic, or acidotic. An increase in amplitude or duration of stimulating electrical impulses will adversely alter the proportion between work demand and energy supply, thus creating a wasting condition of the muscle, an increase in entropy which resembles the effects of disease. Systemic diseases, diabetes mellitus, hyperthyroidism, hypermetabolism, fever, decreased cardiac output will have the same effect, as will use of vasopressors such as catecholamines and calcium ions. Muscular entropy also increases before and after cardiomyoplasty during bouts of congestive heart failure, which, in terms of the heart itself,

may also be thought of as an expression of a defect in the utilization of energy, a partial chemico-mechanical uncoupling, if you will.

Entropy of the skeletal muscle cell, most notably in the muscle flap wrapped around the heart in cardiomyoplasty, tends to be reduced by ACE inhibitors which lower peripheral vascular resistances; by dobutamine, which improve cardiac output; and by drugs which regulate cardiac rhythm and rate. The blood pumped by the heart is the lifeline for the muscle wrap. In the continuously electrostimulated skeletal muscle, cell entropy is also reduced by increased periods of rest, and when the proportion between work demand and energy supply is adequate.

The purely mechanistic concept of converting skeletal muscle fibers from Type II to Type I (fast to slow), for use in biomechanical circulatory assistance is obsolete. Investigators are currently directing their efforts toward transforming skeletal muscular fibers to the "ideal" fast, fatigue-resistant type, but for the continuously electrostimulated live skeletal muscle, ongoing, active transformation is the natural response to the imposed working conditions, and such fiber, transitional in nature, *exists only at one moment in time*.

We propound that, from a thermodynamic perspective, the search for means to retain this transformed state in stimulated myofibers is the most desirable step as mechanical efficiency will improve by enhancement of enthalpy and reduction of entropy.

Acknowledgements

The authors are grateful to Barbara Good, Ph.D., Jane Etherington, and Dinean Miller for their time providing editorial assistance on this manuscript.

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