

Thermodynamics of Skeletal Muscle During Cardiocirculatory Assist

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Abstract

Traditional muscle physiology undergoes radical changes in the setting of continuously electrostimulated skeletal muscle utilization for biomechanical circulatory assist. Healthy "transformed" working skeletal muscle never loses the characteristics germane to striated muscle fibers. It only undergoes a multiplicity of changes which are always dynamic in nature. Thermodynamic parameters applied to the study of biologic phenomena have long provided a unique approach for analyzing the physiology of the skeletal muscle cells. The laws of thermodynamics, with their concepts of *negentropy*, *entropy*, and *enthalpy*, traditionally are applied to the non-living world. However, after forty years of fundamental ground work by Archibald Vivian Hill, other scientists have made it possible to utilize these concepts to study the performance of complex living systems. This essay aims to shed some light and to add a new perspective to the use of striated muscle so it may perform myocardial-like work efficiently for prolonged periods of time. Understanding the basic principles of thermodynamics and applying the concept to designing both stimulators and customized individual programs, may prove beneficial to a number of patients now undergoing cardiomyoplasty, and in the future to others destined to receive muscle assisted cardiocirculatory augmentation procedures now in the experimental stage.

Key words: thermodynamics, skeletal muscle, electrostimulation, cardio-circulatory assist, cardiomyoplasty.

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"Muscles are engines which, like the steam engine and the internal combustion engine, use energy stored in chemical fuel to generate mechanical movement." Richard Dawkins [13]

Historically, the biological behavior of the heart in response to neurologic, biochemical, metabolic, pharmacologic, or electrical stimuli has been related to its mechanical activity. Similarly, action potentials have been related to mechanical contraction of skeletal muscle, and resting potentials to mechanical muscle relaxation. This essay challenges the exclusive use of this mechanistic concept in such a complex phenomenon as the muscle functional cycle.

The application of thermodynamic parameters to the study of biologic phenomena provides a different approach to examining the physiology of the skeletal muscle cell. Hill [16], Szent-Gyorgyi [23], and Weber [25] among others, participated in a discussion on "The Thermodynamics of Muscle" as early as 1950, at the International Congress of Physiology in Copenhagen. During our last

twelve years of research, we have learned that understanding the phases of the contraction/relaxation cycle of the long-term, continuously electrostimulated, "transformed" skeletal muscle utilized for cardiac assist, requires an integrated concept of the multiple facets of the dynamics and function of the skeletal muscle cell.

Thermodynamics, a branch of the physical sciences which studies energy and its transformation, is particularly applicable to the study of bioenergetics, a critical aspect of skeletal muscle function. Most thermodynamic studies are concerned with two forms of energy: heat and work. Three unifying ideas form the core of the thermodynamic theory: 1) all matter has energy, and energy is never created nor destroyed; 2) events tend to move predictably toward a state of equilibrium; and 3) matter in a state of equilibrium can be described by specifying a limited number of observable characteristics.

The laws of thermodynamics were originally enunciated for closed systems, thereby expressing self-sustained me-

chanical or chemical reactions which could approach or even reach equilibrium.

In a closed system there is no exchange of either energy or matter with the immediate environment. According to this, the universe, by being devoid of surroundings, would be the only real closed system. The universe possesses a limited patrimony of order. Its tendency is to transform potential energy into kinetic energy, to move from order to chaos, from structuralization to dispersion. The universe is burning itself out a little bit at the time. Ludwig von Bertalanffy [1] defined all living organisms as open systems, constantly exchanging energy and matter with the environment. For all we know, only living matter constitutes a system capable of opposing, albeit transitorily, this entropic tendency of the cosmos. Living systems are the only ones capable of accumulating negative entropy, *negentropy*, of going "uphill" from chaos to order, from stability to instability, from destruction to creativity. However, living organisms are unable to transform entropy into negentropy.

The concept of *entropy* (S), derived from the second law of thermodynamics, constitutes a special and relevant parameter. In 1864 Rudolph Clausius [12] described the first two laws of thermodynamics. He also coined the word "entropy", from the Greek "transformation". This concept was introduced as a corollary to Clausius' theory, and, in a very simplified manner, can be defined as "a thermodynamic quantity that represents the fraction of the total energy of a system that is not available for doing work." This usually occurs in a chemical reaction because that fraction has been used to increase the random dispersion of the atoms or molecules in the system in the form of heat. It could be said that entropy is a measure of randomness and disarray in a given system. As a system approaches stability or equilibrium, the amount of entropic energy is increased, and the system ceases to be vulnerable. Eventually, maximal or final entropy equals death.

If an isolated skeletal muscle, or strand of convenient size, were to be arranged in an insulated box so that a load was to be lifted when stimulation was applied, each stimulus would elicit two kinds of energy: mechanical energy and heat. As work, mechanical energy is equal to the product of the load and the distance shortened. The first law of thermodynamics states that the sum of all energies in a closed system must remain constant; therefore, the occurrence of energy must be matched by the transformation of energy elsewhere. A loss of internal energy accompanies muscular contraction. It is possible both theoretically and experimentally to measure the disappearance of internal energy by measuring the changes in the chemical composition of contracting muscles.

The net changes in internal energy (-AE) during muscular contraction can be conceptualized as being equal to the chemical energy at the end of the contraction (E2) minus the chemical energy at the beginning of the contraction (E1). The following equation describes this change:

$$-AE = E2 - E1$$

In a closed system, such as the isolated muscle in the example, the sum of energies liberated as heat (Q) and as work (-W) represents the change in the external energy (AE). The equation which describes the net change in external energy during muscular contraction is expressed as follows:

$$AE = Q - W$$

Parameters referred to in this equation can be measured utilizing modern recording and analytical methods. Likewise, through determination of the concentrations of key metabolic compounds at the beginning and the end of the muscle's contractile cycle, the terms E1 and E2 can be evaluated.

Heat produced or heat absorbed during the individual chemical reactions provide a useful index of the energy changes accompanying each reaction and are represented by enthalpy changes (AH). Enthalpy (H) is the heat content or chemical energy of a physical system. Enthalpy is in itself a thermodynamic function equal to internal energy plus the product of the pressure and volume. The net changes of the concentrations of key metabolic compounds determined at points E2 and E1 can be multiplied by the enthalpy changes (AH) in the chemical reactions to approximate the free energy made available. The relationship between AE and AH is given by the equation

$$AE = AH + P \Delta V$$

where P is the pressure at which the reaction takes place and ΔV is the change in volume that accompanies the reaction. In muscle physiology, it is possible to assume that $AE = AH$, because muscular contraction takes place with little or no volume change.

Should more precise estimates for E2 and E1 be required, knowledge of the free energy changes (AG) which accompany each chemical reaction would also be required. The relationship between AH and AG is given in the equation

$$\Delta H = \Delta G + T \Delta S$$

where T is the absolute temperature and ΔS the entropy change. Considering that entropy changes are directly proportional to the "disorder" or randomness of the system under study, it seems to be most convenient to relate the change in internal energy (AE) to the enthalpy change (-AH), although evaluation of -AE clearly requires that certain assumptions be made regarding the relationship between changes in metabolic concentrations and the energy made available.

Recently has been recognized that the myocardial cell appears to be an unusual case of hybridism [6], obeying different thermodynamic laws. In a similar manner a theory may then be constructed to explain the functional cycle of the long-term continuously electrostimulated skeletal muscle.

Electrical activation alters membrane permeability to extracellular calcium and also releases calcium stored in the sarcoplasmic reticulum. Free cytosol calcium binds to troponin which permits the interaction between actin and myosin. Energy is provided by adenosine triphosphate dephosphorylation. Shortening of the sarcomere implies

the transformation of chemical energy into mechanical energy and heat. Contraction is over when sarcoplasmic reticulum calcium concentration has declined to zero. During contraction, the myofiber behaves as an isolated system that complies with the classical laws of thermodynamics, which proclaim the principle of conservation of energy and define the concept of entropy.

The opposite occurs during relaxation, myosin-actin interaction is suppressed by the inhibitory effect exerted by troponin. Calcium is taken by the sarcoplasmic reticulum and extruded from the cell. For relaxation to take place, work must be performed by pumping calcium back into the sarcoplasmic reticulum [5].

During relaxation, a fundamental change occurs when the myocell opens and becomes a system that obeys a different set of laws of non-equilibrium thermodynamics for living systems. The distinct property that characterizes living systems, is their capacity for self-maintenance and self-reproduction.

Classic thermodynamics is applied to the non-living world [14, 15]. With the increased use of recruited muscular power for biomechanical assistance [21] the challenge biology faces for the XXI century is to apply the discipline of thermodynamics to the performance of complex living systems. Bertalanffy [1], Lehninger [18], and Nicolis and Prigogine [22], among others, have already led the way by utilizing the theoretical instruments to make this possible. With the aid of the information theory and cybernetics [26], and the application of the theory of non-equilibrium thermodynamics of the irreversible processes in dissipative systems, we can simplify our perception of complex systems and create a new perspective of the functional skeletal muscle cycle, thereby reaching a better understanding of how continuously electrostimulated striated muscles can be made to do cardiac work efficiently for unusually prolonged periods of time.

In 1985 Carpentier [3] and Magovern [20] performed the first clinical cardiomyoplasties and changed forever the conventional functional picture of skeletal muscle. When continuously electrostimulated in synchrony with the heart beat, the skeletal muscle becomes a permanent integral part of the individual's hemodynamic system. In cardiocirculatory, biomechanical assistance (cardiomyoplasty, aortomyoplasty, skeletal muscle ventricles, skeletal muscle driven mechanical assist devices), the selected skeletal muscle, such as the *latissimus dorsi*, works continuously along with the heart to supply oxygen and nutrients to all the body, including themselves, and to remove waste.

Both heart and muscle require a constant input of energy, ultimately derived from the sun's radiant energy. This energy is stored in the cardiac and skeletal muscles and is utilized at a relatively fixed temperature and pressure. The heart functions as a pulsating pump in this self-regulated system. It pumps blood (fuel) to the muscle flap which functions as a driving engine that provides thermodynamic mechanical assistance (work) to the heart. The heart in turn keeps the cycle going [9] (Figure 1). This system has the

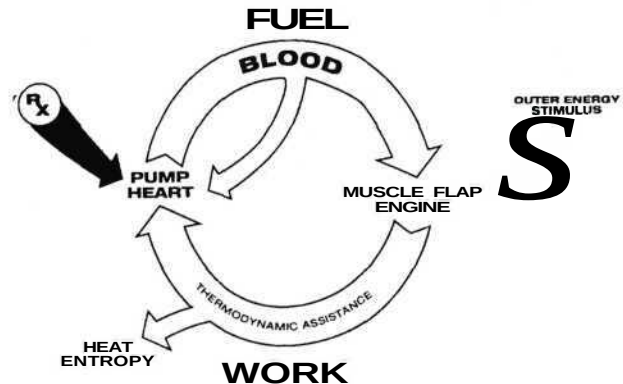


Figure 1. In biomechanical circulatory assistance, heart and skeletal muscle are joined in closed-circle, tandem fashion forming a symbiotic, binomial unit with thermodynamically interdependent parts. Failure in the cycle, at any point, will wreck the entire system.

unique property of transforming chemical energy into work more efficiently than any man-engineered machine [17].

The first physiological function to be studied in cardiac and skeletal muscles was the alternation between mechanical contraction and relaxation. This has long provided the framework for physiological and clinical descriptions of normal and abnormal functions [2, 8]. The mechanical components of contraction form a subsystem in a highly integrated mechano-chemical process, dependent upon the energy-liberating chemical reaction that provides the source of energy for such contraction. Today, the appropriateness of mechanically inspired terminology for the events of myocardial and skeletal muscle contractions may be scientifically challenged [10].

Both the heart and the electrostimulated muscle wrap in a cardiomyoplasty situation may rightfully be conceptualized as thermodynamic systems, with rhythmic and cyclic contractility, even if it is autonomic in one and artificially imposed in the other. Both have an input and output of energy that behave as dissipative structures. The phases of their cycles correspond to a continuous alternation between states of uphill decreasing entropy during relaxation (thermodynamic activity towards non-equilibrium), and downhill increasing entropy during contraction (thermodynamic passivity towards equilibrium). This entropy is greatest at peak contraction when the system is furthest removed from its normal thermodynamic non-equilibrium state. Entropy is reduced again during the subsequent diastole and relaxation when the system regains its thermodynamic non-equilibrium and excitability is restored.

Like with the heart, many properties of skeletal muscle, are related to these entropy changes [7]. However, there are important differences between myocardial and striated muscles. Skeletal muscle lacks, natural built-in insurance against entropy buildup: the refractory period and the application of the "all-or-none" law that applies to the entire ventricular mass in the heart, and only to the single

separate fiber in any given skeletal muscle unit. As partnership time accumulates, some compensatory mechanism (eg, intermittent stimulation with resting periods proportionate to the work load) becomes mandatory for the skeletal muscle.

Equally important is the fact that the coronary circulation fills in diastole and arteriolar perfusion nearly halts during systole, whereas in the muscle flap electrostimulated to contract in systolic synchronism, vascular resistances increase, in time, when aortic pressure is high and decrease when is low, impeding optimal distal capillary perfusion. Everything else being comparable, skeletal muscle diastolic cardiac assist by counterpulsation, such as aortomyoplasty or skeletal muscle ventricles, could improve long-term muscle preservation by a more balanced mean blood pressure than synchronized co-pulsation, by reason of such difference in the blood perfusion phase.

The concept of vascular delay [4], anatomically very important, has shown blood perfusion improvement to the distal and middle canine latissimus dorsi muscle segments, and improved circumferential muscle force generation and fatigue rates when compared with the nondelayed contralateral side [24]. These experiments lack long-term thermodynamic vision, therefore cannot predict the behavior of chronically overstimulated skeletal muscles over a period of several years.

The statement that conditioned skeletal muscle becomes a suitable replacement of the myocardium [19], by virtue of its electrically induced regrouping of fiber types, negates from its inception the thermodynamic differences between the functional cycles of both structures. However, the utilization of skeletal muscle recruited and trained to assist cardiocirculatory function has become an inescapable reality and has proven to be a therapeutic modality with a promising future for selected cases of end-stage myocardial failure [11]. This novel, unorthodox use of skeletal muscle as the engine of a continuously working system requires our efforts to protect its thermodynamic functional life.

We propound that the survival of the system, and therefore, the long-term success of the procedure, depends on the long-term survival of the skeletal muscle selected to do the work.

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