ENTROPY AND THE MYOCARDIAL CONTRACTILE STATE

EDUARDO CÉSARMAN
NORMAN BRACHFELD

The biphasic cardiac cycle alternates rhythmically between contraction and relaxation. Its mechanical function is its most striking attribute and was the first to be recognized and studied by physiologists, yet the initial investigations reflected a mechanistic view. Most observations of cardiac phenomena were correlated with, and largely developed to help describe this cyclic mechanical state, while the underlying biochemical processes were largely ignored.

Although the mammalian heart weighs less than one percent of the total resting body weight, it utilizes about ten the percent of total resting body oxygen consumption. Its metabolic activity quantitatively exceeds that of any other tissue in the body. The biochemical oriented cardiologist is, therefore, uniquely prepared to correlate metabolic function with its mechanical expression. Because oxygen consumption and ATP production and utilization spell "energy metabolism", one should remember the contribution that thermodynamics, the branch of physics that deals with energy and its transformations, have made to our understanding of the proper significance of the two major phases of contractile cycle.

The pioneering of A. V. Hill, and those who followed, in the development of our knowledge of myocardial muscle action, emphasized purely mechanical considerations that can be reasonably challenged when viewed as biophysical phenomena. The mechanical component of contraction is but one subsystem in a highly integrated mechano-chemical process. A chemical reactor must provide the energy necessary to fuel this activity; from the biophysical point of view, a purely mechanical interpretation of cardiac function can be seriously contested.

This paper presents a very superficial review of basic thermodynamic principles and explores the proposition that such reasoning may provide new insights into our understanding of the myocardial performance. It will also distinguish the relative significance and importance between the

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Prolongación Paseo de la Reforma num. 19, 1er. piso, México, D. F., 01330, México. /
eduardocesarman@hotmail.com

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internal and external work of the heart. Such a distinction carries important therapeutic implications.

If we wish to utilize the laws of physics to determine a temporal direction or order to events, we must restrict ourselves to those laws that describe processes and contain a time variable. We must be able to distinguish between cause and effect. Mechanical processes are reversible and thus define temporal order. In mechanistic terms, a filmstrip of a train running on a track is just as plausible when run forward or backwards. Direction is indicated by placing a negative or positive sign before a description of the activity. This concept of a mechanical "clockwork" universe was destroyed by the invention of the steam engine and the recognition that heat always moves by itself from hotter to colder bodies. Recognition of the unidirectional movement of heat was a revolutionary concept; it introduced an intrinsic direction for time and established the irreversibility of natural physical processes, that enabled us to define temporal direction as well as temporal order in physical terms, introducing a vector force to concepts of energy employment. The existence of irreversible processes is essential if we are to distinguish between cause and effect.

It became evident that all forms of energy move in a unique direction from a higher to a lower energy state. The inability of the orthodox framework of mechanical physics to explain these observations lead to the introduction of modern thermodynamic principles in 1865 by Rudolph Clausius. The first law of thermodynamic is straightforward and embodies the principle of conservation of energy: The total sum of all energy transfers in any process must equal zero for the system and the surroundings involved. Thus, energy is neither created nor destroyed during any physical or chemical process but may undergo transformations in type. The increment or decrement in energy for any system studied must complement the loss or gain of a reciprocal amount of energy from the surroundings.

This first law, however, said nothing about direction. The second law restricts the type of energy change that may take place, predicts the direction of reactions, and introduces the concept of entropy. It states that all processes tend to proceed in such a direction that the entropy of a system plus its surroundings (the entropy of the universe) increases until equilibrium is reached.

At equilibrium, entropy is at the maximum that can be attainted at the prevailing conditions of temperature and pressure. Entropy may be defined as the degree of randomness or disorder within the system. Irreversible processes in closed systems are characterized by an increase in entropy. This decay, an irretrievable loss, of some of the energy utilized by the process ensures the irreversibility of the reaction and establishes both time and direction, a true vector concept.

In 1872, Ludwig Boltzmann succeeded in relating the second law with the atomistic picture of the universe that was so popular during the nineteenth century. Boltzmann demonstrated that entropy is the function of a thermodynamic macro-state that occurs according to the realization of many microstates. In other words, he described entropy as a measure of molecular disorder and related it to the concept of probability.

Every process occurring in the material world has a built-in tendency toward molecular disorganization. An increase in entropy may be viewed as a transformation of improbable, ordered arrangements of molecules into more probable, randomly distributed and disordered ones. The change in entropy actually provides the true driving force for chemical reactions and determines their reversibility. The ultimate result of this increase in entropy is equilibrium, defined thermodynamically as a highly random state in which no net physical or chemical change can occur and where there is no capacity to perform work. A randomized system never unrandomizes spontaneously. Entropy is thus inseparable from disorder, probability, and randomness.

Another example may be taken from the chemistry laboratory. If iodine in a solution of carbon tetrachloride is overlaid with water, the iodine will diffuse between the carbon tetrachloride and the water phase until, at equilibrium, the concentration of iodine particles is the same in both solvents. The degree of organization is maximal before the diffusion occurrs; it decreases and entropy increases to a maximum at equilibrium. The work required to displace the iodine from the water phase back into the tetrachloride layer is equivalent to the increase in entropy within the system. If entropy is regarded from the viewpoint of probability, one can say that entropy increases with the increase of probability; in this case, the degree of disorder. The most probable state is obviously the one in which the iodine will be equally distributed between the two phases.

Entropy measures the loss of those characteristics that distinguish a system from its surroundings. All living things establish gradients that enable them to remain remote from equilibrium with their environment. An increase in entropy is accompanied by a decrease in differentiation, structure, and integrity. As equilibrium is approached, the inherent stability of the system is increased and its ability to respond to stimuli reduced.

TYPES OF ENERGY

Energy changes occurring in bioenergetic reactions might best be considered as occupying three separate compartments:

1. *Total energy* defines the absolute quantitative amount available to a system. It cannot be totally utilized unless temperature is reduced to absolute zero. At all other times it must be subdivided into its components: (a) free energy and (b) entropy.

a. *Free energy* is the amount of energy that actually supports the reaction.

b. *Entropy* represents the randomized energy of the system. It is usually expressed as heat, unavailable to perform work and unavoidably accompanies all energy exchanges. It ensures that efficiency can never approach 100 percent.

Total energy, free energy, and entropy are distributed in reciprocal amounts between a system and its surroundings, the universe. The total energy of the universe is finite. Thus, any increase in the entropy of a system must occur at the expense of the free energy available to it. Since free energy drives the reaction, an unavoidable reduction in the amount available makes reversal impossible.

As equilibrium is approached, entropy is maximized, free energy decreases to a minimum, cellular gradient tend to disappear, and the cell approaches death. Much of what has been said, however, is true only for closed systems, the reactions confined to the chemistry laboratory. Our observations tell us that biological system appears to violate the law or at least delay its application. Indeed, paradoxically, such systems tend to become increasingly complex and efficient. Living cell are open systems that conform to the laws of non-equilibrium thermodynamics.

The first and second laws of chemical thermodynamics in isothermal biological systems are:

$\Delta F = \Delta H - T\Delta S$ (1)
$\Delta H = \Delta E + \Delta PV$ (2)

But $\Delta PV = 0$ in biological systems and $\Delta H = \Delta E$, therefore,

$\Delta F = \Delta E - T\Delta S$ (3)
$\Delta E = \Delta F + T\Delta S$ (4)
$\Delta F = -Rt \ln K$ (5)

Where:
F = Free energy of the system,
ΔH = Enthalpy or heat change,
T = Absolute temperature (°C + 273.16 Absolute).
ΔS = Entropy (temperature / degree / mole),
E = Total energy of the system,
P = Pressure,
V = Volume,
R = Universal gas constant,
ln K = Natural log of K = 2.3 log K.

Exergonic reactions are those in which there is a decrease in free energy; endergonic reactions are those in which there is a gain in free energy.

Open systems are in constant interaction with their environment and demonstrate a remarkable degree of self-regulation. They are capable of preserving or restoring homeostasis and thus can resist the disorganization predicted by the second law; therefore, they may temporarily escape, or delay, the rapid increase in entropy defined for closed systems. In addition to self-regulation, they maintain order against constantly growing entropy by performing work. The higher the entropy, the greater amount of work is required to restore the system to its initial state. The processes of nourishment, elimination, and repair result in a continuous exchange of the original material of the cell for new material derived from the environment.

The constant input of free energy derived from the potential energy of substrate and oxygen maintains a high degree of molecular orderliness and steady state function, without which the cell cannot survive. Homeostasis is established and maintained by a decrease in entropy, that must be more than balanced at the expense of the environment into which it "exhausts" heat and other end-products of metabolism, increasing the randomness or disorder of the latter. Life is, therefore, a constant struggle against the growing entropy of the system, to which it must inevitably surrender. Waste disposal ensures that equilibrium is not reached, that entropy is reduced and organization is maintained.

The word that describes this process, "metabolism", is derived from the Greek and means "change" or "exchange". Instead of running down like a clock, the cell continuously creates or maintains order out of creeping chaos and adapting its surroundings to its needs instead of simply reacting to them. The implications of the irretrievable loss of some of the total energy of a system to entropy each time an energy transfer occurs are ominous, and predicts the ultimate disintegration of the universe at a time of maximum entropy and equilibrium. In less cosmic terms, open biological systems have the capability of temporarily escaping, or at least delaying, the increase in entropy that attend the life process.

MYOCARDIAL ENERGY UTILIZATION

As mentioned earlier, the myocardium is the most metabolically active tissue of the body. Thus, thermodynamic and bioenergetic factors that determine the temporal relationships of energy production and its use are important aspects of myocardial metabolism. The heart utilizes energy for both internal and external work and heat production. Because it is almost continuously active and does not develop a significant oxygen debt, its recovery metabolism must be extremely active. Since nutritional coronary flow is the source of the negative entropy necessary for the metabolic processes we have discussed, let us review the factors that regulate such flow.

Intramyocardial pressure is of primary importance in determining the coronary flow volume. During systole, extra vascular pressure on coronary vessels is maximal; at the onset of systole, intramyocardial pressure may exceed aortic perfusion pressure and coronary flow may be reversed.

Coronary flow subsequently follows the aortic pressure curve, then rises acutely in early diastole and falls again when diastole terminates. Systolic flow ranges from 7-45 percent of that during diastole, depending upon heart rate and other hemodynamic factors. Notice also that systolic flow within the wall of the left ventricle is not homogeneous; it is influenced by varying wall tension and describes a transmural gradient. It is two times as great in the subepicardium than in the inner 25 percent of the ventricular wall. During diastole, intramyocardial pressure is low, there is little extra vascular compression, and the transmural gradient is reversed.

Increased intramyocardial pressure (aortic stenosis, hypertrophy) may reduce or eliminate systolic perfusion; an increase in diastolic pressure (left ventricular failure, hypervolemia) may compromise the diastolic flow gradients. An increase in heart rate occurs mainly at the expense of diastole. While total flow augment with increasing rate, flow/beat falls during a shortened diastole at rapid rates. When reserve flow response is compromised by coronary artery disease, nutritional adequacy may be seriously threatened.

Although each cell of the body is a component of the whole organism, we often lose sight of the fact that it has dual loyalties. The first is to its survival, which requires the intrinsic energy requirements necessary for its own viability. Only after these needs are satisfied, it can assume its responsibility to the organism of which it is a part. One may think of "primary" and "secondary" energy needs. Secondary needs are expressed externally. The cell serves as a factory and exports such things as mechanical activity, hormones, enzymes, complex synthetic compounds, most of which play a modest role in its own life. Primary energy use is confined to the support of those processes critical to the survival of the cell.

While energy is utilized during both phases of the cardiac cycle, myocardial oxygen consumption and energy production are primarily diastolic events. Therefore, diastole is essential to myocardial function during normal metabolic activity, and plays a critical role in the maintenance of viability during ischemia.

Roughly 80 percent of myocardial energy consumption occurs during systole in the performance of isometric and isotonic work and by the heat released during this activity. The more essential factors are tabulated in the following outline.

external work (systolic) + internal work (diastolic) = total energy consumption

I. External work-systolic energy utilization

A. Intramyiocardial tension (stress)—contractile element work
  1. Internal (isometric) work-developed tension
  2. External (isotonic) work-shortening versus load
  3. Heat production-function of peak developed tension
  4. Degraded internal work, relaxation, and recovery work
  5. Ventricular pressure, volume, and wall thickness

B. Contractile state of the heart
  1. Force-velocity relationship
  2. Maximal velocity of contraction (V max)

C. Heart care

II. Work of internal maintenance-diastolic energy utilization

A. Restructuring and maintenance of optimal internal milieu
  1. Substrate transport and metabolism, energy production
  2. Synthetic function, protein, carbohydrate, lipid, RNA
  3. Replacement of "worn-out" subcellular particles. (Ribosomes, mitochondria, etc.)

B. Active on transport (Na^+, Ca^{2+})—systolic and diastolic
  1. 20-30 percent of total energy consumption
  2. Major thermogenic component
  3. Sensitive to inotropic agents

C. Cardiac resting heat

D. Activation energy-tension independent heat (increases with rate, related to movement)

Energy utilization, sustained by hydrolysis of ATP, occurs during a period of reduced coronary flow, oxygen consumption, and metabolic activity, and is maximal by the time the pressure pulse reaches its peak. Accompanying this energetic discharge there is a dramatic fall in free energy stores, most of which are ultimately degraded to entropy as heat and randomized to the surroundings. In the process, the cell loses differentiation and internal structure, to a marked degree. As its state of molecular randomness and entropy increases, it approaches equilibrium and stability. It has, in effect, discharged itself. Once activation has occurred, excitability is lost. The cell becomes refractory to stimulation. Further contractile activity cannot occur without restructuring, restocking, the internal cellular milieu which has been depleted. This requires and active bioenergetic process.

DIASTOLE ENERGY UTILIZATION
WORK OF INTERNAL MAINTENANCE

Cellular energy stores and partial oxigen pressure are depleted soon after peak systole; ADP concentration rises rapidly and stimulates cellular respiration. During diastole the process is reversed. Energy consumption is quantitatively smaller, less than 20-30 percent of total consumption, and is utilized to meet different and essential endogenous cellular requirements, together with the restoration of order and structure. By this means, the entropy created during systole is reduced to a minimum, energy stores are repleted, and the degree of cellular differentiation is increased. The cell becomes remote from its environment and furthest from equilibrium. At this point in the cycle it may be thought of as a maximally compressed spring or as a weight raised to a height, a state prepared to release potential energy when a properly triggered. The cell is now no longer refractory to stimulation; it demonstrates maximal capability to perform work if stimulated, or to discharge spontaneously. Heat production during this phase is minimal, thus the energetically "uphill" processes of diastole. The ion fluxes that produce the action potential and are responsible for excitation-contraction coupling are electrogenic, non-actively transported, and therefore also thermodynamically "downhill". All of the restorative ion fluxes that occur during diastole are non-electrogenic, require active transport and, since they require active energy expenditure, are metabolically "uphill".

THE RESTING AND ACTIVE STATES OF THE HEART

The term "resting state" was derived from its temporal coincidence with mechanical relaxation and is more appropriate to the relatively infrequent contractile cycle of a skeletal muscle. The word "resting", used to describe the heart during diastole, at the moment of greatest excitability, instability, and maximal thermodynamic activity, is obviously a misnomer. In contrast, the onset of systole initiates a passive downhill thermodynamic event. The spring has sprung, the weight has fallen, and potential energy has been discharged. The cell has lost a marked degree of differentiation, integrity, internal structure and energy, and has increased its degree of randomness. Thermodynamically and metabolically this may well be called the true "resting state" of the heart. Thus, the phases of the cardiac cycle correspond to a constant alternation between states of increasing and decreasing entropy. In these terms, the "active state" of mechanical diastole is seen to be immeasurably more important to the maintenance of viability than is the passive or "resting state" of systole.

MYOCARDIAL THERMOGENESIS

Heat production in the body is the byproduct of every energy-producing or energy-utilizing biological reaction. Although the skeletal muscles and the liver are the primary sources of endogenous heat, the heart produces more heat per gram than any other tissue, and it does so on a continuous basis. Systemic circulation of this warmed blood not only makes a valuable thermogenic contribution, but also serves as a means for discharging myocardial entropy into its surroundings. Active electrolyte transport and contractile activity, both fueled by ATP hydrolysis, are, therefore, a principal source of heat and a determining factor in cell thermogenesis.

REDUCTION IN ENERGY AVAILABILITY

The systolic and diastolic responses to a reduction in nutritional blood flow differ distinctively and may have significant therapeutic implications. A reduction in energy availability during systole results in a decrement of mechanical performance; the cell ceases to contract normally and eventually becomes asystolic. This is expressed clinically as dyskinetic function, as congestive heart failure, or as shock. Despite its inability to fulfill its "secondary" cellular responsibilities, the performance of external work, the endogenous energy requirements may be met and the cell remains viable.

This degree in flexibility is not matched during diastole. The minimal energy requirement for internal maintenance is relatively fixed. As oxygen consumption falls, the work required to maintain an appropriate cellular environment consumes a proportionately greater percentage of what is available. Nevertheless, it maintains viability, damage is potentially reversible, and function may be restored. All available energy is used to support the diastolic function and to maintain a homeostatic state as close to normal as possible. When flow falls below this irreducible minimum for even brief periods of time, the life of the cell is threatened, and irreversible damage may occur.

One result of this discussion, one would hope, will be a greater interest and attention to diastole in all patients with ischemic, or indeed with any type of heart diseases. Effective treatment of heart disease must be directed toward improvement of the diastolic metabolic function, the internal work of the cell responsible for enabling it to perform the external work necessary for the survival of the organism as a whole. Perfusion pressure, intramyocardial pressure, diastolic time, and adequate nutritional flow are critical to this phase of the cycle. Coronary artery disease, hypertension, high outflow states, dysrhythmias, congestive heart failure, and congenital heart diseases are all accompanied by a decrease in mechanical efficiency and an increase in entropy.

The therapy of heart diseases must be directed toward the reduction of entropy and the improvement of the active state function. Cardiologists currently employ inotropic agents in congestive heart failure. B-blocking drugs, antidysrhythmics, cardio version, hypothyermia or chemical cardiac arrest, and cardiopulmonary or coronary artery bypass surgery for patients with coronary artery diseases. None have proved totally adequate. Further advances in therapy await the development of agents that can significantly improve the diastolic function.

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