


**Thermodynamics of the Myocardial Cell**

**A Redefinition of Its Active and Resting States**

The most recognizably unique inherent quality of the heart is its mechanical ability. This rhythmic alternation between mechanical relaxation and contraction has long provided the framework for physiologic and clinical descriptions of normal and abnormal function.

During the past decade, there has been a reawakening of interest in descriptions of the heart in basic mechanical terms. The earlier investigations of A. V. Hill and others have been applied to the heart, and these pioneer investigations into muscular mechanics have been extended so that the contractile activity of the myocardium may be defined in terms of relationships of force, length, and velocity. Conceptual models and geometric forms of the contracting ventricle have been developed from experiments upon preparations of isolated muscle and have been substantiated in many cases when tested in vitro. Although the complexity of this type of analysis has occasionally led to conflicting interpretations, it has, nevertheless, contributed to our understanding of the components of the contractile process and has introduced a more objective and precise nomenclature for the definition of each phase of the contractile cycle.

Nonetheless, one may challenge the appropriateness of terminology applied to the events of myocardial contraction and derived from purely mechanical considerations. The mechanical components of contraction form but one subsystem in a highly integrated mechanochemical process. Indeed, this component is in all respects dependent upon another subsystem, the energy-generating mechanism or chemical reactor that provides the sources of energy for such contraction.

In 1865, Clausius introduced the concepts of modern thermodynamics as a new discipline which combined elements of mechanics, dynamics, and other physical sciences. The "laws" he described, further refined by others working in this new conceptual field, dealt with heat, energy, and their interconversion. These laws soon proved essential to the development of the engines of a modern society.

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 biologic systems that must obviously conform to the laws of physics. Indeed, the living cell, whose function and viability is totally dependent upon the transformation of energy, is a most appropriate model for 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 normal and abnormal cardiac function.

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

The term, "resting state," was derived from observations of cellular phenomena considered to be at rest due to their temporal coincidence with mechanical relaxation. Such a definition ignores what is actually a complex relationship of physical and chemical energetic events. When examined as real cellular phenomena, distinctions between "active" state and "resting" state blur. Thermodynamically, the phase of contraction that corresponds to mechanical relaxation is actually the most active bioenergetic state of the heart.

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 and ill-defined concept but deals with a measurable physical quantity and describes a quantum of energy that is not available for meaningful work. Entropy is defined mathematically, expressed in units that have the dimensions 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 for all physical and chemical reactions is the tendency toward that state in which the entropy of the system or its surroundings is maximized.

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

In thermodynamic terms the cell may be thought of as having lost a marked degree of differentiation, integrity, internal structure and energy, and has simultaneously increased its degree of randomness and become less vulnerable and more stable as it approaches the state of equilibrium. The stability of the cell is evident by an absolute degree of refractoriness to stimulation and by the greater approximation toward equilibrium of its transmembrane gradient. By the end of ventricular systole, the entropy of the cell is maximal, and it is statistically improbable that it will contract again without a restructuring of its internal milieu. Once activation has occurred, excitability is lost and can be restored only by an active bioenergetic metabolic process.

During mechanical diastole (the so-called resting state), consumption of energy is devoted to the work of internal maintenance, upon which the integrity and differentiation of the cell as a system depends. Energy is utilized for restoration of excitability, the transmembrane action potential is restored by activity of the sodium potassium adenosine-triphosphatase pump, and intracellular negativity is re-established. Indeed, the transduction of energy from adenosine triphosphate to an osmotic pump approaches a thermodynamic efficiency of 100 percent, and little heat is produced and randomized into the environment. Energy utilized for the metabolic requirements of glycolysis and oxidative phosphorylation permits the replenishment of the stores of high-energy phosphates in the cell. Other cellular housekeeping functions are also performed during this period. There is resynthesis of contractile and structural proteins and of nucleoproteins, glycogen, enzymes, lipids, and other macromolecules. Substrate is modified and chemically transformed to a new utilizable or storage form, and the general work of maintaining cellular structure and the integrity of the cellular membrane occurs.

A thermodynamic description of the cell during mechanical diastole would note that the cell has approached maximal differentiation and order, replenished its energy stores, reduced its degree of randomness, is furthest removed from equilibrium, restored its excitability, and enhanced its thermodynamic instability. The cell is no longer refractory to stimulation and retains a maximal capability to perform work when stimulated or, in cells that possess 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 to be subsequently utilized by the mechanical element. Although entropy is difficult to measure in biologic systems, its changes are quantitatively related to changes in free energy, a quantity which may be measured as a function of consumption of substrate and oxygen, production of heat, hemodynamic factors, and efficiency. It is a thermodynamic misnomer to describe diastole, the moment of maximal excitability and instability as the “resting” state.

The mechanical relaxation of the myocardial 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 the entropy and the disorder or chaos of the cell approaches a maximum. During relaxation and contraction, there is a constant alternation between states of decreasing and increasing entropy. The myocardial cellular phenomena, hitherto considered “resting” due to their temporal coincidence with mechanical relaxation, constitute the most active thermodynamic state of the heart.

The entropic status of the cell offers a useful conceptual measurement of function that is of special value for consideration of excitability, automaticity, rhythmicity, conductivity, contractility, and membrane permeability. The cellular entropic status offers a framework for evaluation of diverse pathologic states, as well as for the pharmacologic action of cardiotonic agents. Its importance approaches that currently enjoyed by more easily measured hemodynamic variables. Thus, the entropy of the ischemic or hypoxic cell is increased. An increase in peripheral resistance and diastolic hypertension will also enhance the entropy of the cell, as will hyperthyroidism, beriberi, arteriovenous shunts, hypermetabolic, febrile, and other high-output states, most forms of dysrhythmias (particularly those that lead to a decrease in cardiac output), depolarization due to electric shock, systolic cardiac arrest, the so-called “stone heart,” the response to positive...
inotropic agents (such as the catecholamines, calcium ions, and digitalis), and paired electrical stimulation. Entropy also increases during congestive heart failure, which may be thought of as an expression of a defect in the utilization of energy, a partial chemomechanical uncoupling.

The entropy of the myocardial cell tends to be reduced by negative inotropic agents, such as the β-adrenergic blocking drugs, as well as by antidyssrhythmic drugs. It is also reduced by direct-current conversion of dysrythmias, during hibernation (either natural or induced), during hypothermic or chemical cardiac arrest, by cardiopulmonary bypass, or during the use of mechanical cardiac assistance.

Eduardo Cesaran, M.D., F.C.C.P. 
Mexico City
and Norman Brachfeld, M.D.*
New York

*Chief, Medical Services, Comision Federal de Electricidad de Mexico, and Chief, Department of Epidemiology and Prevention, Instituto Nacional de Cardiologia de Mexico.
**Associate Professor of Medicine, Division of Cardiology, Department of Medicine, and Director, Myocardial Metabolism Laboratory, New York Hospital-Cornell Medical Center.

Reprint requests: Dr. Cesaran, Hamburgo 172-9, Mexico 6 D.F., Mexico

REFERENCE

1 Cesaran E, Brachfeld N: A redefinition of the resting state of the myocardial cell. Mexico D.F., Editorial Fak-S, Mexico, 1976

Nitrous Oxide Administration and Hemodynamics

Nitrous oxide is the oldest and most widely used drug for inhalation-induced analgesia. Nitrous oxide produces surgical anesthesia only at pressures greater than 800 mm Hg; but at lower pressures, corresponding to concentrations between 25 and 80 percent, it produces varying degrees of analgesia, amnesia, and alteration of consciousness which may elicit excitement, movement, laughter, and nausea. The rapid and reversible qualities of this analgesic are now being used in some places to relieve the pain of coronary ischemia. Unfortunately, it is not widely appreciated that there are direct cardiac and peripheral vascular actions of nitrous oxide. These effects are manifest in a moderate decrease in myocardial contractility, an increase in peripheral vascular resistance with reduced peripheral blood flow, and a rise in central venous pressure. These changes have been documented in awake humans, among both healthy volunteers1 and patients with coronary arterial disease.2 Certainly the central effects and probably the cardiovascular effects of nitrous oxide are dependent on dosage.

An article in this issue (see page 318) entitled "Administration of Nitrous Oxide in Normal Subjects: Evaluation of Systems of Gas Delivery for Their Clinical Use and Hemodynamic Effects," written by Lichtenthal et al, describes several systems of delivery for administering nitrous oxide (30 to 50 percent) with simultaneous noninvasive hemodynamic measurements in healthy volunteers. Lichtenthal et al conclude that an airlines mask is superior to nasal prongs or to standard plastic rebreathing masks in terms of attaining nitrous oxide equilibration, expressed as the ratio of expiratory concentration to inspiratory concentration.

Among 22 subjects in this study by Lichtenthal et al, 30 percent nitrous oxide produced significant decreases in mean arterial blood pressure (89.9 to 75.6 mm Hg) and heart rate (78.8 to 64.1 beats per minute). In eight subjects ranging in age from 19 to 28 years, studies of left ventricular function, including end-systolic volume index, cardiac index, ejection fraction, echocardiographic ventricular wall velocity, ejection time, and preejection period/ejection time, indicated no changes during 30 minutes of inhaling 30 percent nitrous oxide. From this, Lichtenthal et al concluded that 30 percent nitrous oxide does not affect left ventricular function, and they speculate that the fall in blood pressure indicates a greater effect (reduction) on aortic impedance than on peripheral vascular resistance. If this were the case, then the preejection period should have been shortened, rather than unchanged, since a fall in afterload should decrease the time of isovolumetric contraction. It is equally plausible to reason that a prolonged preejection period was obscured by the reduced afterload.

In this study the calculated cardiac index was unchanged, while both the measured heart rate and mean blood pressure fell, which indicates a substantial increase in stroke volume. If contractility is unaltered, then an increase in stroke volume should increase the ejection time, yet the reported ejection time was unchanged. Conclusions regarding ventricular function based on noninvasive measurements must be interpreted with caution, since noninvasive cardiac data are strongly influenced by preload, afterload, and heart rate.3-4

The use of nitrous oxide for analgesia for angina and infarctional pain is not new, nor is such usage necessarily safe. In areas where the use of nitrous oxide has been reported, there is no convincing evidence of its effectiveness as an analgesic alone,