Cardiovascular Functions

Edited by ALDO A. LUISADA, M.D.

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Preface

Most of the chapters included in this monograph, *Cardiovascular Functions,* have already been published as Part 2, of Volume 1 of *Cardiology.* The four new chapters which have been added to the original material make the present monograph more complete as a physiologic description of the cardiovascular system. These new chapters include a study of Increased Capillary Permeability (Spector), a contribution on the Regulation of Blood Volume (Pearce), one on Functions of the Pericardium (Duomarco, Giambruno, and Rimini), and one on the Sympathetic Control of the Heart (Peiss and Randall). One original chapter, Dietary Requirements (Pearson), has been revised.

This monograph should prove useful, not only to physiologists and pharmacologists, but also to research workers and teachers in many fields of cardiology, as well as to clinical cardiologists. Although a collection of studies by various contributors, each having his own point of view, cannot be as coordinated and integrated as a book by a single author, this monograph gives a fairly complete physiologic picture of the cardiovascular system and is more complete than many textbooks dealing with the physiology of the heart and blood vessels.

The complete collection of contributions to the various disciplines of cardiology is published in a five-volume, loose-leaf system—*Cardiology, An Encyclopedia of the Cardiovascular System.* Experimental and clinical cardiologists are encouraged to consult the complete treatise. It is believed, however, that teachers and research workers, especially, will benefit from smaller volumes for easier consultation. The success of the first monograph, *Development and Structure of the Cardiovascular System,* published in 1961, established the value of such a work and encouraged the publication of this second monograph, *Cardiovascular Functions.*

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Physiology of muscular contraction

W. F. H. M. MOMMAERTS

It is appropriate to start this part of an encyclopedia of cardiology with a description of the physiology of muscle with special emphasis on *striated muscle*. Not only is the myocardium itself a muscle with similar microscopic structure, so that much can be learned from the similarities as well as from the differences, but skeletal muscle has also been the object of choice for many fundamental investigations upon which many current concepts in biochemistry and physiology are based. This preference has been caused largely by the circumstance that, as Meyerhof (1930) has expressed, muscle is the one tissue in which "the transformation of chemical into other forms of energy takes place in a way which can be quantitatively comprehended." And this transformation is, after all, one of the chief problems of biologic investigation.

There are many angles from which the activity of muscle can be considered; in this discussion, the problem will be divided into questions of function, structure, and metabolism. Such a division is entirely artificial, but will be necessary since we cannot reflect upon the entire problem at once. Morphologic, biochemical, and physiologic investigations have progressed for generations, usually quite independently. A truly fundamental approach uniting all these views is more recent; it is exemplified by work on the structure of muscle by a combination of biochemical and optical (including electron optical and diffraction) methods, on the relation between chemical and physical events, or on the interconnection between structural properties and metabolic reactions. However, a true synthesis of all these disciplines still takes place on a highly hypothetic level, since so many of the basic facts are as yet unknown.

Muscle contracts in response to a *stimulus* which can be supplied by an efferent nerve or, in the heart, by foci of automatic activity within its own structure. The stimulus brings a given tissue into a state of *excitation*, which, in turn, causes the fibrous structure *to contract*. Unexplained as the nature of the contraction process may be, the mechanism of its preceding evocation by the excitatory event is so unknown to us that we do not even have a serious working hypothesis about it. The speeds with which these events occur differ widely, in relation to the velocity required of their function (Hill, 1949a).

The contraction process involves an expenditure of energy generated by metabolism, over and above that yielded by the resting metabolism of muscle, which presumably serves the maintenance of the tissue with respect, for example, to its ionic composition. The necessity of this increase is obvious when the contraction results in the performance of work, which would then be derived from the energy supplied by this additional metabolism. Such added metabolism, however, appears also when no work is done, as would be the case in a contraction without opposing force, or in an isometric contraction. This shows that *chemical energy is used to bring the muscle into the active state, whether work is done or not*. The performance of work, however, causes a recruitment of energy in addition to that needed for the activation and the shortening as such.

It has already been implied that the required energy is generated by muscular metabolism. For the organism as a whole, this metabolism is respiratory or oxidative, consisting of the *combustion of carbohydrates, fats, and proteins to carbon dioxide, water, and nitrogenous waste products.* However, all muscle can contract anaerobically for shorter or longer times, so that the contraction process itself is not aerobic. The most striking anaerobic metabolic process is *glycolysis,* yet this too can be eliminated without directly abolishing contractile performance. In the absence of these two processes, prolonged activity proceeds at the cost of splitting so-called energy-rich phosphate compounds such as *phosphocreatine* and *adenosine triphosphate (ATP)*. A dominant theory of muscle action is, therefore, that the splitting of one of these substances is the energy-yielding reaction and the direct cause of contraction. This theory has been eminently satisfactory because biochemical investigation has shown that respiration and glycolysis both result in a synthesis of these high-energy compounds from their breakdown products (aerobic and anaerobic phosphorylation) and so will resupply the active tissue with its immediate energy sources to the extent that they are used up on activity. With a remarkable anticipation of these recent insights, the high-energy phosphate has been termed "the coinage of the living cell" (Szent-Györgyi, 1937).

Morphologically, the contractile activity of striated muscles is assigned to their *fibrils.* These are composed of proteins, among which *myosin* and *actin* constitute the bulk. Both these proteins have intricate relations to adenosine triphosphate, which lend substance to the view that the interaction between this substance and myosin and actin (perhaps in the form of their complex, *actomyosin*) constitutes the final mechanism of contraction. An especially impressive experimental demonstration of this is Szent-Györgyi's discovery of actomyosin filaments or extracted muscle fiber preparations which contract upon the addition of ATP in a suitable ionic medium

PHYSIOLOGIC ASPECTS

As treated at greater length in monographs of physiology (Wilkie, 1954), a single contraction cycle (*muscle twitch*), consisting of a contraction and a relaxation phase, is elicited by a *stimulus.* Present concepts regard the stimulus as a propagated reversal of the polarity of a surface membrane (Hodgkin, 1951), although the polarization phenomena can be looked upon in terms other than membrane effects. Ingenious experiments by Huxley and Taylor (1955) indicate that the membrane event is conducted inward to the myofibrils by the Z membranes which, bisecting the I bands, form sheets across the muscle which have a certain continuity and which are attached to the sarcolemma.

The mechanical response is separated from the stimulus by a *latency period,* during the approximate span of which a number of events take place, which may be expressions of the coupling between stimulation and activation. In its earliest part is the *action potential* of the impulse itself, accompanied by impedance changes, but, contrary to what happens for nerve, these impedance changes outlast the action potential and merge with changes associated with contraction itself (Dubuisson, 1937). After the absolute latency period, of the order of milliseconds, the muscle first shows a minute slackening prior to its contraction. It is disputed whether this latency relaxation is a property of the contractile matter (Sandow) or of the sarcolemma (Abbott and Ritchie, 1951; Hill, 1951). At approximately the same time, there is a minute constriction of the total volume, the *Ernst effect,* amounting to not more than 0.02 mm/3 Gm muscle (Ernst) probably attributable to electrostriction due to a temporary release of ions. There are also optical changes, with respect to light scattering, diffraction, and birefringence, but these have been difficult to interpret. The absolute lengths of the latency period, contraction phase, and relaxation phase differ for various muscles, in relation to their various speed characteristics. The total duration of the cycle is about 0.1 sec for a frog sartorius at room temperature, and even less for mammalian muscles in situ. The cardiac cycle in larger animals is much slower, but in small birds, for example, the velocity of cardiac systole is fully comparable to that of fast skeletal muscles.

In an *isotonic twitch,* the muscle shortens and work is performed to the extent that weights are lifted or forces displaced. In an *isometric twitch,* there is development of tension without gross shortening, and no external work is evident. Nevertheless, there are muscle structures which are being stretched by the contracting elements, so that a certain amount of concealed work is done which is dissipated as heat. This stretching affects, not only external passive structures such as tendon, but also an internal element named the "series elastic component." It has been proposed that this is located in noncontractile parts of the sarcomere (Philpot and Szent-Györgyi, 1953), and some of its mechanical characteristics have been determined (Wilkie, 1956b).

A stimulus closely following a preceding excitation will again be effective unless it falls within the *refractory period.* This period is very brief in skeletal muscle, of the order of milliseconds, very much shorter than the duration of the mechanical cycle. Hence, the second stimulus still finds the muscle in a state of active shortening, and the activities summate. *In the heart, the duration of total (absolute plus relative) refractory period is of the same order as that of the mechanical cycle, so that summation cannot normally occur.* By the summation of a series of stimuli of sufficient frequency, a muscle goes into a steady state of activity, or *tetanus,* by which a greater tension or shortening is developed than in a twitch. It is believed that a tetanus represents the maximal activity of which a muscle is capable, while in a twitch the fundamental process of activation, also called the active state, declines before the muscle has been able to express this activation macroscopically (Ritchie, 1954; Ritchie and Wilkie, 1955). This is true to a varying extent, dependent on the kind of muscle and the temperature. The active state in a twitch can be prolonged by epinephrine and by replacing the chloride in the medium by nitrate, by which means the twitch tension can be made to approach the tetanic tension. These same influences also prolong the negative *afterpotential* of the excitation wave (Edwards, Ritchie, and Wilkie, 1956). The fact that the "amount" of activity obtainable from a single event of excitation is variable is of great theoretic importance for the interpretation of the link between stimulation and contraction (Hill and Macpherson, 1954), and is also bound to exert a great influence on the understanding of cardiac dynamics and its regulation, e.g., by epinephrine or digitalis. This same variability of the response is also the basis of the type of adjustments of which the classical staircase effect is an example. A renewed interest in this phenomenon has been initiated by Hajdu and Szent-Györgyi (1952a) in terms of delicate ion balances which are, in part, regulated by lipid substances in the plasma (Titus et al., 1956), and is currently being analyzed in terms of fundamental mechanical concepts (Abbott and Mommaerts, 1959). In a tetanus, however, regardless of the size of the twitch, the full level of activation is reached and maintained.

Most of the contractions of skeletal muscles in the body are tetani, although there are exceptions to this rule. In coordinated movements, these tetani are not initiated by direct motor activation of the normal muscle fibers, but start with a stimulation of the muscle spindles through small motor (Aγ) fibers; the contraction of the ends of the spindle fibers causes a stretch of their central parts, stimulating their annulospiral nerve endings, which in turn leads to reflex stimulation of the bulk of the muscle through large motor (Aα) fibers (Kuffler and Hunt, 1952). According to their innervation by the α fibers, the muscle cells are organized into motor units, comprising from a few to several hundreds of fibers. Stimulation of one nerve fiber leads to full contraction of the entire motor unit which it innervates, according to the *all-or-none principle;* this full contraction still depends, however, on the factors discussed above. *Muscle tonus or submaximal tension development is maintained by asynchronous contractions of alternatingly active fiber groups.*

Like any deformable body, a resting muscle develops *elastic tension* when stretched. This elasticity, a part of which may reside in the sarcolemma and in connective tissue elements, is comparable to that of rubber, in that the force opposing stretch originates in the tendency of the molecular chains of fibrous proteins to assume randomly coiled configurations. The elasticity of a contracted muscle, however, is not rubberlike but normal, suggesting additional molecular bonding in the course of the contraction process (Hill, 1953a; Aubert, 1953). Regardless of these distinctions, it is possible to measure the force developed as a function of length to obtain the length-tension diagram. This is difficult, experimentally, because of

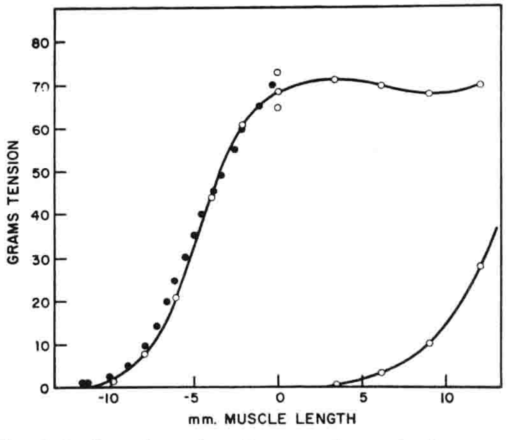

Fig. 2-1. Length-tension diagram of tetanically stimulated (upper curve) and of unstimulated frog sartorius muscle (lower curve). The abscissa gives the length relative to the in situ length of the muscle (in this case 31 mm) in millimeters, shortening (−) or lengthening (+); closed circles, measurements performed isotonically; open circles, measurements performed isometrically, i.e., by stimulation at a predetermined length. (*Redrawn from Wilkie, 1956.*)

hysteresis and differences in force developed isometrically and isotonically at a given length. Painstaking work by Wilkie (1954) with the frog sartorius muscle has largely eliminated these difficulties, and the results may be taken to illustrate the general behavior (Fig. 2-1). Usually, the length of the muscle in the body is such that there is no tension at complete rest and the maximal tension is generated upon stimulation. Both at greater and at lesser length, less tension would be actively developed. When muscles are tetanized isotonically, it is obvious that they will contract until they reach a length corresponding to a force equal to the weight attached to them (see Fig. 2-1). If this load is small, shortening will be nearly maximal, but very little work will be done, since the displaced force is small. With a very large load, work will be small too, because of the short distance of displacement. Maximal work is performed at some intermediary load, at which the product of force and shortening is greatest. This is not a physiologic regulation characteristic for muscle but a simple mechanical rule; of course, the accurate shape of the work-load curve depends on the tension-length curve. These phenomena are basic to determining the work done by the heart also. Increasing the load in isotonic contraction will decrease also the velocity of shortening. The force-velocity curve of muscle has often been expressed by the equation

$$(P + a)(V + b) = (P_o + a)b$$

where P = force
P_o = isometric tension
V = velocity of shortening
a and b = constants (Hill, 1938)

This equation and further derivations based upon it are of great use in quantitatively describing the behavior of muscle (Wilkie, 1956a). Considerable significance has been attached to the constant a, which is identical with one obtained from the proportionality between shortening heat and extent of shortening (Hill, 1949a, 1950), but an exception to this equality has recently been discovered (Abbott and Lowy, 1956). The maximal isometric tensions do not differ greatly for various muscles, 1 to 2 kg/cm^2 cross section, but the velocity scales vary enormously, especially when *smooth muscles* also are drawn into the comparison. *In the latter case, the contractile state persists so long that infrequent stimulation can maintain tension.* Since each activation process represents a roughly constant amount of energy (Mommaerts, 1950), also for smooth muscle (Csapo and Gergely, 1950), it is obvious that the economy of tension maintenance varies inversely with the speed of the muscle. Similarly, the economy for a given muscle is greater at lower temperature. When the speed of contraction is controlled, voluntarily or otherwise, it is found that an optimum speed exists at which both the efficiency of the muscle and the power output are about maximal. An interesting question has been raised (Hill, 1956) with respect to the heart, the speed of which increases during the transition from rest to effort. In which state does it function optimally? Or can it change its velocity characteristics to fit the conditions?

When a muscle is driven to contract for a long time, a state will set in, in which its mechanical responses first diminish and eventually fail. This is known as *fatigue* and is, in the isolated muscle, associated with *an accumulation of lactic acid and a diminution of adenosine triphosphate and phosphocreatine.* In the whole body, progressive failing of the muscle can also be due to *synaptic* or *central fatigue,* but Merton has shown that fatigue is more exclusively a property of muscle itself than has frequently been believed. An important question is why some muscles fatigue readily, others, like the heart, not at all. This difference has a metabolic basis (Chap. 2).

Since muscle contraction is a conversion of chemical into mechanical energy, one would expect the phenomenon to be accompanied by thermal changes. These could occur for two rather different reasons. In the first case, a certain amount of energy would serve to perform some form of work (e.g., mechanical or osmotic) which would subsequently (or even simultaneously) degenerate or dissipate, being quantitatively converted into heat; this will be called dissipational heat production, and is always exothermic. *Dissipational heat* will also develop when work is performed with an efficiency below the ideally possible one, as is always to some extent the case in actuality. In the second case, the heat effect is a necessary accompaniment of the energy transformation as such, because, in this process, owing to a change in entropy, the heat effect (ΔH) and free-energy effect (ΔF) are not equal. This phenomenon, which will be called *obligatory heat*, can be either positive or negative: if the free-energy change exceeds the heat content change, the reaction will be endothermic, since heat is drawn from the surroundings.

Experiments on the course of the heat production in muscle activity have been pursued for a generation with ever-increasing perfection by Hill. Such myothermic studies have the great significance of providing a quantitative measure of the intensity of the energy exchange processes. Its relation to these processes is unspecific, which is at once a strength and a weakness: a weakness, because the measured heat changes cannot be explicitly identified with specific chemical reactions; a strength, because myothermic measurements provide a rigid frame of reference to which proposed chemical mechanisms must conform.

Resting muscle shows a steady heat production of low intensity, called the *resting heat*. This is dissipational heat, largely because the basal metabolism of the tissue serves to accumulate ions against a diffusion gradient, while this osmotic work is continually dissipated into heat owing to the leakage of these ions back into the extracellular fluid. The resting heat and the resting respiration which corresponds to it depend on influences such as stretching the muscle (Feng, 1932) or changing the ionic composition of its bathing fluid (Solandt, 1936).

In contractile activity, one must distinguish between initial heat, associated with the activity itself, and the recovery heat, indicative of the chemical restitution processes taking place after it (Hill, 1924). The total amount of heat developed in the aerobic recovery phase is roughly equal to the total energy output in the initial phase, although it is protracted over a much longer time (Hill, 1939), dependent, of course, on the temperature, but also on the nature of the preceding activity. Anaerobically, the recovery heat is far smaller, often nearly zero, dependent again upon the nature and circumstances of the activity. For example, no measurable anaerobic recovery heat occurs after single twitches, while it does occur after tetanic activity of frog muscle at room temperature. This might well indicate that different chemical processes occur in prolonged and in single periods of activity. The difference between aerobic and anaerobic recovery heat indicates that anaerobic phosphorylation occurs with greater thermodynamic effectiveness than aerobic phosphorylation. In its time course the recovery heat follows the recovery respiration accurately (D. K. Hill, 1940a).

The initial heat has several components, which may, of course, have mechanisms in common. The *activation* or *maintenance heat* is correlated with the onset and decline of the active state, and with its prolonged maintenance in a tetanus (Hill, 1953a). Its time course should be identical with that of the active state, but in reality some discrepancies are noted. When the muscle shortens, a *shortening heat* is developed, in addition to the heat of maintenance. The proportionality between heat and shortening is expressed by the same constant a as was previously encountered in Hill's equation of the force-velocity relation. The *relaxation heat* appears during relaxation, but it merely represents the return to the muscle of the work performed in contraction, and it vanishes when this return is prevented by catching the lifted weight so that it can do no work upon the muscle. When muscle is stretched during its contraction (as frequently happens in the body), the work exerted upon it does not appear as heat, so that work must have been absorbed into some other form or must have prevented a corresponding amount of metabolic heat from being generated. When a muscle not only shortens but also performs work, it is found that the contraction heat is unchanged. This important fact, known as the *Fenn effect*, means that the total energy output in contraction is not constant, but that the normal energy release, as expressed by activation and shortening heats, is augmented by the work performed. This additional energy, which may amount to about as much as the contraction heat itself, appears as relaxation heat when the lifted load is permitted to fall back, and remains as undissipated work if the lifted weight is caught at its highest point. Whether the Fenn effect is due to a regulative process or to some inherent property of the topochemical mechanisms operative in contraction is unknown. The underlying processes may also be related to the absorption of work in a stretched contracting muscle (the *Abbott-Aubert effect*), as referred to previously.

The ratio of the actual work performed to the total energy output is called the *efficiency of the process*. This efficiency, in favorable circumstances, may be about 20 to 25 per cent (Hill, 1939), not unlike that of the heart (Evans, 1936; Bing et al., 1949). Since about half the energy is dissipated in the aerobic recovery process, the efficiency of the initial events themselves is about twice as high. Since the activation and shortening heats appear in any case and are therefore wasted, and since any work performed is not accompanied by additional heat, it might even be stated that the fundamental event leading to external work is 100 per cent efficient, although it would require actual knowledge of the mechanisms to permit judgment whether this last statement is not highly artificial or even incorrect. At any rate, the efficiency is so high as to place definite limitations on any proposed theory for the mechanism of contractility.

This very brief description of the major biophysical aspects of the contraction process has been given with but little reference to the corresponding properties of the heart, which have not been studied to the same degree. Further investigations in that direction should be very beneficial for the understanding of myocardial function and its pathologic aberrations.

GLYCOLYSIS AND OTHER CHEMICAL REACTIONS WHICH ACCOMPANY CONTRACTILE ACTIVITY

The energy requirements of muscular activity are ultimately provided by respiratory metabolism. Experimentally, however, all muscles can support their activity for a shorter or longer interval without oxygen by *glycolysis*, and in the body, too, such anaerobic activity may occur either locally or temporarily.

Until other chemical processes were recognized, it was believed that glycolysis was the fundamental chemical activity of muscle and the immediate cause of contraction. Investigations beginning with the publication of Fletcher and Hopkins (1907) found expression in the "lactic acid theory" of muscular activity, based