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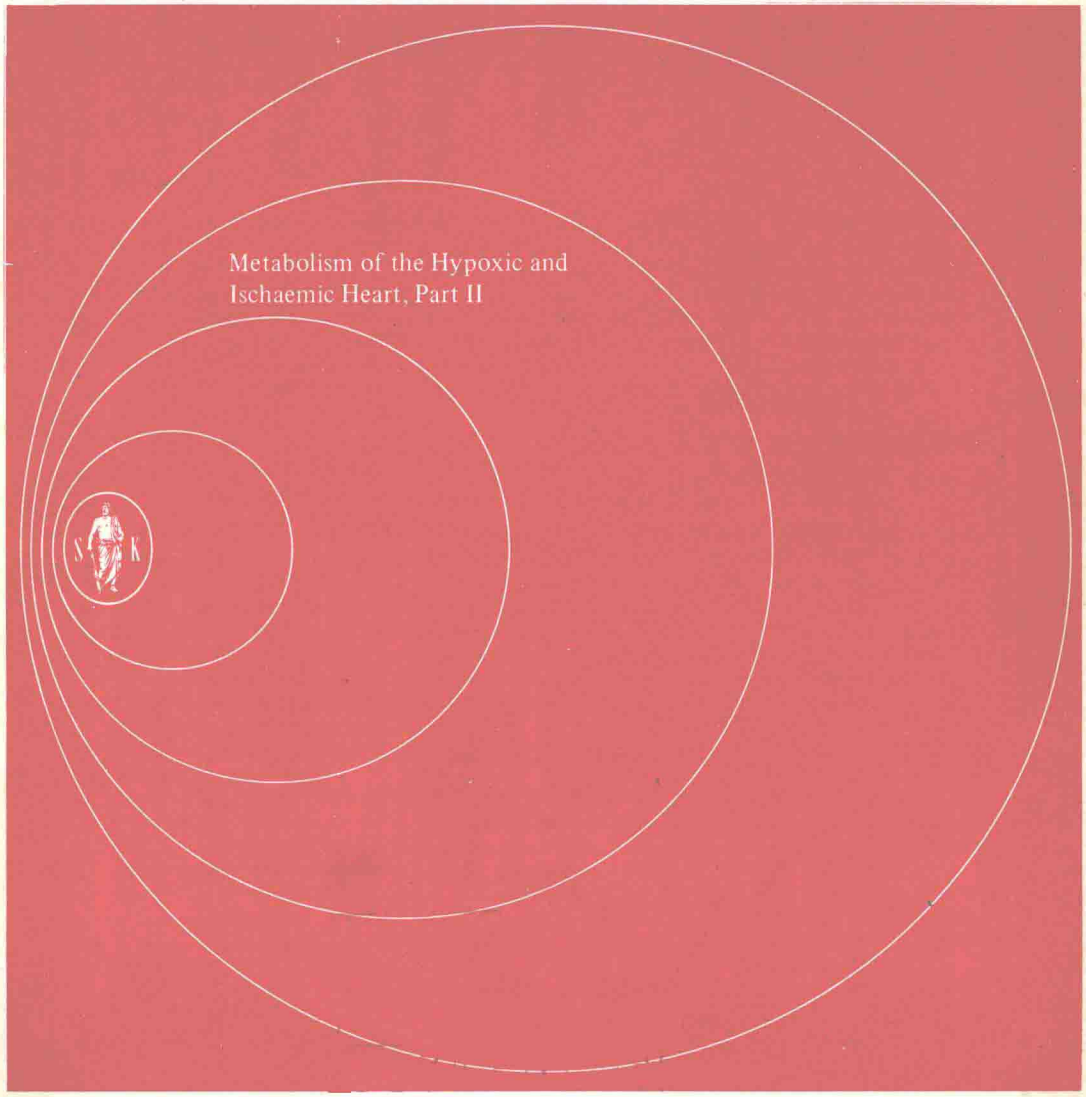
Cardiology



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Metabolism of the Hypoxic and Ischaemic Heart

Part II

Edited by
P. MORET and Z. FEJFAR, Geneva

Content

Controversial Methodological Aspects
Chairman: R. E. OLSON
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Introductory Reports

Cardiology

Succeeding Cardiologia. International Archives of Cardiology

Founded by *Bruno Kisch* and *Wilhelm Löffler*, continued by *Robert Hegglin, Ernst Lüthy* and *Ivan Mahaim*

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In memory of the publisher Heinz Karger an international prize for an important paper on a particular scientific subject is awarded each year. The Council of the Memorial Foundation, Prof. Dr. H. Lüdin (Basel), Prof. Dr. G. Mayor (Zürich), Prof. Dr. R. Richterich (Berne), Prof. Dr. J. R. Rüttner (Zürich) and the publisher Mr. Thomas Karger, has awarded the prize for 1971 to

E. Sorkin and J. H. Wissler (Davos-Platz/Switzerland)

for their paper on *'Biochemistry and Biology of the Anaphylatoxin Related Leucotactic Serum Peptide System'*. This paper will be published in the 'International Archives of Allergy and Applied Immunology'.

Zur Erinnerung an den Verleger Heinz Karger wird jährlich ein internationaler Preis für eine hervorragende Arbeit über ein bestimmtes wissenschaftliches Thema ausgeschrieben. Den Preis für das Jahr 1971 hat der Stiftungsrat, dem die Herren Prof. Dr. H. Lüdin (Basel), Prof. Dr. G. Mayor (Zürich), Prof. Dr. R. Richterich (Bern), Prof. Dr. J. R. Rüttner (Zürich) und der Verleger Thomas Karger angehören,

E. Sorkin und J. H. Wissler (Davos-Platz/Schweiz)

für ihre Arbeit *„Biochemistry and Biology of the Anaphylatoxin Related Leucotactic Serum Peptide System"* zugesprochen. Diese Arbeit wird in „International Archives of Allergy and Applied Immunology" veröffentlicht werden.

En souvenir de l'éditeur Heinz Karger un prix international, destiné à récompenser un travail scientifique d'importance capitale, est attribué chaque année. Le comité de la fondation, composé des Prof. Dr. H. Lüdin (Bâle), Prof. Dr. G. Mayor (Zurich), Prof. Dr. R. Richterich (Berne), Prof. Dr. J. R. Rüttner (Zurich) et de l'éditeur Monsieur Thomas Karger a remis le prix pour l'année 1971 à

E. Sorkin et J. H. Wissler (Davos-Platz/Suisse)

pour leur article entitulé *«Biochemistry and Biology of the Anaphylatoxin Related Leucotactic Serum Peptide System»*. Cet article sera publié dans «International Archives of Allergy and Applied Immunology».

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The Dr. Heinz Karger Memorial Foundation invites the submission of original papers to compete for the 1972 award, on the following subject:

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Submission date: Manuscripts marked 'Competition' must reach the publishers S. Karger AG, Arnold-Böcklin-Strasse 25, 4000 Basel 11 (Switzerland), not later than June 30, 1972. The manuscript shall not exceed 20 typewritten pages, including illustrations, tables and bibliography.
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Die Dr. Heinz Karger-Gedächtnis-Stiftung schreibt für das Jahr 1972 einen Preis aus für eine Originalarbeit über das Thema:

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At the same time, the Foundation invites the submission of original papers to compete for the 1973 award, on the following subject:

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D'autre part, la Fondation met au concours le prix 1973 récompensant le meilleur travail concernant le thème suivant:

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Other Contributions

Closing Session

Chairman: D. E. GREGG

Part I: Published as Cardiology, Vol. 56, No. 1–6 (1971/72)

Controversial Methodological Aspects

Chairman: R. E. Olson
Rapporteur: L. Opie

Cardiology *57:* 2–10 (1972)

The Force-Velocity Curve

A Biochemist's Viewpoint, 1971[1]

A. M. KATZ[2]

Division of Cardiology, Department of Medicine, The Mount Sinai School of Medicine of the City University of New York, New York, N.Y.

Measurements of cardiac mechanics can either be interpreted as *empirical indices* of one or another aspect of myocardial function, or the measurements can, themselves, be presented as *direct and valid determinations* of specific properties of the contractile process. If the first approach alone were to be common usage, the current controversy would remain primarily one of methodology and data analysis. Then any mechanical measurement, direct, extrapolated or derived, would itself be valid as long as it could be reproduced by other workers in the field. The utility of such a measurement as an index of any specific aspect of myocardial function would rest primarily on a documented correlation between independent assessments of other parameters of myocardial function and the mechanical measurement itself. If, on the other hand, the measurements, extrapolations and derivations from mechanical studies are themselves to be regarded as direct and valid determinations of specific biochemical and biophysical parameters of myocardial contractile function, then the conclusions reached from the mechanical studies of cardiac muscle must be in accord with our present understanding of the biochemistry and biophysics of cardiac muscle. In this regard serious discrepancies have arisen.

Before defining the discrepancies between the interpretations of mechanical studies of cardiac muscle on the one hand, and biochemical and

[1] Supported by Research Grants HE-13191, US Public Health Service and a New York Heart Association Grant-in-Aid.

[2] PHILIP J. and HARRIET L. GOODHART Professor of Medicine (Cardiology), The Mount Sinai School of Medicine of the City University of New York.

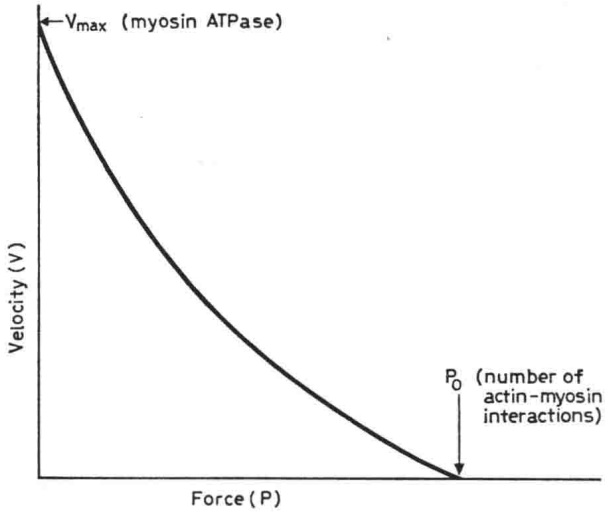

Fig. 1. Schematic drawing of a force-velocity curve illustrating the postulated dependence of V_{max} (rate of shortening at zero load) on myosin adenosine triphosphatase (rate of chemical reaction), and of P_0 (maximal tension developed) on the number of actin-myosin interactions that generate tension. Reprinted from KATZ, A. M.: Amer. J. Cardiol. *26:* 331–332 (1970).

biophysical analyses of purified contractile systems on the other, it will be necessary to review in some detail the nature of the proposed direct relationships between mechanical and biochemical studies of the contractile process. These relationships have been considered in detail elsewhere [13, 14], and will be reviewed only briefly at this point.

The force-velocity curve of a skeletal muscle has two intercepts, one of which can be measured directly while the other can be obtained by extrapolations that are subject to rigorous criteria (fig. 1).

The directly-determined intercept is P_0, measured as the maximal force developed in an isometric tetanic contraction. The extrapolated intercept at maximal velocity, V_{max}, can be evaluated by applying the equation for a rectangular hyperbola to measurements of muscle shortening velocity at intermediate loads. In 1938, HILL [11] proposed that the inverse relationship between force and velocity could be explained if the active points in the muscle existed in two states (fig. 2).

In the first of these, corresponding to P_0, all active points are engaged in holding tension and shortening does not occur. Isometric tetanic ten-

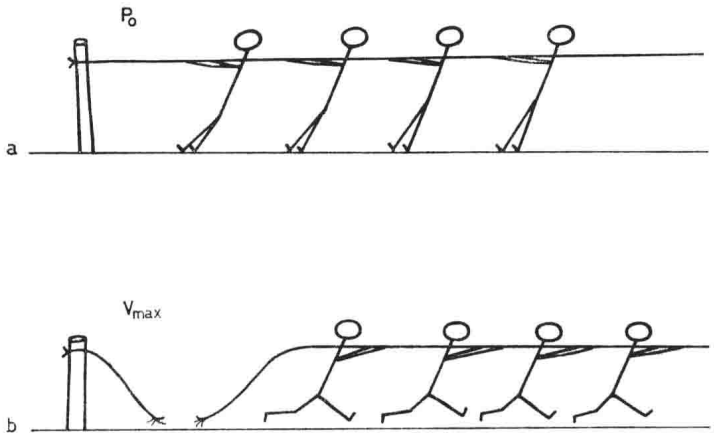

Fig. 2. Schematic diagram of two possible states of active muscle. In the upper diagram (a), corresponding to isometric contraction during which the muscle is not permitted to shorten, all active points are combined and are generating tension, which is maximal (P_0). No shortening can occur so that velocity is zero. In the lower diagram (b), corresponding to freely shortening muscle bearing no load, all active points are engaged in the chemical reactions that lead to shortening. Velocity is thus maximal while developed tension is zero.

sion (P_0) will thus provide a measure of the number of active points in the muscle. In the second state, corresponding to V_{max}, all active points are undergoing mechanochemical transformations and none are holding tension. In freely shortening muscle, therefore, the velocity will be limited by the rate of turnover of the active points in muscle. A corollary to this formulation of muscle mechanics was defined in 1957 by HUXLEY [12] who indicated that if the load on a muscle is truly zero, then the velocity of muscle shortening (V_{max}) should be independent of the number of force generating sites (table I). P_0 and V_{max}, therefore, appear in theory to reflect entirely different parameters of muscle function. At loads (P) between P_0 and zero, the active points will be distributed in both of these two states; hence, both force and velocity will be less than maximal. In analysing the mechanical data, therefore, it is the intercepts of the curve that are of greatest importance. Unfortunately, in heart muscle it is the evaluation of these intercepts that has given rise to the greatest difficulty [5–7, 13, 20, 22, 24].

These concepts of muscle mechanics remained largely in the realm of the physiologist until the mid 1960's, when a number of groups, working

independently, provided data that indicated a highly significant correlation between the V_{max} and myosin ATPase activity of different muscles. The lower ATPase activity of cardiac myosin, compared to that of myosin from rabbit white skeletal myosin, had been recognized since the 1950's [14], but it was not until 1965 that differences between the ATPase activities of red and white skeletal myosins were clearly defined [1, 15, 19, 23]. Red skeletal myosin was found to have a lower ATPase activity than the myosin from white skeletal muscle, these differences being found within a given species. At this same time, careful studies of the mechanics of the skeletal muscles *in vivo* demonstrated that V_{max} of red skeletal muscle was significantly less than that of white skeletal muscle [27]. In an elegant study, in which muscles differing over 100-fold in V_{max} and myosin ATPase activity were compared, BÁRÁNY [2] defined a close correlation between myosin ATPase activity and the maximal velocity of muscle shortening. More recently, this correlation has been extended to cross-innervated red and white skeletal muscles, in which the motor nerve has been shown to influence in a parallel manner both V_{max} and myosin ATPase activity [3]. Thus, V_{max}, the maximal rate of mechanochemical transformation in a freely shortening muscle, is closely correlated with myosin ATPase activity, the maximal rate of liberation of the chemical energy of ATP *in vitro* (fig. 1).

It is not possible, at this time, to explain this close correlation between V_{max} and myosin ATPase activity, although it may be postulated that the same rate-limiting step which defines the *in vitro* rate of ATP hydrolysis by myosin also limits the maximal rate of interaction between the myosin cross-bridge and thin filament in living muscle. Such a relationship could be explained if the product-dissociation of the myosin-ATP complex, which appears to limit the rate of ATPase activity by myosin alone [26], also was the rate-limiting step in the interactions between actin, myosin and ATP. In the latter system, which is more analagous to the situation in the intact muscle than is the interaction between ATP and myosin alone, it appears that actin accelerates ATPase activity by modifying product-dissociation without changing the rate constant for either ATP binding or hydrolysis [E. W. TAYLOR, personal communication]. However, the identity of the rate constant for myosin-product dissociation with that of the limiting step in the actin-myosin-ATP interaction has not been established, and the rate constant for muscle shortening velocity appears to be approximately an order of magnitude greater than that of any of these biochemically-measured rates. Thus, a direct

Table I

Mechanical parameter	Interpretation
V_{max}	Maximal rate of energy turnover per unit of length
P_o	Number of force-generating sites per unit of cross-section
dP/dt	Rate of activation of force-generating sites per unit of cross-section

relationship between the rate constants of mechanical transformations and specific biochemical reactions cannot yet be defined.

The other intercept of the force-velocity curve, P_0, does not bear a clear relationship to the ATPase activity of the contractile proteins [2, 14], but, as predicted by HILL, is instead related to the number of force-generating sites per unit of cross-sectional area [2]. These force-generating sites now appear to be points of interaction between the (myosin) cross-bridge of the thick filament and actin, the major protein of the thin filament of muscle. The descending limb of the length-tension curve appears to be simply an expression of this relationship between the number of potential interactions between thick and thin filaments and P_0 [10]. At a given rest length, a change in P_0 can thus be interpreted to reflect an alteration in the number of force-generating sites or actin-myosin interactions (fig. 1). Such an alteration, as discussed above, should not, however, influence V_{max}.

A third parameter of active muscle can be defined which, according to the theoretical analysis outlined above, reflects still another property of muscle chemistry. This parameter, dP/dt, the rate at which tension appears in an isometric contraction (assuming that the damping effects of the series elasticity can be eliminated) will be determined by the rate at which activator reaches the contractile machinery. Like P_0, dP/dt should be independent of V_{max}, the maximal turnover rate of the interactions which effect shortening (table I).

The role of Ca^{++} as activator of the contractile process has already been reviewed in this volume. Most evidence available at this time strongly indicates that the role of Ca^{++}, mediated by its binding to one component of troponin, is to relieve the pre-existing inhibition of the primary interaction between actin and myosin by the troponin-tropo-

myosin complex [14]. Thus, the current biochemical interpretation of a change in P_0 would be an alteration in the amount of Ca^{++} delivered to the contractile proteins in systole, whereas a change in dP/dt would reflect an alteration in the rate of delivery of Ca^{++} to the contractile proteins.

It is at this point that serious discrepancies between these biochemical and biophysical postulates and the interpretations of force-velocity data from cardiac muscle arise. These discrepancies center on the mechanical changes observed to accompany alterations in myocardial contractility. If the formulations presented in the preceding paragraphs are correct, the enhanced myocardial contractility accompanied by an *augmentation of* P_0 should be due to an increase in the amount of Ca^{++} delivered to the heart contractile proteins at the height of systole; if accompanied by *elevated* dP/dt, then the rate of Ca^{++} delivery must be increased; whereas, if V_{max} *is increased* then the rate of interaction between actin and myosin should be enhanced. In the latter case, furthermore, it is apparent from comperative biochemical studies [e.g. 4, 16] that V_{max} is independent of the source of actin, tropomyosin and troponin, so that any change in V_{max} is most likely to reflect a primary modification of the myosin molecule which, *in vitro,* should be apparent as a change in myosin ATPase activity. Thus, agents which alter V_{max} can be presumed to act primarily upon the hydrolytic site of myosin, whereas agents which modify P_0 or dP/dt should act on those systems responsible for delivery of Ca^{++} to the heart contractile proteins. The conflicts between the mechanical findings based on studies of force-velocity data of cardiac muscle and a number of *in vitro* studies of the cardiac contractile proteins can be illustrated by two examples: the reported actions of cardiac glycosides and of Ca^{++} upon cardiac mechanics and the contractile proteins of the heart.

Enhancement of myocardial contractility by digitalis, if due solely to changes in P_0 and/or dP/dt, could be readily explained by an increased amount, and/or rate of Ca^{++} delivery to the contractile proteins during systole. An augmentation of V_{max}, however, should reflect an increase in the rate of mechanochemical transformation by the heart's contractile proteins during systole. Assuming that this latter rate is, in fact, governed by a property of the myosin molecule, it would follow that for cardiac glycosides to increase V_{max}, *in vivo,* they should increase the rate of energy turnover by the actomyosin. This could be achieved either by a direct action upon myosin to effect a change that would, *in vitro,* be

manifest as enhanced myosin ATPase activity, or possibly upon actin to increase the rate of turnover of actin-myosin interactions. A primary action of these drugs upon the modulatory proteins troponin and tropomyosin is also possible. Although the findings in studies of the action of cardiac glycosides upon various contractile protein systems *in vitro* remain somewhat contradictory, it is my own opinion that the overwhelming weight of evidence on this point is negative, and that cardiac glycosides do not influence the ATPase activities of myosin alone, myosin plus actin, or the 'complete' actin-myosin-troponin-tropomyosin complex [14, 17, 18]. Yet, in spite of this negative evidence from biochemical studies, extrapolations of V_{max} from force-velocity curves of cardiac muscle after administration of cardiac glycosides have been reported to show an increase in V_{max} [9, 25]. This important discrepancy could be explained if cardiac glycosides do, in fact, modify the rate-limiting step in the interactions between actin, myosin, tropomyosin, troponin and ATP, but this action has been overlooked in studies on these systems after disruption and preparation *in vitro*. The evidence to be discussed in the following paragraph, however, indicates the existence of a still more serious conflict between mechanical and biochemical measurements.

The ability of Ca^{++} to initiate contraction can be explained as resulting from the removal of a pre-existing inhibition of the actin-myosin interaction. This action of Ca^{++}, which is manifested as an apparent activation, appears to be initiated by binding of the cation to the high-affinity Ca-binding sites on one component of the troponin complex. This view, if correct, would limit the role of Ca^{++} to triggering an 'on-off switch' mechanism which allows a Ca^{++}-insensitive interaction between actin and myosin to proceed, thereby initiating systole. The evidence for this viewpoint is based largely upon the finding that actomyosins made up only of actin and myosin are insensitive to Ca^{++}, and that troponin appears to have a single class of high-affinity Ca-binding sites [see ref. 14 for a review of some of these data]. Thus, if V_{max} reflects a property of myosin which is not altered by Ca^{++}, and if the modulatory proteins can influence the contractile process only in an 'on-off switch' manner, then variations in the amount of Ca^{++} delivered to the contractile proteins would be expected to influence only the number of active sites and not their rate of interaction (table I).

If the foregoing conclusions are valid, it follows that variations in the amount of Ca^{++} delivered to the heart contractile proteins should modify P_0, but should be without effect on V_{max}. Extrapolations of force-ve-