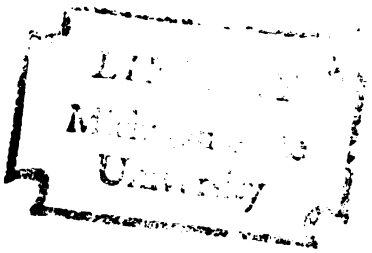
MYOCARDIAL MECHANICS AND CONTRACTILITY

Thesis for the Degree of M. S.
MICHIGAN STATE UNIVERSITY
Chang-Yi Wang
1976



MYOCARDIAL MECHANICS AND CONTRACTILITY

By

Chang-Yi Wang

A THESIS

Submitted to

Michigan State University

in partial fulfillment of the requirements

for the degree of

MASTER OF SCIENCE

Department of Physiology

1976

ABSTRACT

MYOCARDIAL MECHANICS AND CONTRACTILITY

By

Chang-Yi Wang

This work is a study of the mechanics of cardiac contraction and its quantification.

A comprehensive review of both theorectical and experimental reports shows that differences of opinions exists regarding the basic characteristics of the contractile properties of the myocardium. Controversy still rages as to which index best describes contractility.

A theoretical analysis, based on Hill's three element models, yields the following result:

1. The maximum velocity of shortening of muscle at no load (Vmax), obtained from isotonic contraction experiments, does not characterize the contractility of cardiac muscle.
2. The only index of contractility that is theoretically sound is the maximum velocity of shortening of the contractile element at no load (V_{mCE}).
3. The index V_{mCE}, calculated from the Maxwell model, is less dependent on preload than that calculated from the Voigt model.

ACKNOWLEDGMENTS

The author wishes to express sincere appreciation to Professor Jerry B. Scott, who has given encouragement and guidance throughout the course of this research, and to Professors Lester F. Wolferink and Donald K. Anderson who served as members of the guidance committee.

The author also expresses his gratitude for the support of Professor Joseph E. Adney, Chairman of the Department of Mathematics.

Thanks are due to Dr. John C. Yeager and Mr. Ronald Kienitz for their help in obtaining the experimental data, to Dora Wang for the reading of the manuscript and to Jill Shoemaker for the typing.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER I

INTRODUCTION

The sole function of the heart is to maintain adequate circulation through its pumping action. The output of the heart is directly proportional to the frequency of contraction, which is regulated through the nervous system, and the stroke volume. The stroke volume is in turn dependent on three factors: the degree of filling at end diastole (preload), the arterial pressure at systole (afterload), and the contractility of the myocardium.

The present investigation is concerned with the contractility of the heart, an inherent property of the heart muscle. It should be independent of extrinsic factors such as loading or heart rate, which fluctuate with changes in postural movements and in physical and/or psychological environment. How can we tell whether a certain heart is intrinsically strong or weak? In other words, what is contractility and how do we measure or calculate it?

The quantification of contractility or an index of contractility is important in the clinical evaluation of heart patients. Because of the various compensatory mechanisms in the human body, severe cardiac dysfunction may not be detected until late in the course of the heart disease. Also, some criterion is needed to assess the recovery of post-surgical heart patients.

Unfortunately, such an index is still elusive in spite of the voluminous literature published on the subject. About twenty indices have been proposed, most of which appeared in papers published in the past decade. Some are better accepted than others, but none has gained universal acceptance.

The profusion of papers published on contractility (one hundred in the past five years) erupted about fifteen years ago when it was discovered that the analysis of skeletal muscle mechanics developed by Hill in the late thirties did not apply to cardiac muscle. The complex properties of both the myocardium and the intact heart, alone with difficulties in physical measurements, have resulted in confused and contradictory opinions. The experiments are seldom reproducible; the theories are based on assumptions which are inadequately justified; and the conclusions seldom agree with each other, not only between different groups but also within the same group, published in different years. Indeed, if a single report is read, the proposed index, at a first glance, seems to be perfect both in theoretical and in experimental justification. But after a year or two the same index is invariably refuted and another "perfect" index is proposed. This does not, however, imply carelessness or the incompetence of the researchers, but rather reflect the complexity of the problem and lack of precision in the definition of the term "contractility".

the

ind

fol

whic

dete

the

art

It is not the object of the present report to add to the controversy by proposing another "better" contractility index. Instead, the purpose of this work is to present the following:

1) A modern review of Hill's theory of muscular contraction incorporating more recent work based on Huxley's sliding filament hypothesis,
2) The differences and similarities between skeletal and cardiac muscle,
3) Derivation and comparison of the principle mechanical models.
4) A critical objective review of the different contractility indices proposed in the recent literature, and,
5) The proposal of theoretically sound indices and methods of measurement.

Therefore, this thesis reports the necessary analysis which must precede attempts to theoretically and experimentally determine the elusive, and hopefully ideal, index. Perhaps the present study will help clarify the current state of the art regarding controversial subject.

CHAPTER II

REVIEW OF LITERATURE

Functional Anatomy of Muscle Contraction

Under the electron microscope, cardiac muscle differs from skeletal muscle only slightly. Due to the greater energy requirements, cardiac muscle contains a proportionally larger amount of mitochondria and capillaries. Cardiac muscle cells also appear to form a syncytium, in that their outlines are indistinct and they seem to fuse with one another. A closer look reveals this syncytium is only a functional one. The cells are actually distinct, separated from one another by sarcolemma (cell membrane) and by intercalated disks.

Unlike skeletal muscle, cardiac muscle has the ability to generate spontaneous, rhythmical contractions. After stimulation , a longer delay is required (40 msec) before contraction starts in cardiac muscle, as compared with skeletal muscle (3 msec). Also the absolute refractory period is much longer, lasting throughout systole. Because of the long absolute refractory period, tetanic contractions cannot be attained by artificially increasing the frequency of stimulation. As we shall see later, this fact restricts the determination of certain myocardial properties. A recent paper (Ford and Forman, 1974) showed that tetany can be attained with large amounts of caffeine and calcium, however, the side effects of such drugs on other pertinent properties of the myocardium have not been delineated.

bas

(A

ser

Hux

(19

was

ext

ver

the

of

and

the

act

the

ther

com

The

Was

the

laid

work

of

1912

Cardiac and skeletal muscle are both striated. The basic unit is the sarcomere, composed of the thicker myosin (A band) and the thinner actin (I band). On the basis of a series of x-ray diffraction and electron microscopic studies, Huxley and Hanson (1954), Hanson and Huxley (1955), Huxley (1957) proposed the "sliding filament" hypothesis. The theory was originally applied to akeletal muscle but was subsequently extended to cardiac muscle (Huxley 1961) and subsequently verified (Stenger and Spiro 1961). The sliding filament theory is based on the observation that the actual lengths of both actin and myosin filaments are constant, both at rest and during contraction. With the activation of the sarcomere, the proposed "cross bridges" on the myosin begin to propel actin filaments further into the A band, causing contraction.

Assuming the strength of the sarcomere is porportional to the amount of overlap between actin and myosin fibers, one can then relate muscle length to developed tension in what is commonly called the length-tension relationship.

The Law of the Heart and the Length-Tension Relation

The fact that muscles contract more forcibly when stretched was known well before Starling's time. Notable experiments on the frog heart was done by Roy (1879) and Frank (1895) who laid down the fundamental concepts. Howell and Donaldson (1884), working on the heart of the dog, constructed the ascending limb of "Starlings curve". Starling's own work did not appear until 1912 (Knowlton and Starling 1912, Patterson and Starling 1914,

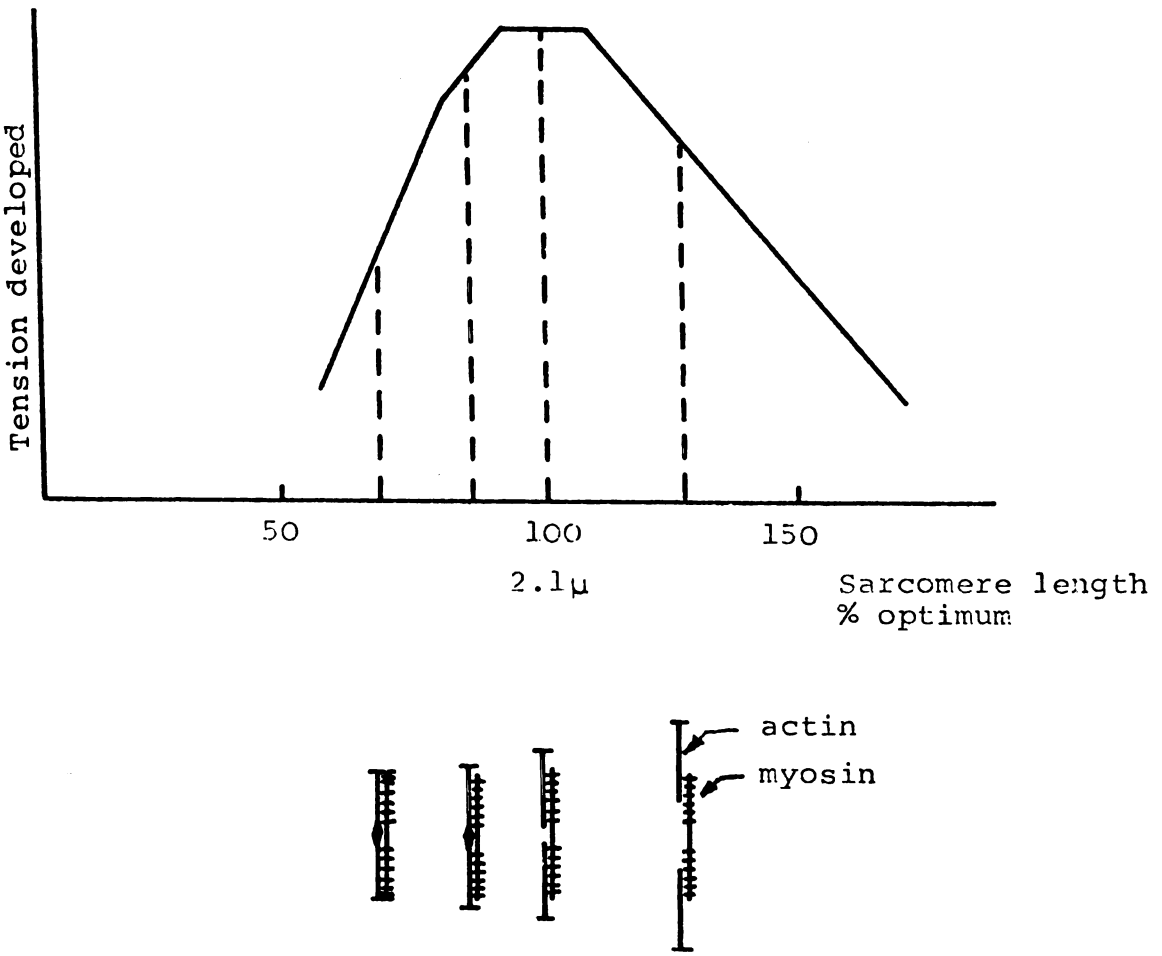


Fig. 1 Sarcomere length and active tension

Star

Star

Howe

in c

Law

law"

can

curve

was d

(1964

shows

Maxim

tween

At th

occurs

length

when t

amount

gaged)

the wh

rounde

ments

Append

Wi

the sli

ments p

Starling 1918). Although his experiments were more refined, Starling's works appear almost 30 years later than that of Howell and Donaldson. Perhaps we should define the increase in contraction due to the stretching of heart muscle as the Law of the Heart instead of the conventional term "Starling's law", of the "Frank-Starling relation".

It is now generally accepted that the Law of the Heart can be explained by the ascending portion of the length-tension curve constracted by Huxley's sliding filament theory. This was done by Sonnenblick et al (1963), Spiro and Sonnenblick (1964), Hanson and Lowy (1965), Gordon et al (1966). Fig. 1 shows the length-tension relation of a single sarcomere. Maximum active tension is developed at sarcomere lengths between 2.0 and 2.2 microns for both skeletal and cardiac muscles. At these lengths the maximum interaction of cross bridges occurs. The active tension decreases for shorter sarcomere lengths due to interference of actin fibers. It again decreases when the sarcomere is stretched beyond 2.2 microns where the amount of overlap (and thus the number of cross bridges engaged) becomes less. For a population of sarcomeres, as in the whole muscle, the length-tension curve is similar but rounded at the corners. The theory agrees well with experiments on tetanized, isometrically contracting muscles (See Appendix A for dexcription).

With the development of increasingly accurate instruments, the sliding filament theory was obscured by several new experiments published in recent years. Rüdel and Taylor (1971) found

tha

gre

et

sce

fac

hit

duce

ever

qual

it w

slid

The

that

reas

vatio

Resti

prope

resti

is ca

tensi

be mea

length

the fi

restin

that the tension produced at short sarcomere lengths were greater than the theoretical predictions set forth by Gordon et al (1966). Furthermore, Close (1972) found that the descending part of the curve changes slope at 2.8 microns. These facts lead to the speculation that there exists another, hitherto unknown, mechanism of contraction besides that introduced by the sliding filament theory. Most experiments, however, were done on skeletal muscle and no evidence of comparable quality was available from studies of cardiac muscle, although it would be natural, albeit presumptuous, to assume that the sliding filament theory would apply to all striated muscles. The reason for the poor cardiac muscle data lies in the fact that tetany is impossible for cardiac muscle, the contraction measurements are highly time-dependent, and the degree of activation is questionable (Close 1972).

Resting tension

One of the greatest differences between the mechanical properties of skeletal muscle and those of cardiac muscle is resting tension. As distinguished from active tension which is caused by the stimulated contraction of myofibrils, resting tension represents the elasticity of the fiber itself and can be measured by pulling the unstimulated sarcomere to different lengths. The total tension, or the maximum force produced by the fiber after stimulation, is the sum of active tension and resting tension.

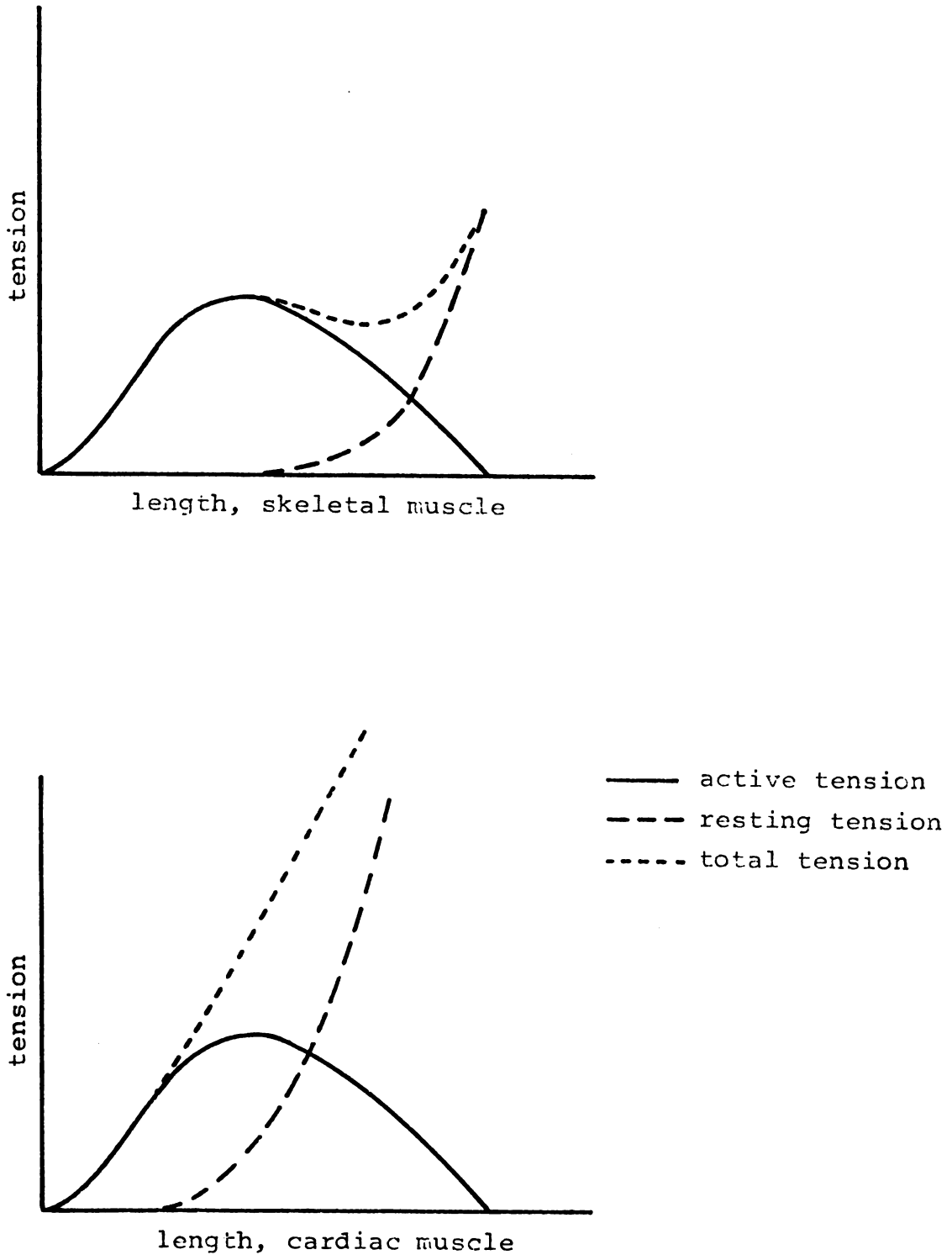


Fig. 2 Comparison of resting and total tensions

In skeletal muscle, the resting tension (resistance to passive pulling) is negligible until the sarcomere is pulled to 2.42 microns (110% of optimum length of contraction). Thus, the total tension is equal to the active tension in most physiological stiuations. Unlike skeletal muscle, there is conclusive evidence that the myocardium develops considerable tension when stretched (Sonnenblick 1962, Brady 1965, Parmley and Sonnenblick 1967, Edman and Nilsson 1968, Grimm et al 1970, Brutsaert et al 1971). Fig. 2 shows a comparison between the resting tensions of skeletal and cardiac muscle adapted from the results of Spiro and Sonnenblick (1964). Although active tension is similar (but not identical) for both muscles, resting tension is much larger for cardiac muscle. Grimm et al (1970) showed that when cardiac muscle is pulled beyond 2.2 microns (85% of optimum length of sarcomere), resting tension cannot be ignored. After 2.2 microns, resting tension contributes to an appreciable amount to total tension, reaching nearly one half of total tension at 110% of optimum length. Since, in normal intact hearts the sarcomere lengths are usually increased to 92% of optimum and sometimes beyond optimum (Braunwald et al 1968), resting tension becomes an important factor in the modelling of the myocardium.

Due to resting tension, the shape of the total tension curve is also quite different for skeletal and cardiac muscles. While the total tension of the myocardium rises monotonically with initial length, that of the skeletal muscle shows a characteristic decrease between optimum length and 120% of optimum.

Measurements on skeletal muscle are thus easier since the slope of total tension is zero near optimum length, making contractile forces insensitive to initial stretching in the neighborhood of optimum. Cardiac muscle does not have this property.

CHAPTER III

MUSCLE MECHANICS

Mechanics and Modelling

The steady state or time independent behavior of muscle has been discussed in Chapter II where the maximum force developed was related to the initial length of the fiber. Steady states occur when the muscle is at rest or at tetany. Although skeletal muscle shows some steady state behavior, normal cardiac muscle functions without any discernable steady state. This time dependence greatly complicates both the experimental and the theoretical investigations. During unsteady motion, the relationship among time, force and velocity is called mechanics.

The first step in formulating a mechanical theory is to utilize experimental observations to construct a simple mechanical model which may describe the behavior. From the model an equation linking force, displacement or velocity is written. The solution of this equation is then checked with the original experiments. Modifications of the model is usually necessary to eliminate gross discrepencies between theory and experiment.

There are times when the phenomenon is so complicated that no simple model is able to describe the behavior. Difficulty with the experimental isolation of the effects of certain factors is usually a deterrent to the construction of a successful model.

Hill's Basic Models

Based on a series of experiments using the frog sartorius muscle, Hill (1939, 1950, 1953) laid the foundation of muscle mechanics by constructing mechanical models to describe skeletal muscle behavior. He idealized the muscle into passive, elastic elements and active, contractile elements. These elements exist as separate entities only functionally. There is no structural or anatomical separation in the muscle itself. For instance, the elastic behavior of the elastic element may represent the sum of the elasticity due to the sarcolemma, the connective tissues between the muscle fibers, the crossbridges and the proteins in the myofibrils. Similarly, the contractile element may be composed of the action part of the crossbridges, say, in the sliding filament theory and/or some other hitherto unknown contractile mechanism discussed previously.

Since the muscle does show active contraction when stimulated, there is no doubt about the existence of a (functional) contractile element (CE). The existence of an elastic element (SE) in series with the contractile element is suggested by the following experiments. Firstly, when the muscle is tetanized isometrically the force developed does not rise instantaneously to the maximum value determined by the length-tension curve. Some delay (milliseconds) is needed for the tension to rise gradually from zero (Fig. A1, Appendix A). This indicates the contractile element may be pulling some spring-like material in

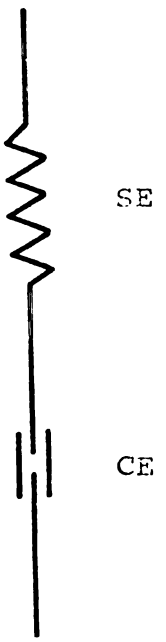
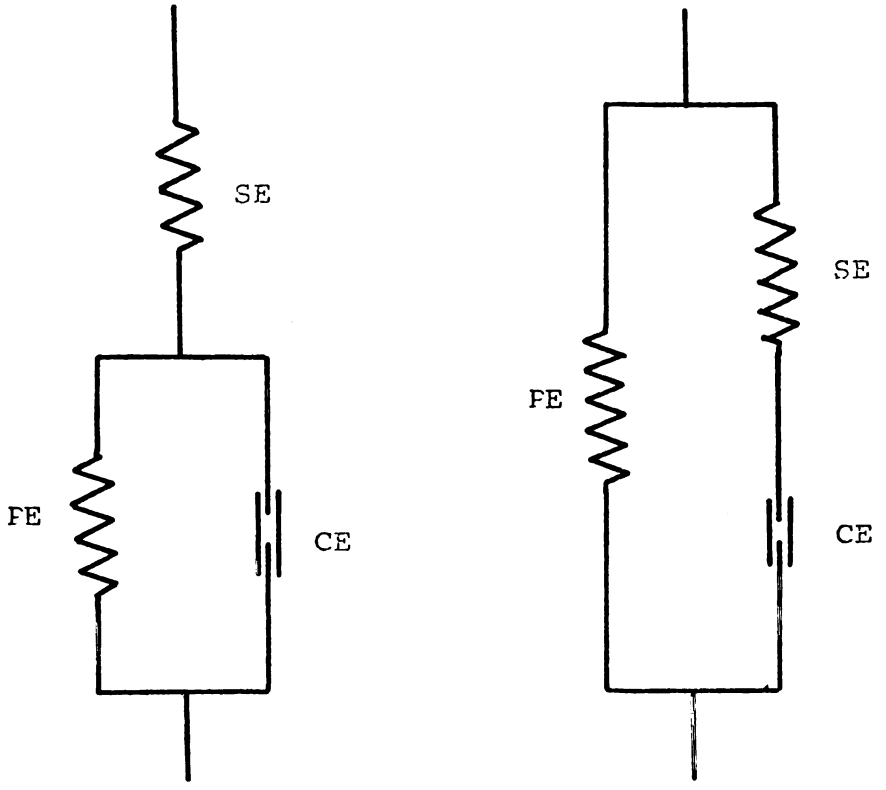


Fig. 3 Hill's two element model



"Voigt" model "Maxwell" model

Fig. 4 Hill's three element models

the muscle. Furthermore, if a muscle at isometric tetanus is suddenly released to a smaller constant load (isotonic quick release), there is an initial instantaneous shortening followed by a slower shortening of the fiber (Fig. A5, Appendix A). The initial shortening is attributed to the elasticity of an elastic element in series with the contractile element which reacts more slowly. Some oscillation in the length is also observed, suggesting a spring-like behavior. Appendix A describes some of these experiments.

Hill then suggested the two element model for skeletal muscle (Fig. 3). Since the sliding filaments in the contractile element cannot sustain any tension in the unstimulated steady state, because the "crossbridges" are unattached, the two-element model can not produce any resting tension. In order to take into account the resting tension development by both skeletal and cardiac muscles, Hill further suggested the three element models (Voigt and Maxwell) in Figure 4, where a parallel elastic element (PE) has been added for the resistance to passive stretch. These three element models are discussed in more detail in the next chapter.

The manner in which the stimulated model would respond to external loads depends primarily on three factors:

1) The shortening properties of the CE defined by a "force-velocity" relation at a given instant,
2) The elastic properties of SE, PE defined by "stress-strain" relations of these "springs".

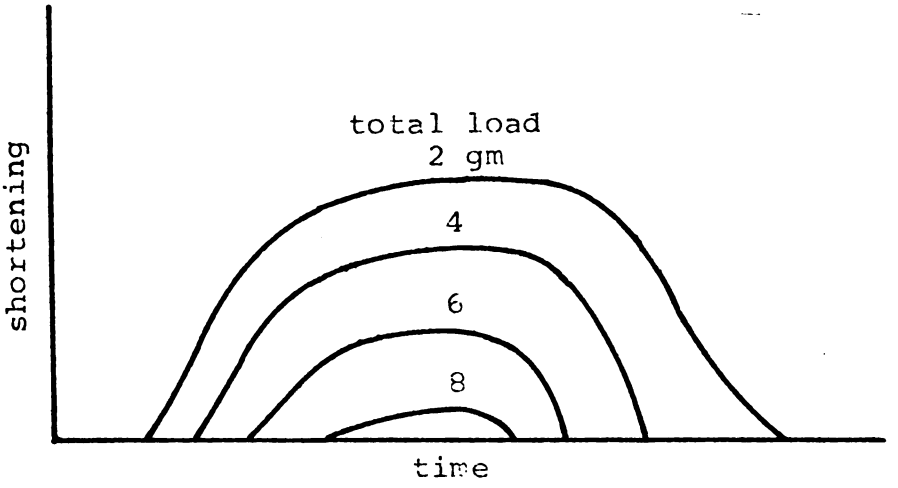


Fig. 5 Length response during isotonic twitch

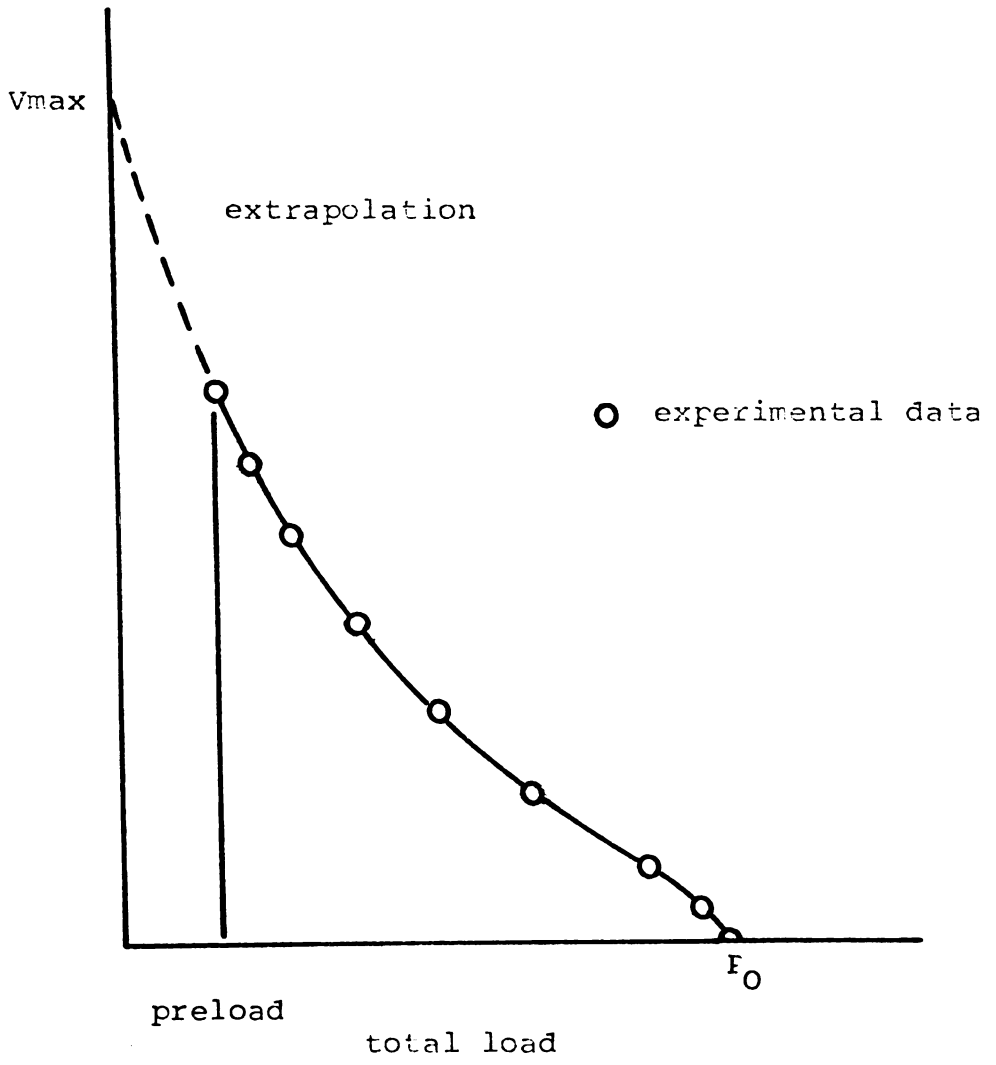


Fig. 6 The force-velocity curve

3) The time allowed for the force to develop, defined by an "active state" of contraction.

These factors shall be discussed subsequently.

The Force-Velocity Relation

The basic experiment which relates the load and the velocity of shortening of CE is the isotonic contraction experiment described in Appendix A. By increasing the weight of the afterload (and thus the total load), the amount of shortening of the muscle fiber after a twitch can be represented as a series of time dependent curves shown in Fig. 5. In these experiments, the initial length is the same, determined by the same small preload. It is seen that the larger the afterload, the longer the delay in shortening of the fiber. The amount of shortening is also less. There exists a maximum total load P_0 beyond which the muscle is unable to show any shortening after stimulation. Such contractions are entirely isometric.

The maximum slope for each curve in Fig. 5 (the maximum velocity) is usually at the initial instant of shortening. This is plotted against total load P in Fig. 6. Since the minimum total load is the preload, which maintains the initial length and cannot be zero, the curve has to be extrapolated to zero load by mathematical or visual extension of the curve. This is the famous force-velocity curve of Hill (1938) showing the inverse relationship between load and maximum velocity of shortening.

as fo

devel

cross

short

tach

Since

time,

decre

Hill

ening

ening

short

the m

linea

modyn

the

we ha

Here

short

most

Conceptually, this inverse relationship can be explained as follows. From the sliding filament theory, the tension developed at any instant is proportional to the number of crossbridges attached. When an active muscle is allowed to shorten, some crossbridges must be allowed to detach and retach as the myosin and actin filaments slide past each other. Since the process of detachment and retachment takes finite time, the number of attached (force producing) crossbridges decreases in proportion to the shortening velocity.

By measuring the heat produced in isotonic contractions, Hill (1938) found that the extra heat produced during shortening is independent of both the load and the time of shortening. It is, however, directly proportional to the distance shortened. Furthermore, the rate of extra energy released by the muscle during isotonic contraction is found to be decreasing linearly with increasing tension. Since the first law of thermodynamics states that

$$\text{the rate of extra energy released} = \frac{d}{dt}\ (\text{work done} + \text{extra heat released}) \qquad (1)$$

we have

$$b(P_o - P) = \frac{d}{dt}(Px + ax) = (P + a)V. \qquad (2)$$

Here a,b are proportional constants, x is the distance shortened, and V is the initial velocity of shortening when most of the heat is released.

F

on the

veloci

tonic

the cu

S

ruscle

rodel

During

rises

elasti

muscle

with r

for th

the ac

and fi

longer

rodel

load,

an inh

load,

the wh

itself

T

uscle

From the values of a and b obtained from experiments on the frog sartorious, Hill found that the theoretical force-velocity curve (Eq. 2) agreed well with that from the isotonic contraction experiments. Rearranging Eq. 2 we find the curve is actually a hyperbola:

$$(P + a)(V + b) = b(P_o + a) = \text{constant} \qquad (3)$$

Since the resting tension is negligible for skeletal muscle at physiological lengths, Hill used the two element model to explain the contractile behavior in his experiments. During the isometric phase after a stimulated twitch, tension rises because the contractile element pulls against the series elastic element. When tension exceed the total load, the muscle shortens with a jerk. The isotonic phase then starts with no further changes in the length of the series element, for the toad it sustains is now constant. With the passing of the active state of the muscle, the shortening becomes slower and finally the muscle begins to relax and the CE can no longer lift the load. The important result for the two-element model is that Vmax, defined as the maximum velocity at zero load, is independent of both preload and afterload. It is thus an inherent property of the muscle. Fig. 3 shows that without load, the length of SE would remain the same and Vmax of the whole muscle would be identical to the max velocity of CE itself. It is thus a measure of contractility.

The similarities in structure between skeletal and cardiac muscles led naturally to the application of Hill's concepts to

the myocardium. In 1959, Abbott and Mommaerts concluded that the behavior of cardiac muscle was similar to that of skeletal muscle, on the basis that cardiac muscle also seemed to show a hyperbolic force-velocity relation. Two years later, Sonnenblick (1961, 1962) conducted experiments on the papillary muscle of the cat and observed that the force-velocity relation for different initial fiber lengths could be extrapolated to a single Vmax at zero load. Following Sonnenblick, numerous papers were written using Vmax thus obtained as an index of contractility. The differences between cardiac and skeletal muscle were not seriously appreciated unitl the appearance of a paper by Pollack (1970) disputing the use of Vmax (from the force velocity curve) as an index of contractility. Although Pollack's work was quite convincing, contemporary texts in cardiovascular physiology (Folkow and Neil 1971, Berne and Levy 1972, Montacastle 1974) still carry Sonnenblick's earlier analysis. The reason is perhaps partly due to a lag in the spread of knowledge and partly due to the fact that there exists no universally accepted substitute index to gain insight into the contractility of cardiac muscle.

Pollack (1970) recognized that the resting tension in cardiac muscle could not be ignored and that one must go back to Hill's three element models which have extra parallel elastic elements (PE). There is, thus, a distinction between the force-velocity curve of the cardiac muscle and the force-velocity curve of the contractile element of cardiac muscle.

Pollack then used Sonnenblick's (1962) original data to calculate a new force-velocity curve for the CE alone. It was found that for both three-element models (Fig. 4), the maximum velocity of CE at no load (V_{mCE}) is not independent of preload or initial fiber length. Conceptually from Fig. 4, it is apparent that the velocity of CE is definitely altered by the elastic properties of PE. The mathematical proof is given in the next chapter.

Pollack's work, being theoretical, is devoid of the uncertainties encountered in experimental reports. Although Noble et al (1969) experimentally refuted the independence of Vmax earlier, his quick-release methods are now under criticism.

It is apparent that the contractile element of one model is not the same as the contractile element of another model. Pollack's recalculation of Sonnenblick's data shows a smaller variation of V_{mCE} with respect to preload for the Voigt model than for the Maxwell model. However, even using the Voigt model the variation is still about 50%. There are two points one should keep in mind in regards to Pollack's analysis. Firstly, the cardiac muscle data of Sonnenblick (1962) is atypical of the many experiments published by this group (Sonnenblick 1970). This does not, however, seriously affect Pollack's conclusions. Secondly, in the analysis, the maximum velocity of shortening is assumed to be immediately after the initiation of isotonic contraction. Studies by Parmley and Sonnenblick (1967),

100

90

80

70

% of maximum

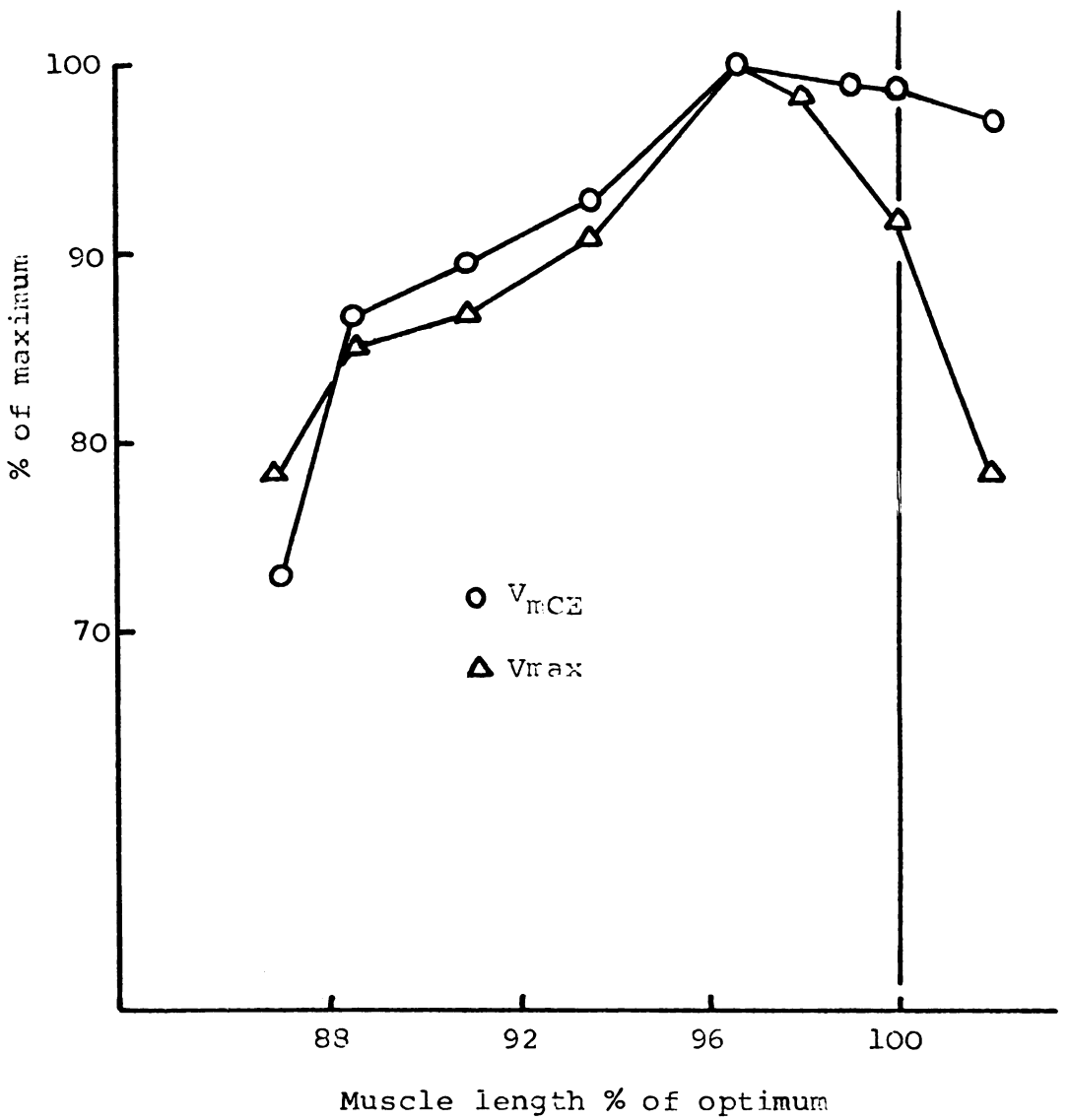


Fig. 7 Comparison of Vmax and V_{mCE}

(Parmley et al 1972)

Farmley

shorten

Ta

account

ments a

maximum

calcula

model i

for the

index t

1)

2)

3)

Parmley et al (1972) indicated that a significant amount of shortening had already taken place at the time of peak velocity.

Taking the above two criticisms of Pollack's work into account, Parmley et al (1972) conducted the isotonic experiments again, using on-line differentiation to obtain the maximum velocity of shortening. Both Vmax and V_{mCE} were calculated, using Pollack's method. The result for the Maxwell model is shown in Fig. 7. For some reason, similar calculations for the Voigt model was not done. It seems V_{mCE} is a better index than Vmax due to the following:

1) V_{mCE}, the maximum velocity of CE at no load, is independent of the elastic elements by definition. It is, thus, theoretically length independent. Vmax is not.
2) As shown in Fig. 7, V_{mCE} is experimentally less dependent on initial length or preload than Vmax, especially at higher loads.
3) The calculation of V_{mCE} does not require extrapolation to zero total load. This extrapolation, necessary in the calculation of Vmax, induces a good deal or error. In some cases Vmax can not be calculated for muscle lengths longer than optimum length, because the force-velocity curve is sufficiently removed from the usual hyperbolic form, making extrapolation impossible.

Also evident from Fig. 7 is the fact that even the better index, V_{mCE}, shows 20% variation with preload. The ideal index is thus still elusive.

Let us return to the shape of the force-velocity curve. Hill showed, from simple thermodynamics and semi-empirical results, that the curve should be hyperbolic (Eq. 3). Perhaps this hyperbolicity has been overly emphasized by later workers. As far as we know, there exists no theoretical proof showing that the force-velocity curve should be hyperbolic. Furthermore, whether the curve is hyperbolic or not has no relation to Hill's mechanical models. Consider the following:

1) There exist other forms of the force-velocity relation. Fenn and Marsh (1935) and Aubert (1956) used exponential relations of the type

$$P = P_0 e^{-bv} - cV \tag{4}$$

or

$$P = (P_0 + c)e^{-bv} - c \tag{5}$$

Polissar (1952) found

$$V = c(a^{1-P/P_0} - b^{P/P_0-1}) \tag{6}$$

By adjusting the constants a, b, c, P_0, all the above forms fit the experimental ata perfectly. Hill, however, has thermodynamic data to support his constants.

2) In Hill's original (1938) experiments, the heat of shortening was found to be independent of load. This point was investigated again by Hill (1964) using more sophisticated instruments. It was found that the heat of shortening was in fact proportional to both P_o and P. This conclusion effectively invalidates the thermodynamic support of his earlier hyperbolic relation.

3) Fung (1970) showed theoretically that if Hill's equation were used, the time to reach the maximum force P_o in an isometric contraction would be infinite. This would contradict the experimental results. Fung suggested using a force-velocity relation of the type

$$b(P_o - P)^{\alpha} = (P + a)V \qquad (7)$$

where α is an exponent between zero and one.

4) Experiments on cardiac muscle showed that the force-velocity relation deviated appreciably from Hill's equation. Unlike Hill and Sonnenblick (1961), Brady's (1965) investigations showed no such hyperbolic relation. Similarly, Yeatman, Parmley and Sonnenblick (1965), using isotonic and isometric experiments; and Noble, Bowen and Hefner (1969), Brutsaert and Sonnenblick (1969), using quick-release experiments showed hyperbolic relation only at lower loads. Hefner and Bowen (1967) even found bell-shaped force-velocity curves.

Finally, we note that Hill's force-velocity relation was obtained from skeletal muscle which can be tetanized. The contractile force was maximally activated before the load was lifted. For cardiac muscle, the degree of activation of contraction is very much dependent on the transient qualities of the active state of the twitch. Sonnenblick (1965, 1967), Civan and Podolsky (1966), Parmley and Sonnenblick (1967), Parmley et al (1972) showed that there was a delay and a complex velocity transient before a steady velocity of shortening was achieved. Due to this delay, measurements of peak velocities of lightly loaded cardiac muscles would register lower values than those more heavily loaded, since the former are less activated at the time they are measured.

Another objection to the force-velocity curve was raised by Jewell and Wilkie (1958). According to Hill's theory, the transient rise of tension during isometric tetranus of skeletal muscle must be precisely governed by the force-velocity curve and the force-length curve of the series element. Now

$$\frac{dF}{dt} = \frac{dF}{dL}\frac{dL}{dt} = \frac{dF}{dL} V \tag{8}$$

or

$$t = \int \frac{1}{\frac{dF}{dL} \cdot V} dF \tag{9}$$

Here F is the force, L is the length and the slope dF/dL can be obtained from the properties of SE as a function of the load F (assuming a two-element model) and the velocity

V is also a function of F in the force-velocity curve. Jewell and Wilkie compared the rise of tension from experiment and from Eq. (9). It was found that the actual rise was not as fast as the theory predicted (50% error). It was suggested that the velocity of shortening at maximum activation depended not only on the load but also on the load history of the muscle.

The Elastic Properties of Cardiac Muscle

Since the active contractile element cannot be physically isolated, the calculation of the properties of CE requires the knowledge of the passive elastic elements SE and PE. The basic assumptions about the elements of the mechancial models are:

1. The contractile element, like the shock absorber on a screen door, does not resist extension but resists the extension rate. In other words, it is compliant to slow stretching and does not contribute to resting tension. For quick stretches and quick releases CE behaves as if it were rigid. This assumption is not imcompatible with the sliding filament theory.
2. The stiffness of the elastic elements is a function of extension only. It is not effected by either the velocity of extension or the contractile state or inotropic drugs. This is an assumption of convenience. As we shall see later, the elastic elements in the muscle are not analogus to a mechanical spring.

the

the

quic

the

that

mati

forc

stra

deta

vest

auth

and

case

the

incr

expo

or

Here

k_c

mono

area

Assuming both assumptions to be valid, one can see that the resting tension curve discussed in Chapter II represents the stiffness of PE in the Maxwell model. The result from quick release experiments yields the stiffness of SE in the Voigt model. Properties of SE of the Maxwell model and that of PE of the Voigt model may be obtained from mathematical calculation from the above experiments. Instead of force-length relations, it is more practical to use stress-strain relations for elastic material. Chapter IV gives the details of the calculations.

The series elastic element (Voigt model) has been investigated through the isotonic quick-release method by several authors (Abbott and Mommaerts 1959, Sonnenblick 1964, Parmley and Sonnenblick, 1967, Yeatman et al 1969, 1971). In all cases, the stress-strain relations were found to be nonlinear - the stiffness, or the slope or stress as a function of strain, increases nonlinearly with increasing strain. An empirical exponential curve can be fitted to the data:

$$\sigma = \frac{c}{k}(e^{k\epsilon} - 1) \tag{10}$$

or

$$\frac{d\sigma}{d\epsilon} = k\sigma + c \tag{11}$$

Here σ is the total stress, ϵ is the natural strain and k,c are constants. From Eq. (11), we see that k must be nondimensional, while c has the dimension of stress (force/area). For cat papillary muscle, Sonnenblick (1964), Yeatman

(1971) found k to be approximately 32; Hefner and Bowen (1967) obtained the value 34; while Parmley et al (1967) gave $k = 40$. In general, each investigator agreed that Eq. (11) is a linear function, independent of preload. It is probably true that k is indeed a constant, implying an exponential stress-strain curve. The variation of reported values may have been due to the different experimental apparatus used. According to Parmley and Sonnenblick (1967), equipment distensibility error may amount to 30%. The value of c was obtained from the slope of the stress-strain curve at zero load. Since all experimental results can only be extrapolated to zero load, this value is more uncertain. Yeatman (1971) gave the value of c (at 37°C) as 20 gm/mm^2 or 147 mm Hg. Assuming the magnitude of c to be of this order, and the pressure during systole to be equal to the stress in the muscle (i.e., wall thickness approximately equal to the mean inner radius of left ventricle), then the value of $k\sigma$ ranges from 640 to 3800 mm Hg and c can be ignored in comparison with $k\sigma$, except at very low pressures.

There seems to be comparatively less discussion of the empirical equation for the passive stress-strain curve of the resting tension in the literature. Earlier works plotted the data in terms of force and length which is quantitatively useless. For instance, on a thicker muscle, a larger force would be needed to achieve the same extention. Since the cross-sectional area and the resting length were not given, it is not possible to translate the force-length relation into the

stress-strain relation. Qualitatively the curve is still exponential, about half as stiff as the series element (Parmley et al 1972).

In experiments on the myocardium, the papillary muscle was invariably used. This was probably because strips of ventricular wall muscle are impossible to separate without destroying contractile behavior, and papillary muscle is more uniformly oriented. The elastic properties of the papillary muscle, however, do not reflect that of the ventricular wall muscles. Furthermore, it is not known whether there is a difference between the muscle of the domesticated cat or dog and the muscle of the human heart.

Is the series element truly passive as assumed? Wildenthal et al (1969) found that stiffness was affected by hypertonic solutions. Yeatman et al (1969) determined the influence of temperature on SE. These factors, however, can be controlled in the experiments. The in situ conditions are probably constant. However, the properties of SE and also PE are found to be dependent on velocity.

Although velocity dependence (viscosity) of muscle had been discounted by Hill (1938), more recent studies (Sonnenblick et al 1966, Little and Wead, 1971) clearly demonstrated stress relaxation (a fall in tension following sustained extension) in both SE and PE elements. Pollack et al (1972), Noble and Else (1972) showed that the "passive" properties of SE depended on cardiac timing and duration of contraction. The interdependence of SE and CE raises serious questions not

only about the determination of SE properties using quick stretch and quick release (which affects velocity), but also about the fundamental assumptions using mechanical models.

The Active State

Because cardiac muscle can never truly be at rest or at tetany, the contractions are highly transient in nature. The time behavior of a contraction is loosely called "active state" (in contrast to the "resting state").

The first definition of an "active state intensity", defined as "the force development at constant contractile element length", was due to Gasser and Hill (1924). The idea is to maximize contractile element force-velocity development by holding velocity of CE at zero. From the force-velocity curve discussed previously, we know that contractile force is markedly reduced with increase in shortening velocity. If we hold the muscle length constant, as in isometric contraction, the time course of force development during a twitch cannot represent the active state of CE, since the contractile element would be shortening at the expense of the lengthening series elastic element.

The problem then lies in the interpretations of different experiments, which attempt to depict the active state of the functional contractile element. Four different techniques are discussed below. Appendix A gives further details.

1) Isometric quick stretch technique (Hill 1949, Abbott and Mommaerts 1959, Brady 1965).

In the isometric contraction experiment, muscle tension develops after a twitch stimulation. For a short time, the time course of tension development follows closely to that developed at the start of tetany. But soon after, the active state passes and tension falls. The idea of quick stretch immediately after stimulation is to try to offset the initial shortening of CE. It was found that tension rapidly increases to a maximum both greater and occuring earlier than the curve corresponding to the isometric contraction alone. This technique was originally applied to skeletal muscle and later extended to cardiac muscle. The method cannot guarantee constancy of the length of CE.

2) Isometric quick release technique (Ritchie 1954, Brady 1966).

Ritchie measured the maximum tension developed following isometric quick release at various times. The argument is that at the time of peak tension, the tension is neither increasing or decreasing and therefore the length of the contractile component must be constant. By plotting the various maximum tensions with respect to the time they occur, one obtains a curve for the active state of CE. This method does not give information about the rise in tension during the initial instant.

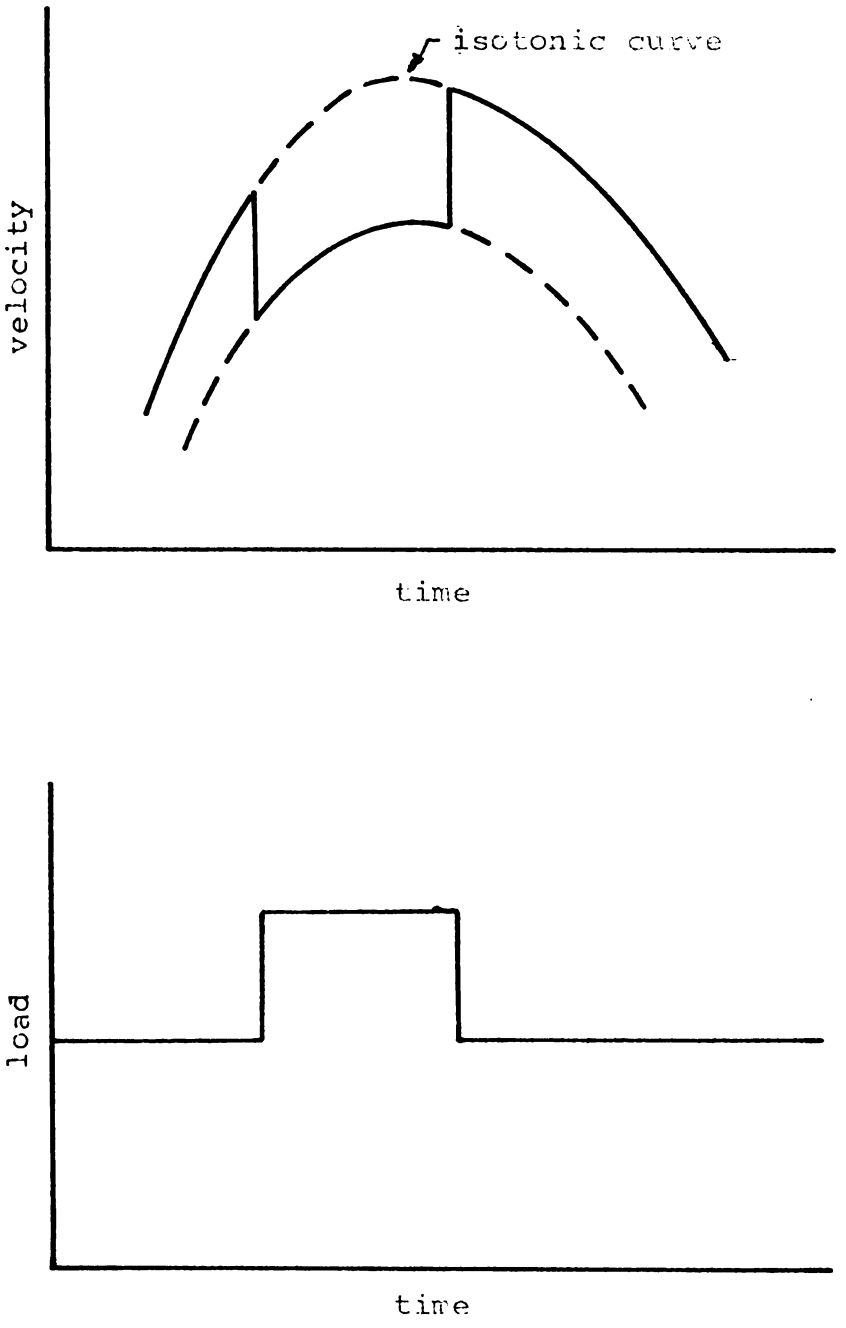


Fig. 8 Load clamp (Brutsaert 1971)

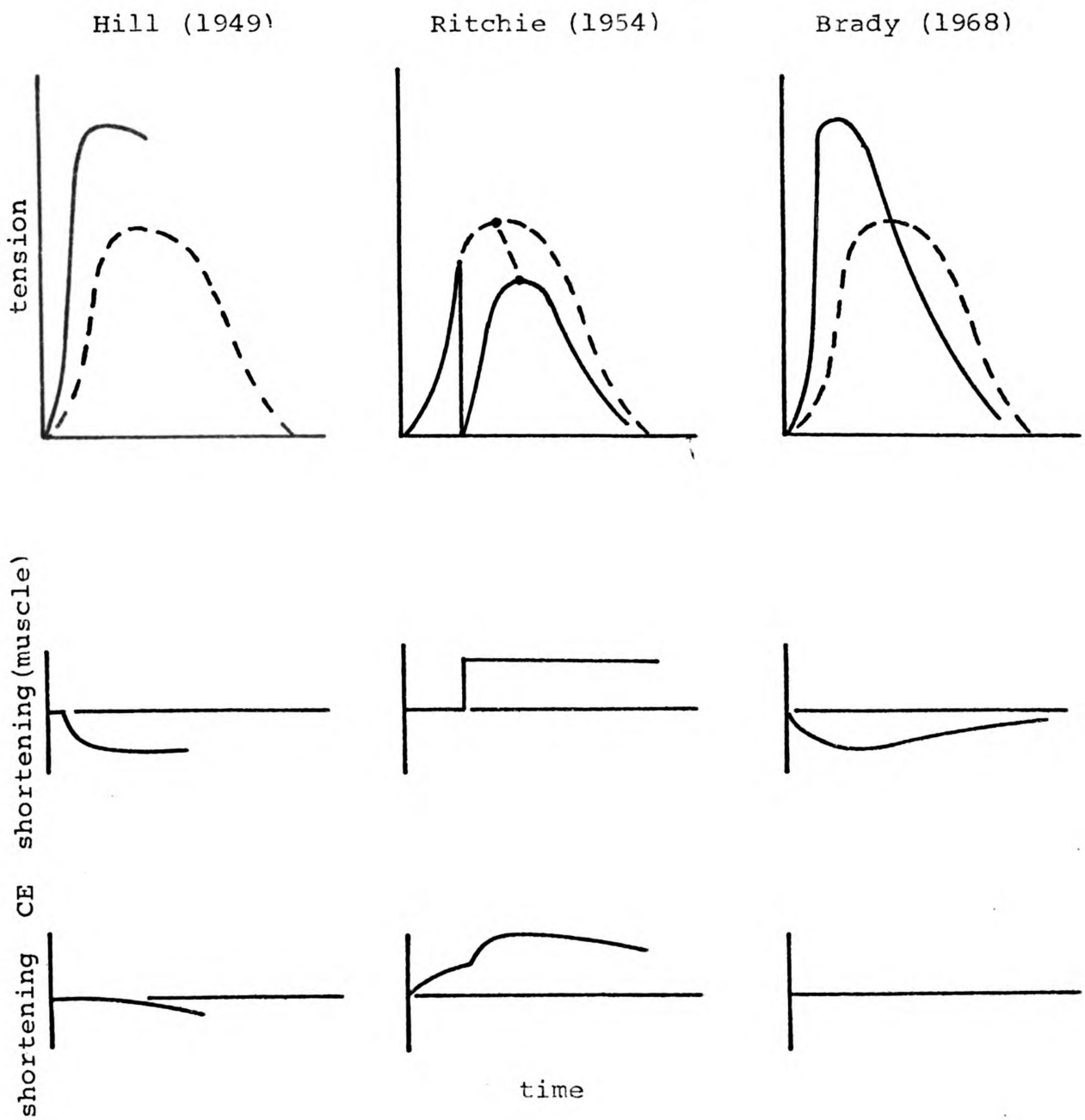


Fig. 9 Techniques in studying the active state

3) Length clamp technique (Brady 1968).

This method requires the determination of the elastic properties of the series element using the isotonic quick stretch method. A mechanical model is then chosen and the amount of stretch is calculated through a computer such that the length of CE is kept constant. Using the length clamp technique, Brady found that the tension of CE rises slowly, in a similar fashion but somewhat faster than the isometric curve. The method of course assumes all the inadequacies of the mechanical modes.

4) Load clamp technique (Brutsaert el al 1971, a,b).

By using abrupt load clamp during isotonic shortening, Brutsaert was able to show that the velocity of shortening was dependent on the instantaneous load and length and independent or prior load history. By switching the isotonic load it different values at different times, it was found that the velocity-length curve for any given load can be reproduced (Fig. 8). This independence of prior changes, occuring from onset of contraction until peak of shortening, led Brutsaert to conclude that maximum active state occurs immediately and is steady at maximum for a considerable portion of the time.

Fig. 9 depicts some typical results of various techniques. It was found that all agreed that the activity of CE occurs

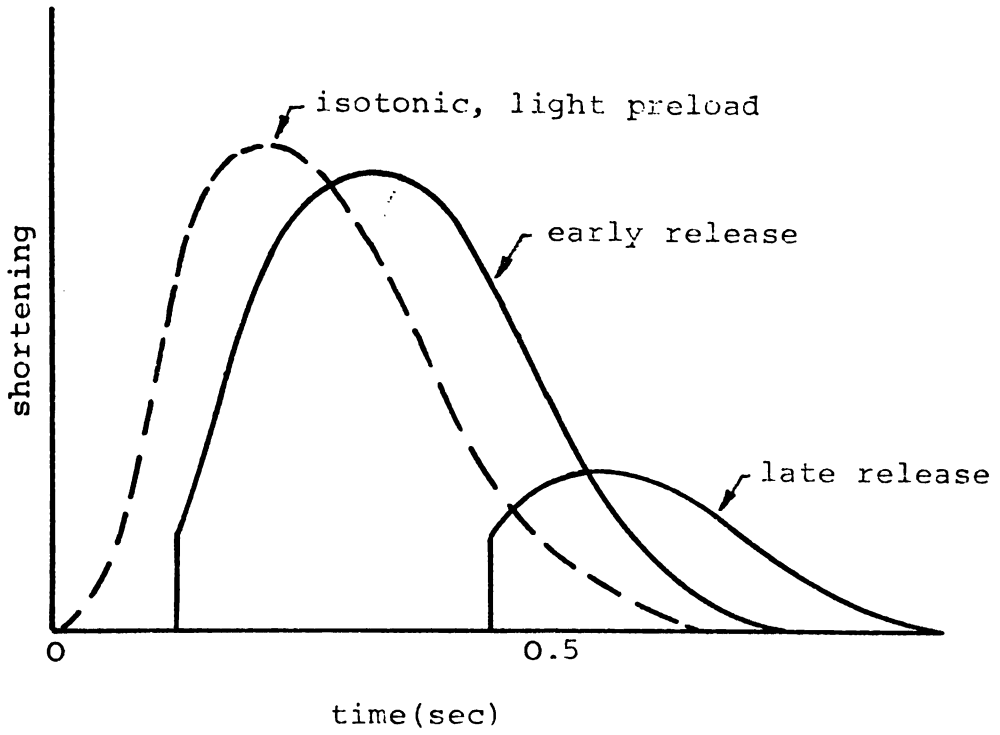


Fig. 10 Effect of quick release on active state (Jewell and Wilkie 1960)

earlie

develo

load c

recent

rise c

cles a

questi

itsel

in de

state

Jewel

isoto

durin

for t

muscl

tract

allow

Bruts

as cl

incre

ray s

deter

earlier and the tension developed is stronger than that developed by isometric stimulation. Both length clamp and load clamp are sophisticated techniques developed relatively recently. However, they yield conflicting results as to the rise of the active state. In both cases, the papillary muscles are subjected to non-physiological maneuvers. The question is whether these maneuvers affect the active state itself. For instance, the quick-release method, so important in determining the elastic properties of SE and active state properties, has been shown to alter the active state. Jewell and Wilkie (1960) studied length changes following isotonic release against the same load at different times during a twitch. Fig. 10 shows the results. It is seen that for the same twitch at the same time (at 0.5 sec, say) the muscle is found to be relaxing if release is early, and contracting if release is late. In other words, if a muscle is allowed to shorten, the duration of active state becomes less. Brutsaert et al (1972), using velocity clamping, found that as clamped velocity decreases, the duration of active state increases, reaching a maximum at isometric contraction.

The question of "active state" is still unsettled. We may safely say confusion still exists in its definition, determination, and interpretation.

CHAPTER IV

ANALYSIS OF THE THREE ELEMENT MODELS

The Three Element Models

The three element models were proposed by Hill (1938) to account for the resting tension in muscle. Later, authors used the names "Voigt" model and "Maxwell" model (Fig. 4). These are actually misnomers, for although Voigt and Maxwell both worked on similar two element models in viscoelasticity (contractile element replaced by a dashpot), it was Kelvin who devised the three-element viscoelastic model.

The most appropriate model for cardiac muscle is still unclear. Using quick release experiments to test the properties of SE and PE, investigators favored either the Voigt model (Yeatman et al 1969) or the Maxwell model (Hefner and Bowen 1967) or both (Parmley and Sonnenblick 1967). Brady (1967) found that it was necessary to classify each muscle individually into either "Voigt" of "Maxwell" types. However, Fung (1971) showed mathematically that by changing the parameters and allowing force-length relations to be velocity dependent, in general, one model would be identical to another in performance. Thus, any one model would be sufficient to describe the muscle.

Proof that Vmax (of Myocardium) is Length Dependent

Presented here is Pollack's (1970) refutation of Sonnenblick's (1962) claim that Vmax (of myocardium) is length (and load)

independent. The proof is slightly different from the original version, but the idea remains the same. Let us define the following symbols

F = force

L = length

V = velocity

$S = \frac{dF}{dL}$

Vmax = maximum velocity of muscle at no load on muscle

V_{mCE} = maximum velocity of CE at no load on CE

and subscripts

CE = contractile element

PE = parallel elastic element

M = muscle

P = preload

A = afterload

First, consider the Voigt model (Fig. 4). It is evident that

$$F_M = F_{SE} = F_{PE} + F_{CE} \tag{12}$$

$$V_M = V_{CE} + V_{SE} = V_{PE} + V_{SE} \tag{13}$$

Sonnenblick plotted F_M against V_M. However, "contractility" arises from CE alone and F_{CE} should be plotted against V_{CE} instead. During isotonic contractions, F_M is constant and $V_{SE} = 0$. Therefore,

$$F_{CE} = F_M - F_{PE} \tag{14}$$

$$V_{CE} = V_M \tag{15}$$

If the parallel element is absent (as in the two element model), then muscle force and velocity is identical to CE force and velocity. However, if resting tension is considerable, then Eq. (14) shows that a correction of $-F_{PE}$ should be made to F_M.

Now in Sonnenblick's work, the velocity of muscle is plotted as a function of force on muscle:

$$V_M = f(F_M) \tag{16}$$

Thus, using Eqs. (14-15),

$$V_{CE} = f(F_{CE} + F_{PE}) \tag{17}$$

In these experiments, Pollack estimated that F_{PE} is maximum when the muscle is unstimulated. The elastic elements should also have no resistence to compression. Therefore,

$$0 \leq F_{PE} \leq F_P \tag{18}$$

At the initial instant of shortening, however, $F_{PE} = F_P$ and $F_{CE} = 0$. Therefore,

$$V_{mCE} = f(F_P) \tag{19}$$

i.e., the maximum velocity of CE is a function of preload or initial length.

For the Maxwell model, the analysis is more complicated. From Fig. 4 we see

$$F_M = F_{SE} + F_{PE} = F_{CE} + F_{PE} \tag{20}$$

$$V_M = V_{PE} = V_{SE} + V_{CE} \tag{21}$$

During isotonic contractions, F_M is constant. Differentiating Eq. (20) with respect to time,

$$0 = \frac{dF_{SE}}{dt} + \frac{dF_{PE}}{dt} = \frac{dF_{SE}}{dL_{SE}} \frac{dL_{SE}}{dt} + \frac{dF_{PE}}{dL_{PE}} \frac{dL_{PE}}{dt} \tag{22}$$

or $$0 = S_{SE}V_{SE} + S_{PE}V_{PE} = S_{SE}V_{SE} + S_{PE}V_M \tag{23}$$

Using Eq. (21),

$$V_M \quad \frac{S_{PE}V_M}{S_{SE}} + V_{CE} \tag{24}$$

and $$V_{CE} = (1 + \frac{S_{PE}}{S_{SE}})V_M \tag{25}$$

Then Eq. (16) gives

$$V_{CE} = (1 + \frac{S_{PE}}{S_{SE}}) f(F_{CE} + F_{PE}) \tag{26}$$

At the initial instant, again $F_{PE} = F_P$, $F_{CE} = 0$. Also, the ratio of the slopes at the initial instant S_{PE}/S_{SE} is a function of the initial length or a function of preload.

$$S_{PE}/S_{SE} = g(F_P) \tag{27}$$

Thus,

$$V_{mCE} = [1 + g(F_P)]f(F_P) \tag{28}$$

This is again a function heavily dependent on preload or length.

Calculation of V_{CE} for Three Element Models

Presented here is the general form for V_{CE}. The analysis is similar to those suggested by Hefner and Bowen (1967) and Pollack (1970).

First, consider the Voigt model. From Eq. (13), we have

$$\begin{aligned} V_{CE} = V_M - V_{SE} &= V_M - \frac{dL_{SE}}{dt} \\ &= V_M - \frac{dF_{SE}/dt}{dF_{SE}/dL_{SE}} \\ &= V_M - \frac{dF_M/dt}{S_{SE}} \end{aligned} \tag{29}$$

For isotonic contraction, $dF_M = 0$ and Eq. (29) reduces to Eq. (15) found previously. For isometric contraction, $V_M = 0$ and

$$V_{CE} = -\frac{1}{S_{SE}} \frac{dF_M}{dt} \tag{30}$$

S_{SE} is difficult to obtain for this model, since the force-length relation for resting tension measures the sum of the lengths of SE and PE. However, due to the assumption that CE is not responsive to velocity changes, quick stretch or quick release experiments should show the response of SE

alone. It seems the Voigt model is more suited for isotonic measurements, since V_{CE} is in simple form,

$$V_{CE} = V_M \tag{31}$$

As discussed previously (Parmley 1972), maximum V_{CE} may not occur at the initial instant. If so, Eq. (19) does not hold and V_{mCE} may occur during the isometric phase.

For the Maxwell model, in general, Eq. (21) gives

$$\begin{aligned} V_{CE} = V_M - V_{SE} &= V_M - \frac{dL_{SE}}{dt} \\ &= V_M - \frac{dF_{SE}/dt}{dF_{SE}/dL_{SE}} \\ &= V_M - \frac{dF_M/dt - dF_{PE}/dt}{S_{SE}} \\ &= V_M - \frac{dF_M/dt - S_{PE}dL_{PE}/dt}{S_{SE}} \\ &= V_M - \frac{1}{S_{SE}}\frac{dF_M}{dt} + \frac{S_{PE}}{S_{SE}}V_M \\ &= (1 + \frac{S_{PE}}{S_{SE}})V_M - \frac{1}{S_{SE}}\frac{dF_M}{dt} \end{aligned} \tag{32}$$

In the case of isotonic contractions, the last term is zero and Eq. (32) reduces to the correct form, Eq. (25). For an isometric contraction, Eq. (32) yields the same form as Eq. (30).

$$V_{CE} = -\frac{1}{S_{SE}}\frac{dF_M}{dt} \tag{33}$$

Although the force-length relation for PE of the Maxwell model can be obtained by passively stretching the muscle by

varying the preload, the property of SE must be obtained by first using quick stretch or release to get the sum of the force response of both SE and PE, and then subtracting the response of PE from the resting tension. Whether quick stretch would alter the properties of PE and SE is still in question.

Elastic Properties from the Resting Tension Curve and Quick Release Experiments

The mechanical behavior of elastic material is best described by the stress-strain relation, which is the normalized form of the force-length relation. Stress (σ) is defined as the tension divided by the cross sectional area of the muscle, and Strain (ϵ) is defined as the increase in length divided by the original length. Two experiments are then performed. The muscle is first slowly passively stretched and the following stress-strain relation is obtained for the resting tension curve

$$\sigma_1 = G(\epsilon_1) \tag{34}$$

or inversely

$$\epsilon_1 = G^{-1}(\sigma_1) \tag{35}$$

Then, the isotonic quick release experiment (Appendix A) is conducted and the decrease in total load ΔF and the instantaneous decrease in length ΔL are recorded as a function of total load.

$$\frac{\Delta L}{\Delta F} = \frac{d\epsilon_2}{d\sigma_2} = h(\sigma_2) \tag{36}$$

Integration gives

$$\epsilon_2 = \int_0^{\sigma_2} h(\sigma_2) d\sigma_2 = H^{-1}(\sigma_2) \tag{37}$$

or

$$\sigma_2 = H(\epsilon_2) \tag{38}$$

For the Voigt model,

$$\sigma_1 = \sigma_{SE} = \sigma_{PE} \tag{39}$$

$$\epsilon_1 = \epsilon_{SE} + \epsilon_{PE} \tag{40}$$

$$\sigma_2 = \sigma_{SE} \tag{41}$$

$$\epsilon_2 = \epsilon_{SE} \tag{42}$$

From Eqs. (38, 41, 42), the stress-strain relation for SE is

$$\sigma_{SE} = H(\epsilon_{SE}) \tag{43}$$

The properties of PE are obtained from Eqs. (35, 39, 40), and

$$\epsilon_{PE} = \epsilon_{PE}(\sigma_{PE}) = [\epsilon_{PE}(\sigma_{PE}) + \epsilon_{SE}(\sigma_{PE})] - \epsilon_{SE}(\sigma_{PE})$$

$$= G^{-1}(\sigma_{PE}) - H^{-1}(\sigma_{PE}) \tag{44}$$

This indicates that the stress-strain curve of PE can be obtained from the difference between the inverse of G and H curves.

For the Maxwell model, the following holds

$$\sigma_1 = \sigma_{PE} \tag{45}$$

$$\epsilon_1 = \epsilon_{PE} \tag{46}$$

$$\sigma_2 = \sigma_{PE} + \sigma_{SE} \tag{47}$$

$$\epsilon_2 = \epsilon_{PE} = \epsilon_{SE} \tag{48}$$

Eqs. (45-46) show

$$\sigma_{PE} = G(\epsilon_{PE}) \tag{49}$$

From Eqs. (47-49)

$$\sigma_{SE} = \sigma_{SE}(\epsilon_{SE}) = [\sigma_{PE}(\epsilon_{SE}) + \sigma_{SE}(\epsilon_{SE})] - \sigma_{PE}(\epsilon_{SE})$$
$$= H(\epsilon_{SE}) - G(\epsilon_{SE}) \tag{50}$$

Fig. 11 shows schematically the stress-strain curve for both models. Curves A and B are obtained from the experimental results of Parmley (1972) and are drawn approximately to scale. Curves C and D follow from the above analysis.

Some Important Deductions from the Analysis

1) Current literature (e.g. Parmley et al, 1972) assumed that

$$\sigma_{SE} = H(\epsilon_{SE}) \tag{51}$$

in the Maxwell model. This is not correct. Although in Eq. (50) $G(\epsilon_{SE})$ is small, this term cannot be ignored, especially at higher loads. Fig. 11 shows

shows curve D, using Eq. (50), and curve A, using Eq. (51) to differ by 20%.

2) If the cardiac muscle can be represented by the three element models, and if the maximum velocity of shortening indeed occur at the initial instant of shortening during isotonic experiments, then V_{mCE} calculated from the Maxwell model is a better index than that from the Voigt model. The proof is as follows.

The equivalence of performance for both models, as shown by Fung (1971), does not imply the equivalence of the corresponding elements. For instance, for the same muscle, Fig. 11 shows that the stiffness of PE in the Voigt model (curve C) is much higher than that in the Maxwell model (curve B). The properties of the contractile elements are also different. Eqs. (19) and (28) show that V_{mCE} in the Voigt model is smaller than V_{mCE} in the Maxwell model. Now which one is <u>less</u> dependent on F_P?

For a given load σ, Fig. 11 shows that the slope of PE in the Maxwell model (curve B) is smaller than the slope of SE in the Maxwell model (curve D). Thus from Eq. (27),

$$S_{PE}/S_{SE} = g(F_P) < 1 \qquad (52)$$

Also from the same figure, $g(F_P)$ decreases with load because S_{SE} increases faster than S_{PE}. Isotonic experiments show the function $f(F_P)$ increases with load (e.g. Sonnenblick 1962). Since $[1+g(F_P)]$ decreases with F_P and $f(F_P)$ increases with F_P, Eq. (28) shows that V_{mCE} in the Maxwell model would be <u>less dependent</u> on F_P than V_{mCE} in the Voigt model (Eq. 19).

The relative magnitudes of V_{mCE} for the two models can be obtained using Eq. (52)

$$f(F_P) < [1+g(F_O)]f(F_P) < 2f(F_P) \tag{53}$$

or

$$V_{mCE}(\text{Voigt}) < V_{mCE}(\text{Maxwell}) < 2V_{mCE}(\text{Voigt}) \tag{54}$$

3) One does not really need an isotonic or an isometric phase to measure V_{mCE}. As long as the muscle is maximally activated (during active state) and $V_M(t)$ and $F_M(t)$ can be experimentally measured, V_{CE} for the Voigt model can be obtained from Eq. (29) and V_{CE} for the Maxwell model can be obtained from Eq. (32). Then V_{CE} at each instant can be plotted against the load at the instant. Extrapolation to zero load gives V_{mCE}.

Experiments reported in current literature are either isotonic (using isolated muscle) or isometric (using intact heart). If simultaneous

measurements of both $V_M(t)$ and $F_M(t)$ can be made, there is no reason why the full equations (Eq. 29 or Eq. 32) cannot be used to calculate V_{mCE}.

CHAPTER V

MECHANICS OF THE INTACT HEART

Geometry

The fibrous "skeleton" of the heart consists of four rings of dense connective tissues joined together to which the atria, ventricles, valves and arterial trunks are firmly attached. The four chambers of the heart are separated by partitions or septa. In terms of wall thickness and contraction power, the strongest chamber is the left ventricle, then the right ventricle, the left atrium and the right atrium, in that order. The inner surface of the ventricles show a lattice of muscular columns called trabeculae carneae. Some of these project into the cavity and are called papillary muscles. From the summits of the papillae, strands of fibrous chordae tendineae extend upward to be attached to the atrioventricular valves.

The walls of the heart are composed of layers of myocardial muscle fibers encircling the ventricles like a turban. The traditional view asserted that the ventricular walls are composed of four different muscles: the superficial sinospiral and bulbospiral muscles, and the deep sinospiral and bulbospiral muscles. This view was challenged by Grant (1965), Streeter and Bassett (1966), Streeter et al (1969). They found that the orientation of the fibers changes continuously accross the wall like an oriental fan, implying separate muscle layers do not exist.

The cavity of the right ventricle is cresent shaped, bounded by the convex septal wall and the concave right ventricular wall, which is only one-third as thick as the left ventricular wall. In contrast, the cavity of the left ventricle is almost ellipsoidal and is most suited for pressure generation during contraction. The pressure (and work) produced by the left ventricle is about five times that of the right ventricle. Thus, barring gross abnormalities, the performance of the intact heart can be represented by the performance of the left ventricle alone.

Properties of the Intact Ventricle

Implanting beads on the wall of the pumping heart and using biplane angiography (Ross et al 1967, Mitchell 1969) it was found that isovolumic contraction was initiated by an abrupt shortening of the inflow tract (distance between the apex and the mitral valve) and an expansion of the outflow tract (distance between the apex and the aortic valve). During ejection, the circumference decreased 10-35%, inflow tract remained the same, outflow tract decreased 1-5%, and wall thickness increased 25%. These data suggest that, firstly, the major contractile work is done by the circumferential fibers, and secondly, the contraction is not symmetric.

Although the pressure in the left ventricle is easily obtained, the stress developed in the ventricular wall cannot be measured directly. Since the wall thickness is almost one half the inside diameter of the ventricle, Laplacés law (which

is only good for thin walls) cannot be applied. Feigl et al (1969) used strain gauges to measure wall stress on the surface, and then calculated the mean stress in the wall using the thickness of the wall and an assumed geometry of the ventricle. It was found that although the form of the wall stress-versus-time curve mimiced the pressure tracing, the magnitude calculated varied with the assumed geometry (spherical, ellipsoidal, constant thickness, etc.)

With the development of the mechanics of the isolated cardiac muscle (Chapter III), attention was directed to the elastic properties of the intact heart. Fry et al (1964) and Forward et al (1966), using the canine left ventricle, obtained series elasticity estimates that are quite close to those obtained from the isolated muscle. Using a quick-release method whereby the volume was quickly withdrawn during systole, Covell et al (1967) found the stress-strain curve of SE to be exponential:

$$\sigma = 16.99(e^{24.84\epsilon} - 1). \qquad (55)$$

The passive stiffness was determined by the pressure-volume relation of exercised hearts. Ross et al (1966) concluded that the $p-V$ relation was a sigmoid curve, while Forrester et al (1972) found the curve to be exponential. Templeton et al (1972) imposed sinusoidal perturbations on the isovolumetrically contracting heart and found a similar exponential relation.

The force-velocity relation was studied by Ross et al (1966), Covell et al (1966), Taylor et al (1967). The fiber

shortening velocity and wall tension were estimated at various times during ejection. The preload, or end diastolic pressure was controlled by a cannula that by-passed the right heart. The afterload was adjusted by a baloon constricting the aorta. It was found that an inverse relation, although not quite hyperbolic, existed between force and velocity.

Problems Associated with the Intact Heart

The intact heart, being more complex than the isolated muscle, presents numerous additional problems, both in measurement and modelling. The published literature on the properties of the intact heart are much less and the results less reproducible than those obtained from the isolated muscle. Besides the influence of external control mechanisms (which can be minimized by Starling's heart-lung apparatus), one must also be aware of the following factors:

1) Excitation is not synchronous. Due to the wave of depolarization travelling along the specialized conduction system in the walls of the heart, contraction is not synchronous. The asynchrony is approximately 10% of the rise time of sytole. This not only obscures the time axis in the determination of a contractile state but, more important, causes 15-20% variation in wall tension, altering the ventricular shape and sarcomere length distribution. (Monroe et al 1970).

2) The shape of the heart is difficult to model. There have been numerous efforts to model the left ventricle as thick-walled ellipsoids (Sandler and Dodge 1963, Fry et al 1964), or thin-walled spheres (Levine and Britman 1964). Even for these simplified geometries, the analyses are quite complicated (Mirsky 1969). As discussed previously, the estimation of stress inside the wall (which cannot be directly measured as in the isolated muscle) is quite model dependent. Furthermore, the heart changes in shape during isovolumic contraction and ejection (Tanz et al 1967), and the muscle fibers buckle during systole (Gay and Johnson 1967). None of the current models took these into account.

3) The walls are neither homogeneous nor isotopic. Homogeneity means that the elastic properties do not vary at different points on the wall. This is not true, for the area near the base of the ventricle, including the valves, is collagenous and passive while the rest of the walls are elastic and active. Isotropy has to do with the orientation of the muscle fibers in one direction. In the intact heart the orientations vary not only about the surface but also across the wall as well. These factors invalidate the use of pressure-volume measurements as the stress-strain relation of the contracting fibers.

4) Experimental results differ. The size of the experimental animal, whether it is conscious or anaesthetized, whether or not it is denervated; and the technique used, whether it is closed or open chest, whether or not it is isolated on a Frank-Starling apparatus, all alter the measurements (Van Den Bos et al 1973).

The above factors are important only for the intact heart and have little effect on the results of the isolated muscle.

CHAPTER VI

CONTRACTILITY

The Index of Contractility

Cardiac output is the product of stroke volume and frequency. It was noted by Starling (1918) that stroke volume increased with end diastolic volume. Later, Sarnoff and Mitchell (1962) provided a measure of the contractile state of the ventricle by using stroke volume and pressure. Another measure of contractility was provided by Rushmer (1962). When stoke work was plotted as a function of ventriclar end diastolic pressure (EDP), a ventricular function curve was obtained. It showed that as EDP increased, stoke work increased - a fact consistent with Starling's results. The administration of an inotropic drug, such as norepinephrine, shifted the curve to the left, showing an increase in stroke work for the same EDP. Thus, the ventricular function curve seems to characterize cardiac performance. However, Rushmer (1962) also found that in intact, unanesthetized animals, the many compensatory mechanisms of the heart often obscured changes in stoke work. Noble et al (1966) found that stoke volume and output were unrelated to the contractile state. Furthermore, stroke volume can be influenced by factors extrinsic to the heart, such as anemia, neural and humoral changes, as well as loading conditions caused by aortic constriction or peripheral resistance.

In

heart, o

been wid

inition

at its d

the card

factors

Fro

III, we

element

and a fo

are very

pretatio

for the

experime

on the p

tractili

reflect

Evi

unlikely

the compl

simple

tility.

How

perimenta

quantitie

factors,

In order to quntify the intrinsic properties of the heart, one has to define "contractility", a term that has been widely used and misused. There exists no simple definition of contractility. Suffice it to say that any attempt at its definition must incorporate the inherent property of the cardiac muscle to contract, independent of extrinsic factors such as preload or afterload.

From the discussion of the isolated muscle in Chapter III, we see that the properties of the active contractile element should be described by both a force-velocity relation and a force-time (active state) relation. These properties are very tedious to obtain. Even when obtainable, their interpretation is still most controversial. Problems are compounded for the intact heart (Chapter V). Not only that, clinically, experiments that can be performed without irreversible effects on the patient are limited. The search for an index of contractility, measurable, simple to calculate, and able to reflect the intrinsic state of the heart continues.

Evidently we are asking too much. A simple index is unlikely to be universally applicable, since it cannot describe the complicated force-velocity-time relation of contraction. A simple index can only reveal a certain aspect of contractility. Some indices, of course, are more revealing than others.

How then do we obtain an index of contractility? The experimentalist is tempted to put together groups of measured quantities to see if the combinations vary with outside factors, such as loading. The success is often shortlived.

The index thus found is invariably repudiated in one or two years after its advocation in open literature. Two reasons deter arbitrarily grouping experimental data without strong theoretical support. Firstly, there are too many combinations from which to choose. For example, when only two kinds of data are measured: pressure p and time t, the pressure could be maximum pressure, average systolic pressure, developed pressure, pressure at fastest rise, etc.; and time could be time to peak pressure, systolic time, isometric contraction time, time from end diastole to fastest pressure rise, etc. Furthermore, p and t could be combined into powers as (p^{α}/t^{β}), where α,β could be any (even fractional) constant. There is no reason to reject transcendental groups, such as log p/exp t, either. Secondly, the sought-after index may not entirely depend on the quantities measured. For example, the derivative dp/dt, which may be important, cannot be obtained by any finite juggling of the quantities p and t. The theoretician is in a worse position than the experimentalist, for numerous problems arose (Chapter III) even when constructing a model for the isolated myocardium, to say nothing of constructing one for the intact heart which contains problems of its own (Chapter V). No theoretical model has been able to take into account even some of these factors. Furthermore, when the mathematical model is formulated, the elastic and visco-elastic constants are unknown. Where and how do we obtain these numbers? From the patient? Or from the papillary muscle dissected from the dog?

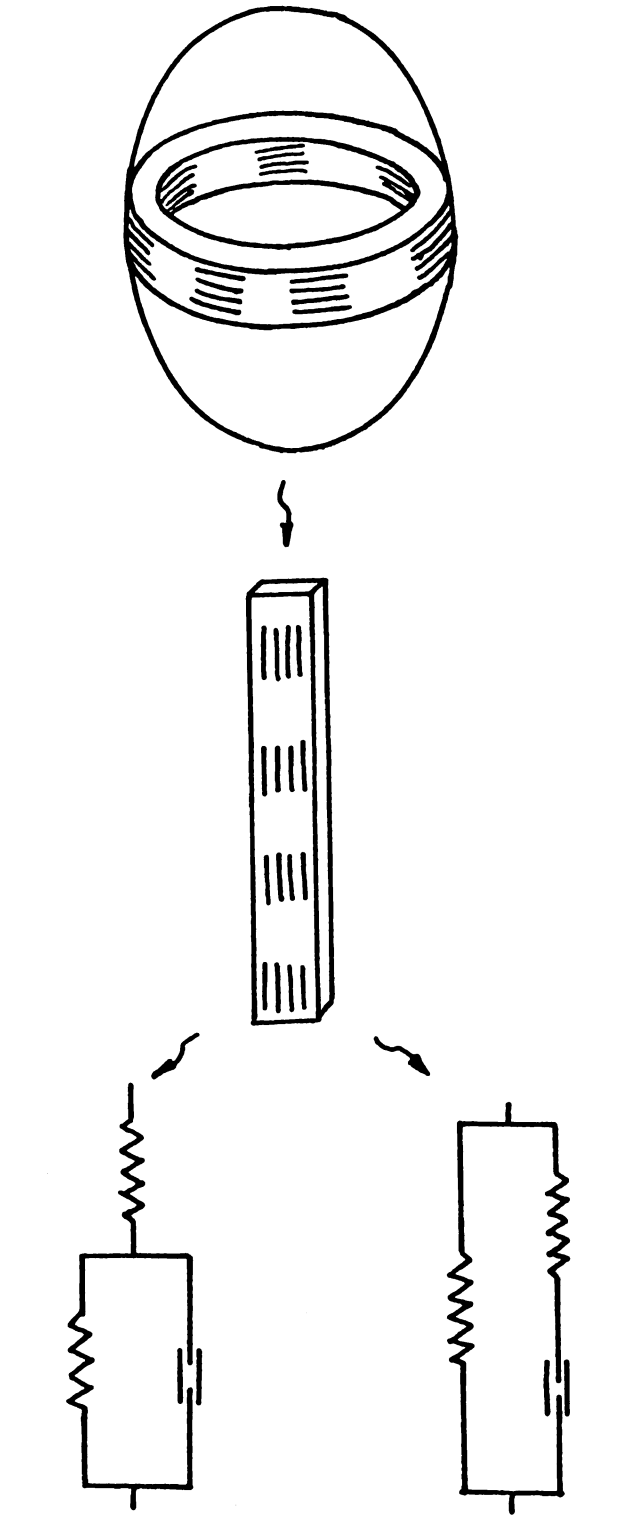


Fig. 12 Modelling the ventricle

heoreti

It
at all,
and hope
are not
lated m
shorten
slightl
of V_{mC}
As
element
assumed
the hor
is done
Le
the cir
If norm
the cir

Differe
shorter

No
from th

Theoretical Basis of V_{mCE} for the Intact Heart

It is evident that in order to model the intact heart at all, one must be ready to make drastic simplifications and hope that the essential characteristics of contractility are not sacrificed in the process. From the study of isolated muscle mechanics (Chapter III), V_{mCE}, the maximum shortening velocity of CE at no load, seemed to be a slightly better index. In what follows, simplified theory of V_{mCE} for the intact ventricle will be presented.

Assuming the heart muscle can be described by a three element model, current theory (e.g. Mirsky and Ghista 1972) assumed that the myocardium is circumferentially oriented in the horizontal plane of the left ventricle, where most work is done (Fig. 12).

Let b_0 be the end diastolic radius. The decrease in the circumferential fiber is then $2\pi b_0 - 2\pi b$ during systole. If normalized by the initial length $2\pi b_0$, the "strain" for the circumferential fiber is

$$\epsilon_{CF} = \frac{(2\pi b_0 - 2\pi b)}{2\pi b_0} = \frac{b_0 - b}{b_0} \tag{56}$$

Differentiating Eq. (56) with respect to time, the normalized shortening velocity of the whole fiber is

$$V_{CF} = \frac{d\epsilon_{CF}}{dt} = \frac{-1}{b_0}\frac{db}{dt} \tag{57}$$

Now for the series element SE, the empirical results from the isolated muscle (Parmley and Sonnenblick 1967, Covell

et al 19

relation

Thus,

Her

series e

constant

But for

the cir

contrac

Thus

and, fr

Fu

is calc

1966, T

geometr

We furt

et al 1967, Yeatman et al 1969) - that the force-length relation is approximately exponential - can be applied. Thus,

$$\sigma = \sigma_o + \sigma_{SE} = c'e^{k\epsilon_{SE}} - c \tag{58}$$

Here, σ is the total stress, ϵ_{SE} is the strain of the series element of the Voigt model, and c, c' and k are constants related to stiffness. Differentiating Eq. (58),

$$\frac{d\sigma}{dt} = c'e^{k\epsilon_{SE}} k\frac{d\epsilon_{SE}}{dt} = (\sigma + c)kV_{SE} \tag{59}$$

But for both "Maxwell" and "Voigt" models, the shortening of the circumferential element is equal to the shortening of the contracting element minus the lengthening of the series element. Thus

$$V_{CF} = V_{CE} - V_{SE} \tag{60}$$

and, from Eqs. (57) and (59),

$$V_{CE} = V_{CF} + V_{SE} = -\frac{1}{b_o}\frac{db}{dt} + \frac{1}{k(\sigma + c)}\frac{d\sigma}{dt} \tag{61}$$

Further simplification of Eq. (61) is possible if V_{CE} is calculated from the isometric contraction phase (Ross et al 1966, Taylor et al 1967). Assuming there is no change in geometry, set b to be constant and

$$V_{CE} = \frac{1}{k(\sigma + c)}\frac{d\sigma}{dt} \tag{62}$$

We further assume stress is proportional to the pressure,

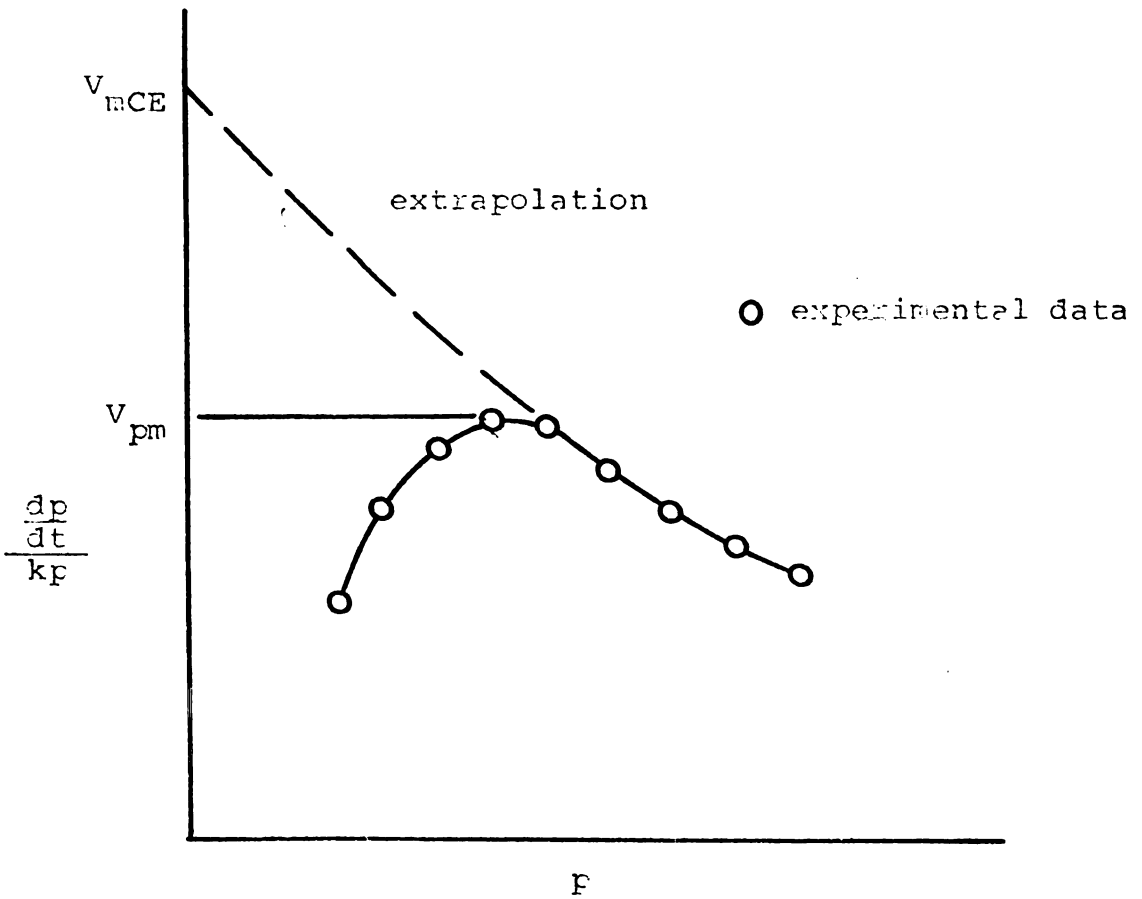


Fig. 13 Extrapolation for V_{mCE}

here A

hen

n Eq. (

nity, o

f diffe

V_{BCE}, t

Fig. 13

Some Cri

The

p curve

dvantag

only pre

ethods.

assumpti

criticis

1)

Thi

The disc

Chapter

history

eeded.

he mode

easons

$$\sigma = Ap \tag{63}$$

where A is a factor related to the geometry of the ventricle. Then

$$V_{CE} = \frac{1}{k(Ap + c)} \frac{Adp}{dt} = \frac{dp/dt}{k(p + c/A)} \tag{64}$$

In Eq. (64), with c/A neglected and the constant k set to unity, only $\frac{dp/dt}{p}$ is plotted against pressure for a number of different preloads (LVEDP). Extrapolating to zero load, V_{mCE}, the maximum velocity of contractile element at no load (Fig. 13) is obtained.

Some Criticisms of the Simplified Theory

The extrapolation of V_{mCE} from the $(dp/dt)/p$ versus p curve at the isometric contraction phase offers two great advantages. Firstly, it is relatively easy to obtain since only pressure tracing is required, as compared to angiographic methods. Secondly, the index is theoretically sound, if the assumptions hold. The assumptions, however, are not without criticism. These are discussed as follows:

1) The heart can be described by a three element model.

This assumes the existence of idealized SE, PE, and CE. The discussion on the elastic properties of the isolated muscle (Chapter III) showed that not only the existing element may be history dependent, but also additional viscous elements may be needed. The proposal of adding more elastic elements (making the model four or more elements) was never carried out. The reasons are several. Firstly, even multi-element models still

m not
ycardi
nduly
he ext
2

An
aligned
and Ran
nated.
ventric
if an e
ent of
of fibs
Non-syn
to base
3

Th
muscle
muscle
used in
1969).
weakes
4
A
systole

can not adequately explain the anomalous behavior of the myocardium. Secondly, mathematical calculations become unduly complicated. Thirdly, it is impossible to obtain the extra elastic constants by current experimental methods.

2) The intact heart is approximated by a circumferentially oriented myocardial strip.

Anatomy shows the fibers of the cardiac muscle to be aligned at relatively steep angles to the horizontal (Armour and Randall 1970). Thus, the Vmax obtained is underestimated. Furthermore, the fibers encompass not only the left ventricle but also the right ventricle and the atria. Even if an ellipsoidal isolated left ventricle and horizontal alignment of fibers were accepted there would be graded extension of fibers during diastole due to the three dimensionality. Non-synchronous contractions (spreading generally from apex to base) add to the complexity.

3) The elastic property of the series element is exponential.

This conclusion was drawn from experiments on the papillary muscles of the cat and dog, which may not represent the spiral muscles of the human. In addition, the quick release method used in the experiments is in question (Brutsaert and Sonnenblick 1969). The use of empirical data for SE is probably the weakest link in the theory.

4) The isovolumic phase is isometric.

Actually, they are not equivalent. What happens during systole is isovolumic but may not be isometric (constant fiber

length'.

showed th

probably

homogene

the inde

1973), a

volumic

isovolum

5)

Thi

stress m

negligib

the wall

half the

6)

Th

1966, T

Yeatman

and Van

factor

Vmax.

7)

Th

like 32

specie

in the

length). Ninomiya and Wilson (1965), Tanz et al (1967) showed there were shape changes in the isovolumic phase, probably due to non-synchronous contraction and non-homogeneity of fibers. Also, care must be used in applying the index to hearts with mitral regurgitation (Parmley et al 1973), aortic valve defects, or septal defects where no isovolumic phase exists. Finally, in cardial infarctions, the isovolumic phase has no connection with isometric contraction.

5) The stress is proportional to pressure.

This assumption was obtained from Laplacés law, where stress must be uniform (shape circular) and wall thickness negligible in comparison to the radius. This is not true of the wall thickness of the left ventricle, which is almost one half the mean radius.

6) The factor c/A in Eq. (64) can be neglected.

This was generally done in the early days (Ross et al 1966, Taylor et al 1967, Parmley and Sonnenblick 1967, Yeatman et al 1969), but has now been refuted by Noble (1972) and Van Den Bos et al (1973). The inclusion of this unknown factor introduces serious difficulties in the calculation of Vmax.

7) The constant k in Eq. (64) is set to unity.

This would be legal if k were an absolute constant like 32. Being an elastic constant, however, k varies from specie to specie, from heart to heart, and from time to time in the same heart (for instance, elasticity changes in the

urse o

rastica

he sing

8)

The

duratior

to be tr

patients

1971).

hand, l

fitting

Af

does th

as an i

and doe

conclud

Mason e

Wolk et

(1973),

said Ed

(1969),

the con

other i

Indices

To

contrac

course of myocardial disease or healing, and differs drastically before and after surgery). This is probably the single factor that affects V_{mCE} most.

8) Extrapolation to zero load gives V_{mCE}.

The extrapolation is inaccurate because of the short duration of the isometric contraction. Large distances have to be traversed before zero load is reached, especially for patients with high end-diastolic pressures (Mirsky et al 1971). Extrapolation also varies with the method used: free hand, linear regression, exponential fitting or hyperbolic fitting (Guyton and Jones 1974).

After all these objections to the theoretical analysis, does the quantity V_{mCE}, as measured, qualify experimentally as an index of contractility? I.e., is it load independent and does it respond well to inotropic interventions? Yes, concluded Taylor et al (1967), Parmley and Sonnenblick (1970), Mason et al (1970), Nejad et al (1971), Falsetti et al (1971), Wolk et al (1971), Ross and Peterson (1973), Nejad et al (1973), Krayenbuehl et al (1973) and Hisada et al (1973). No, said Edman and Nisson (1968), Urschel et al (1970), Nejad et al (1969), Parmley et al (1972), Escudero et al (1973). Due to the contradictory experimental evidences for V_{mCE}, numerous other indices were proposed.

Indices Using Pressure Tracing

To the author's knowledge, V_{mCE} is the only index of contractility which has some support of a theory. Pressure

racing,

artery

acceptal

indices

without

measure

1)

2)

3)

4)

5)

6)

tracing, obtained from a catheter inserted through a brachial artery into the left ventricle, is probably the simplest acceptable method clinically. The following is a list of indices derived from pressure tracing, and are advocated without a theory. Indices derived from other methods of measurement shall be discussed later.

1) $\int pdv$ or stroke work

It is responsive to inotropic effects, but very much load dependent (Sarnoff and Mitchell 1962, Covell et al 1966, Furnival et al 1970).

2) p_{max}

Parmley et al (1972) showed that this is quite dependent on preload.

3) t_1

Time to peak dp/dt was suggested by Mason et al (1965) and Morgenstern et al (1970).

4) t_2

Duration of systole is unreliable (Furnival et al 1970).

5) t_3

Time to peak $(dp/dt)/p$ was suggested by Mehmel et al (1970).

6) $\int pdt$ or Impulse

This was suggested by Rushmer (1964). Actually, this belongs to one of the ejection phase indices, which

is claimed to be better than isometric phase indices (Peterson et al 1974).

7) $(dp/dt)max$

Used by Wallace et al (1963), Furnival et al (1970), Morgenstern et al (1970) and Nejad et al (1971), it is sensitive to inotropic effects, but it is also sensitive to preload thus making it a poor index. (Abbott and Mommaerts 1959, Sonnenblick 1962).

8) $(d^2p/dt^2)max$

This was studied by Mirsky et al (1969), Nejad et al (1971). The index did not show any particular advantage.

9) $(dp/dt)max/\pi t$

Here πt represents the area under the rising slope of pressure tracing, and was suggested by Reeves et al (1960), Seigel and Sonnenblick (1963), Hisada (1969), Gleason and Braunwald (1972).

10) $(dp/dt)/(p/t)$

Claimed to be better than Vmax in both normal and abnormal hearts (Kumada et al 1973), this is a truly "non-dimensional" parameter and should be investigated further.

11) $(dp/dt)max/p$

This represents peak CE power since $(V_{CE}p)max = \left(\frac{dp}{dt}\right)max$, and was used by Taylor et al (1967), Taylor (1970), Mirsky et al (1971).

12) $[(dp/dt)/p]max$ or $(V_{CE})max$ or V_{pm}

This index was obtained from the maximum of the V_{CE} curve (Fig. 13) and thus avoids the extrapolation problem of V_{mCE} (Mirsky et al 1969, 1971, 1972; Nejad et al 1969, 1971, 1973; Grossman et al 1971, Escudero et al 1973, Ross and Peterson 1973). It was found to be sensitive to inotropic effects and insensitive to loading. This conclusion was questioned by Urschel et al (1970) and Mehmel et al (1970).

13) $[(d^2p/dt^2)/p]max$

This was calculated by Nejad et al (1971).

14) $(dp/dt)/Dp$ at 40 mm Hg.

Here Dp is the "developed" pressure, equal to the total pressure less the end diastolic pressure. It was first suggested by Urschel et al (1970). The requirement that the ratio be calculated at 40 mm Hg seem quite arbitrary.

15) V_{mCE} using developed pressure.

This index uses the same extrapolation procedure as V_{mCE}, except that the developed pressure is used as abscissa (Urschel et al 1970a, 1970b; Grossman et al 1972). The theory is based on the assumption that resting tension can be ignored (not true at higher loads). It is also poor at lower loads, since at the start of systole, the developed

pressure is zero, causing the index to approach infinity. Thus, the increased "sensitiveness" of the index is artifical, since it is due to a mathematical singularity.

Discussion and Other Methods

Controversy still rages as to which index best describes contractility. The values given for the same index from different laboratories vary according to the extrapolation method and the experimental techniques (Ross and Sobel, 1972) used. Comparisons between different indices from the same laboratory are still inconclusive. The index Vmax, using developed pressure, is favored (Urschel et al 1970b), as are peak $(dp/dt)/p = V_{pm}$ (Mirsky 1969) and V_{mCE}, using absolute pressore (Nejad et al 1973). Experiments performed, however, do not show clear cut advantages for the preferred indices.

The present study convincingly shows V_{mCE} to be a better index in terms of theoretical justification. Although the theory is still primitive, it can be improved by incorporating certain of the criticisms discussed earlier. In comparison, the other indices are empirical at best. There is absolutely no theoretical support for using developed pressure or peak $(dp/dt)/p$.

Herein, extrapolation must be circumvented before V_{mCE} can be determined with confidence. Most investigations reporting on data from the heart in situ were unable to extrapolate V_{mCE} at all, due to the large distances traversed.

Perhaps a theory could be developed linking V_{mCE} with the existing data from the descending isovolumic curve (utilizing its position, slope, and curvature), and thus eliminating extrapolation.

Finally, the velocity of contraction, no matter how calculated, is not the only factor characterizing contractility. Contractility is governed by the full force-velocity-length-time relations of a muscle. For instance, a vigorously fibrillating heart may involve large contraction velocities, but the "beat" would be too abbreviated to serve any useful function. Perhaps some measure of the duration of the active state, where maximum velocity occurs, should be a part of the contractility index.

Data from methods other than pressure tracing are used clinically to reflect cardiac performance. Cardiac output can be measured by the Fick principle, using oxygen consumption, or by indicator dilution techniques. Electrocardiogram and heart sounds are also used to detect the failing heart. Recently, apex cardiogram, a low frequency record of precordial displacement measured from the chest, was observed to correlate well with $(dp/dt)_{max}$ (Vetter et al 1972, Motomura et al 1973, Denef et al 1973). Biplane angiocardiography (Tsakiris et al 1969, Bove and Lynch 1970a, 1970b, Karliner et al 1971), using X-ray and cine films to measure changes in cardiac volume, can obtain two indices the ejection velocity and the ejection fraction.. Both are quite sensitive, however, to end diastolic volume and aortic pressure (Mitchell

et al 1969, Tsakiris et al 1969). Echocardiography utilizer ultrasound reflection to estimate cardiac dimensions (Bishop et al 1969, Burgge-Asperheim 1969, Feigenbaum 1972). This method seems to be less accurate than angiocardiography.

Methods which enhance the sensitivity of an index should not be overlooked. Leg elevation was used by Mason et al (1970) and Grossman et al (1972). Handgrip isometric exercise was used by Grossman et al (1973, Krayenbuehl et al (1973); and dynamic exercise by Mason et al (1970). All reported better differentiation of the diseased and healthy hearts for the indices tested. These maneuvers are easy to apply and should be studied more deeply, both experimentally and theoretically.

Two other factors in cardiac contraction that seem to be important are: the effect of drugs, especially local release of norepinephrine induced by myocardial tension, (Monroe et al 1966, Jewell and Blinks 1968), and the effect of frequency (Meijler and Brutsaert 1971, Guyton and Jones, 1975). These factors await further study.

CHAPTER VII

AN EXPERIMANT ILLUSTRATING THE CALCULATIONS

Purpose of Experiment

The purpose of this part of the study is to illustrate the method of calculating some of the currently used contractility indices obtained from left ventricular pressure tracing.

Materials and Methods

One female mongrel dog, weighing 35 lbs. was anesthetized with 5% solution of sodium pentobarbitol (30 mg/kg).

The heart was exposed by a left lateral thoracotomic incision and artificial respiration was maintained.

A needle was attached to a piece of small diameter polyethylene tubing (1.5 inches long) which in turn was attached to a pressure transducer (Statham P_{23}). The needle was then inserted directly into the exposed side of the left ventricle. A pressure transducer was also connected to the femoral artery. Both pressure signals were registered on a Hewlett-Packard recorder (HP 7796A). The recorder was programmed to take the on-line time derivative of the left ventricular pressure (dp/dt).

After a normal pressure tracing was taken as the control, a bolus dose of epinephrine (0.5 cc of 5γ or 5×10^{-6} gm per liter) was injected into the femoral artery. An increase in both mean arterial pressure and dp/dt was observed.

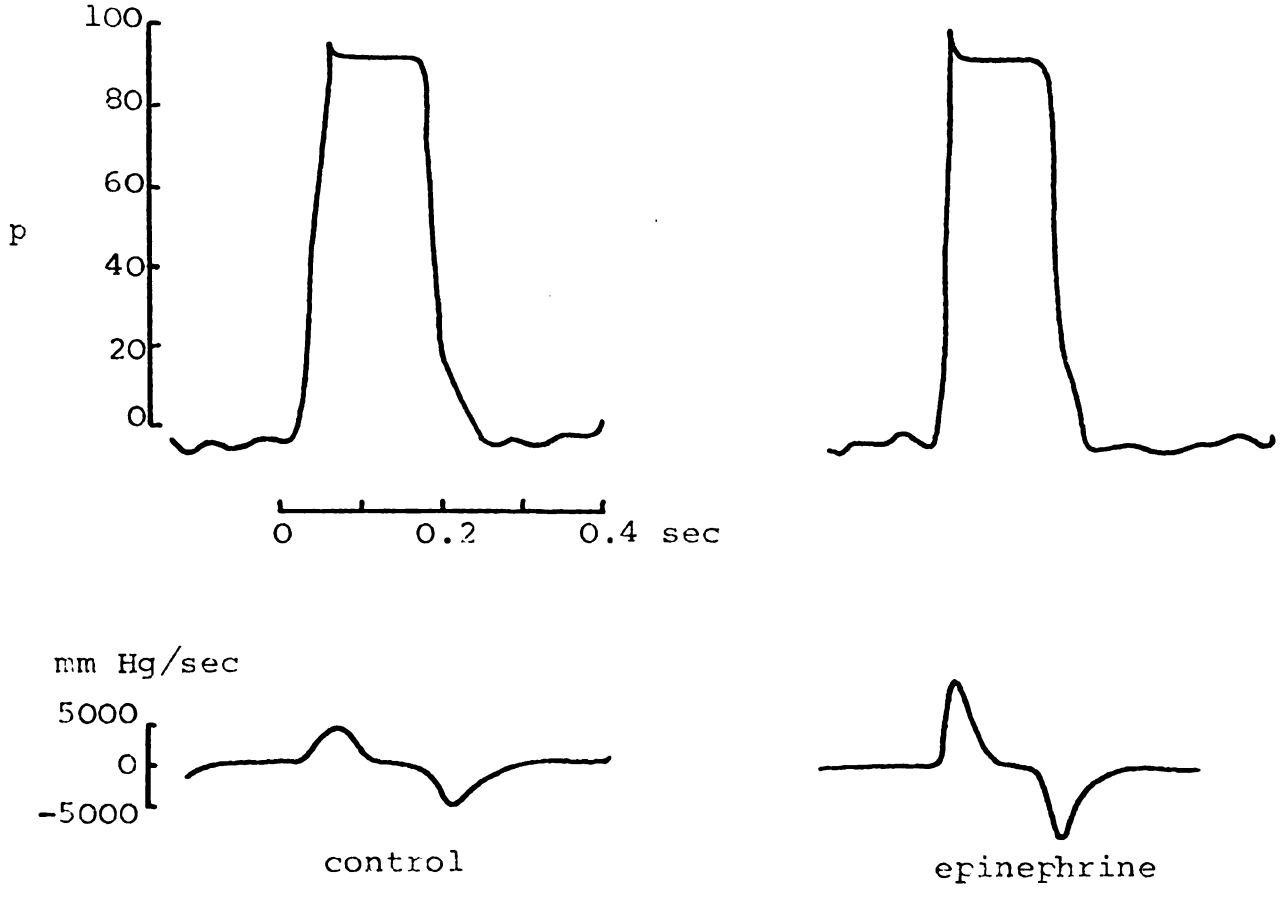


Fig. 14 Effect of epinephrine on p and dp/dt

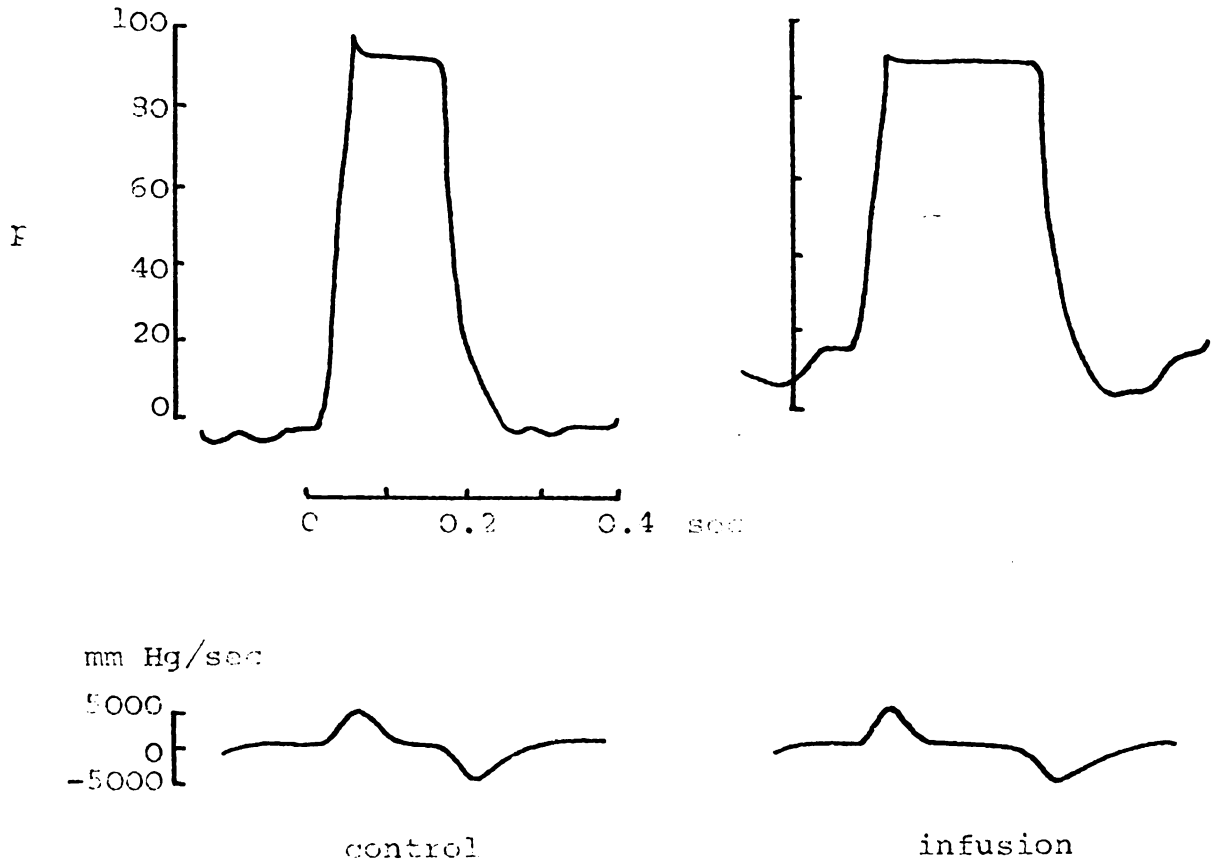


Fig. 15 Effect of volume infusion on p and dp/dt

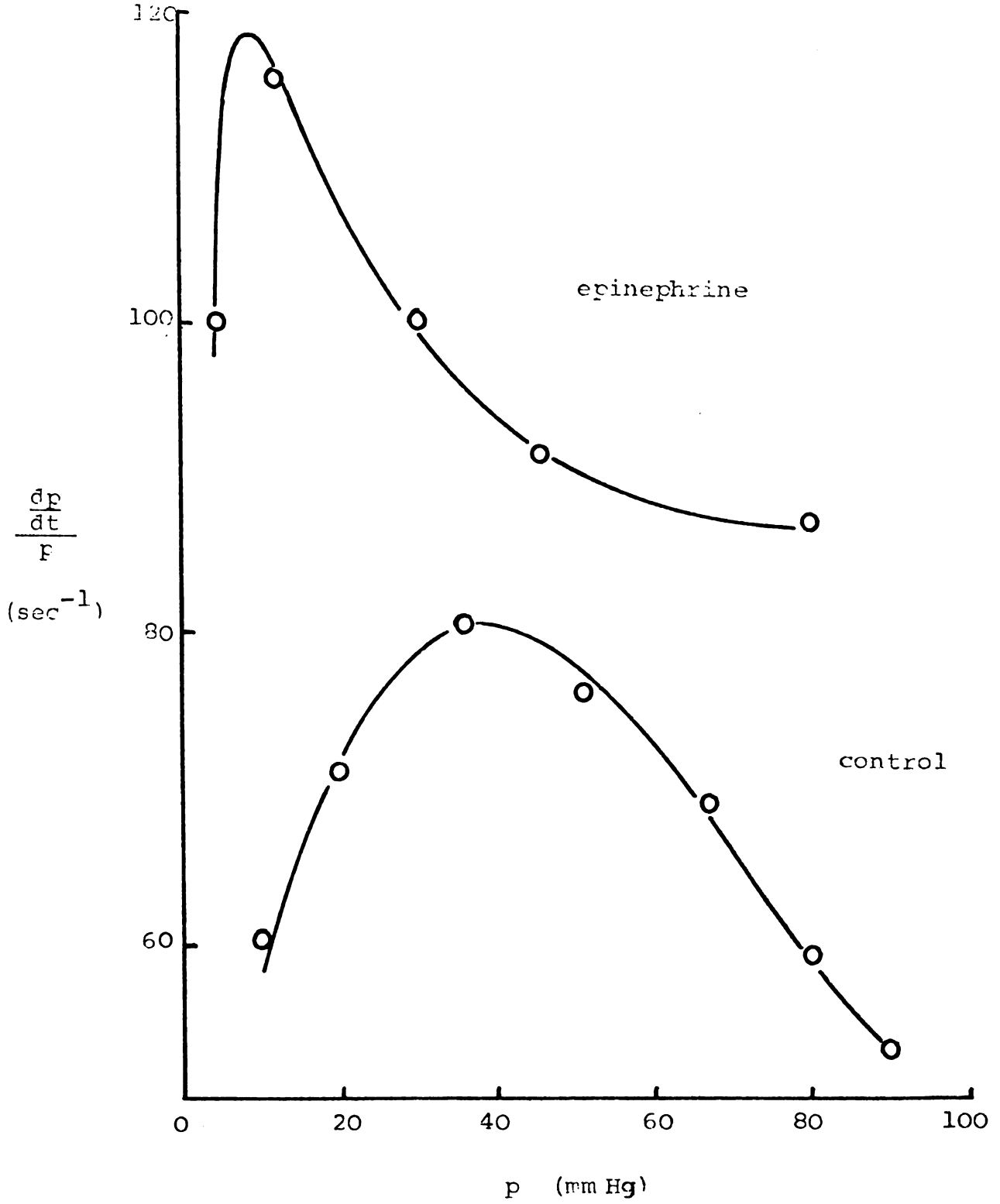


Fig. 16 Effect of epinephrine on (dp/dt)/p

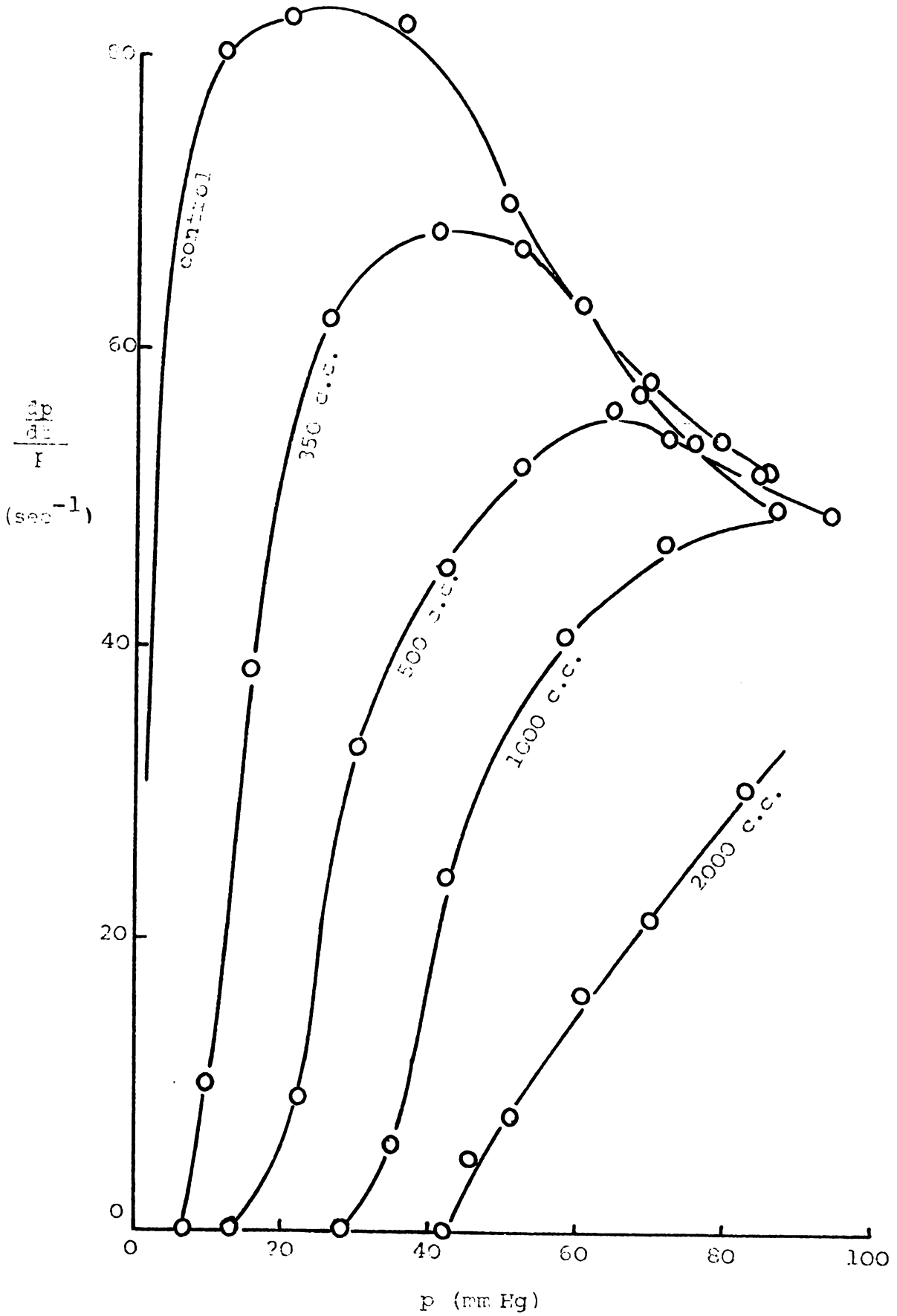


Fig. 17 Effect of volume infusion on (dp/dt)/p

The effect of the epinephrine decayed in one minute. Another control tracing was taken and then 6% Dextran-70 (in 0.9% NaCl solution) was pumped continuously into the right fermoral vein. The pumping rate was 284 cc/min, until one liter of infusion had been accumulated, after which the rate was decreased to 170 cc/min, until a total of two liters had been infused. The end diastolic pressure had been rising steadily throughout the infusion.

Result of Experiment

Figure 14 shows pressure tracings with and without epinephrine. The slope (or dp/dt) is seen to rise several fold due to the inotropic effect. Fig. 15 shows a typical pressure tracing with a 500 c.c. Dextran infusion. Minimum pressure and especially end diastolic pressure increased with increasing volume infusion. The flattened tops of the pressure curves are probably due to the amplitude limitation of the recording pen. This did not affect the result significantly, since most of the isovolumic phase had been recorded.

Using a magnifying glass the pressure tracings of (dp/dt) and p were read off for various times during systole. The ratio $(dp/dt)/p$ was then plotted against pressure. The error involved from the reading was about 10%. This can be minimized by using an on-line computer to calculate the ratio. The effect of epinephrine is shown if Fig. 16. It is seen that the positive inotropic effect of epinephrine greatly increases the ratio. Figure 17 shows that volume

infusions lower the peak $(dp/dt)/p$, and the curves shift to the right. The end diastolic pressures (the intercepts on the abscissa) also increase with volume infusion.

Discussion

We were unable to calculate any index which involved time explicitly. This was because an electrocardiogram had not been done and the "R" peak of ECG was needed to set the starting time. It is also evident from Figs. 16-17 that extrapolation to zero load was impossible due to the large distances involved. We were, however, able to calculate that $(dp/dt)max$, $(dp/dt)max/p$, $[(dp/dt)/p]_{max} = V_{pm} \cdot k$. These are listed in Table 1.

Table 1. Comparison of three indices

	$\left(\frac{dp}{dt}\right)max$ (mmHg/sec)	$\frac{1}{p}\left(\frac{dp}{dt}\right)max$ (sec^{-1})	$k\ V_{pm}$ (sec^{-1})
Control	4500	52	82
epinephrine	11000	110	118
Dextran 350 c.c.	4700	90	68
500 c.c.	4700	94	56
1000 c.c.	5100	96	50
2000 c.c.	5900	100	--

All three indices were sensitive to norepinephrine (inotropic effects). All three were also affected, although not as much, by Dextran infusion (hypervolema, including

effects of preload increase). Since volume infusion should not influence contractility, these indices are not perfect measures of contractility.

Some significance, however, can be deduced from Fig. 16. The falling parts of the curves, those due to isovolumic contractions, seem to coalesce. This is the same region upon which V_{mCE} depended, before the extrapolation to zero load. Thus, V_{mCE} can indeed be independent of preload, as predicted by the theory.

One must stop here before making further inferences. The experiment was done on <u>one</u> dog under less than ideal conditions. Each curve was laboriously plotted by hand over a single contraction. Statistically the curves do not lead to conclusions that can be generalized. The use of 7 to 14 dogs, as practiced by investigators, is not statistically significant either.

CHAPTER VIII

CONCLUSIONS AND SUGGESTIONS

The forgoing review of the literature, and particularly the analysis of the three element models, results in the following conclusions of physiological importance.

1) The index Vmax, obtained by traditional isotonic experiments, can not represent cardiac contractility. Contemporary texts on medical physiology still carry the earlier erroneous conclusion that cardiac muscle is similar to skeletal muscle, thus making Vmax a measure of contractility for both muscles.

2) Most current indices advocated in the literature are empirical, at best. The only index which has theoretical support is V_{mCE}. All other indices investigated in this thesis cannot be justified theoretically.

3) The present work shows that V_{mCE} calculated from the Maxwell model is better than that calculated from the Voigt model. I.e. the index is less dependent on preload when the Maxwell model is used.

4) A period of pure isotonic or pure isometric phase contraction is not necessary for the calculation of V_{mCE}.

Suggestions for further work include the following:

1) The theory for V_{mCE} can be improved by incorporating some of the criticisms discussed earlier. More experiments must be done on the intact heart in order to obtain viable elastic constants for the theory.

2) The extrapolation process must be circumvented before V_{mCE} can be extrapolated with confidence. A theory may be formulated utilizing the existing data on the descending isovolumic curve.

APPENDIX A

EXPERIMENTS ON ISOLATED MUSCLE

Isometric Contraction

Isometric means constant length. The basic idea is to hold the muscle at the ends between two fixed supports, one of which is attached to a tension transducer. The muscle is then simultaneously stimulated electrically at various points to assure synchronous contraction. Tetany (for skeletal muscle) may be achieved when the frequency of stimulation is above a certain "fusion frequency". A typical time response is shown in Fig. A1. The resulting maximum tension, plotted against the length of the sarcomere, is called the length-tension curve.

The experiment is not as simple as it may seem. Huxley and Peachey (1961) found that sarcomere lengths in single muscle fibers are not constant along the length of the fiber, being shorter at the ends. Krueger and Pollack (1975) found that during contraction, the degree of contraction differs for individual sarcomeres, and some sarcomeres are actually being stretched by the shortening of others. In order to assure a truly isometric contraction, Gordon et al (1966) used an elaborate electro-optical feedback system on a small segment of the muscle, where the sarcomeres are almost identical in length and behavior. The feedback mechanism adjusts the supports to ensure constant sarcomere length in the segment during contraction.

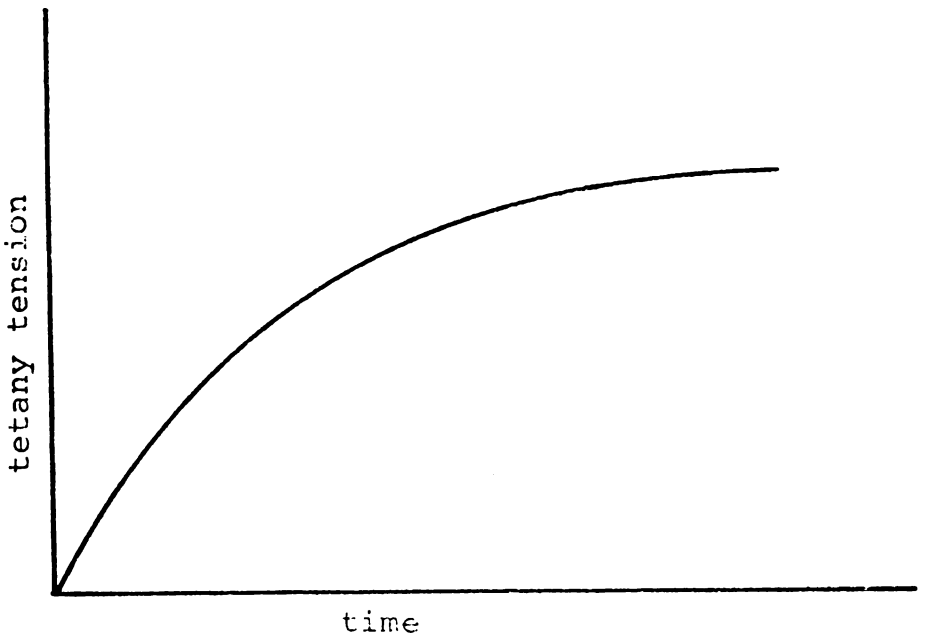


Fig. A1 Tension development for isometric tetany

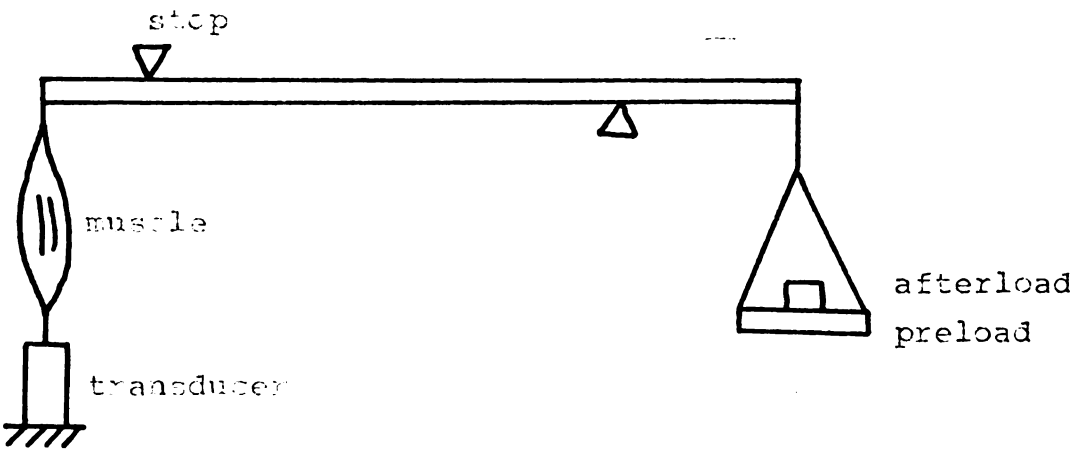


Fig. A2 Isotonic contraction setup

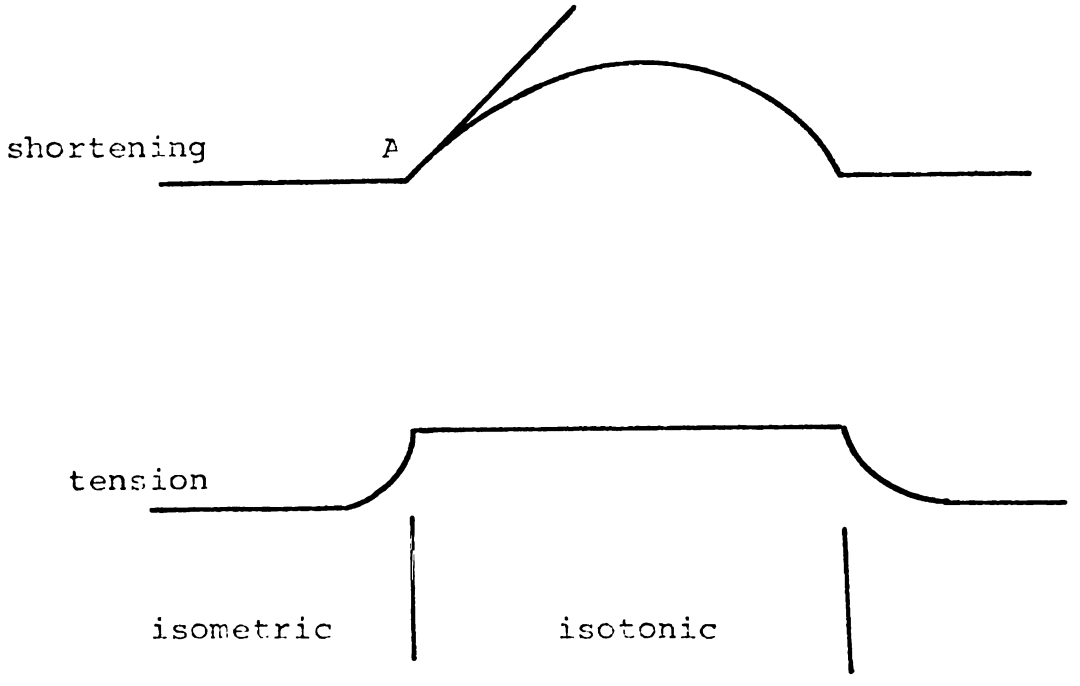


Fig. A3 Isotonic response

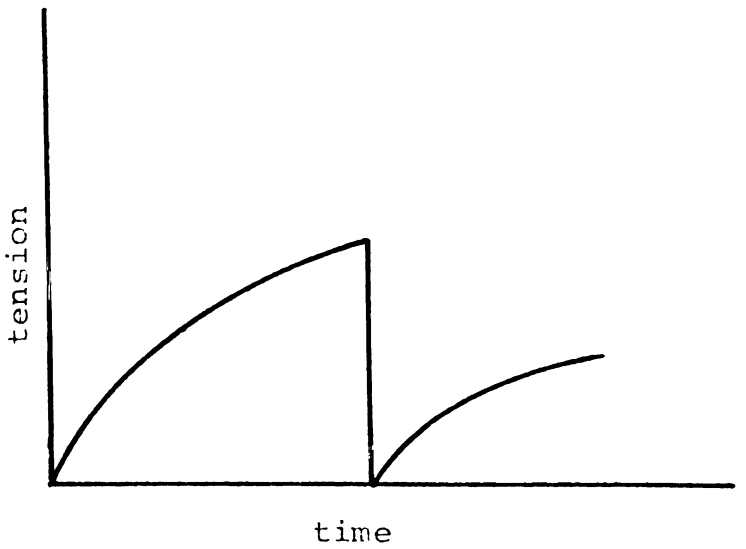


Fig. A4 Isometric quick release

Isotonic Contraction

Isotonic means constant load or tension. There are two kinds of loading. In free-loaded experiments, the muscle at rest is loaded and then stimulated. Since the initial length cannot be controlled, this kind of loading is seldom used. In after-loaded experiments, the initial length of the muscle is first determined by a suitable pre-load on a balance shown in Fig. A2. The stop and tension transducer are then adjusted. The muscle is not loaded at rest, but must lift a load in order to shorten. The movement of the lever, which reflects changes in muscle length, is then recorded. A typical response of a muscle twitch is shown in Fig. A3. The maximum velocity of shortening (the slope at A) is then plotted against different total loads. This is called the force-velocity curve.

Since the force-velocity curve is the result of a time dependent dynamic phenomena, care must be taken to minimize the error due to acceleration. This is usually done by shortening the lever arm on the side of the loads.

Quick Release Methods

When a muscle at isometric tetanus is suddenly shortened to a new constant length, the tension drops abruptly then rises to a new maximum determined by the length-tension curve (Fig. A4). This is called isometric quick release. The rise of tension with respect to time from quick release experiments, however, is not identical to the rise of tension starting from rest at the same shortened length.

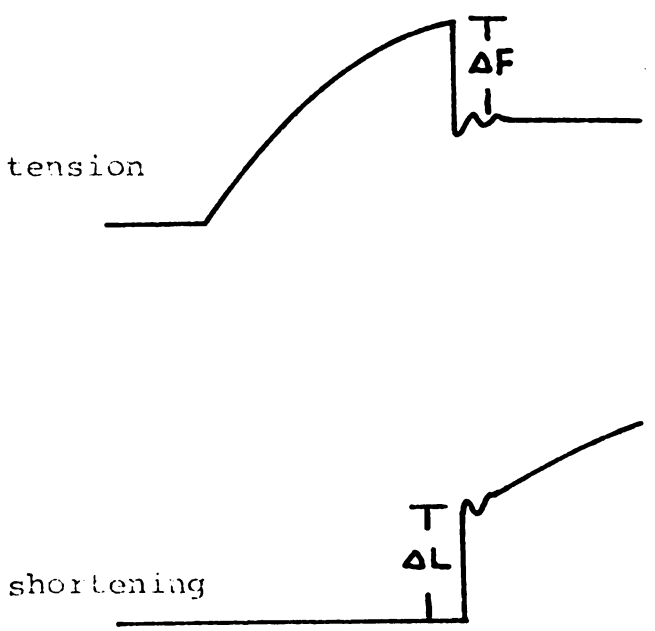


Fig. A5 Isotonic quick release

Another method is isotonic quick release. The apparatus is similar to that shown in Fig. A2, except there is a release relay stop below the lever on the muscle side. At the beginning of stimulation, the muscle contracts isometrically and the tension rises to its maximum value. When the release stop is withdrawn, the tension abruptly falls to a lower level which is equal to the loads. A typical response is shown in Fig. A5. The shortening of the length is abrupt at first, followed by some oscillations, and then proceed at a slower, constant rate.

Also used are isometric and isotonic quick stretches where the muscle is suddenly lengthened. All the above methods not only help to determine the transient properties of the muscle, but also the elastic properties of SE, since CE is assumed to be non-responsive to quick changes in length.

Length Clamp on CE

This experiment is used by Brady (1968) to determine the transient force response of the contractile element at a fixed length of CE. Since during isometric contraction, CE shortens at the expense of SE, the method calls for active pulling of the muscle to compensate for CE shortening. The amount of pulling is dependent on time and the elastic properties of SE and PE. To illustrate this idea, Hill's two element model can be used.

Suppose the elastic properties of SE if found by quick stretch or other methods, giving the following relation between the length of SE and the force on SE

$$L_{SE} = fn(F_{SE}) = fn(F_M) \tag{A1}$$

then

$$L_M(t) = L_{SE} + L_{CE} = fn(F_M(t)) + L_{CE} \tag{A2}$$

Since L_{CE} is held constant, one can obtain the instantaneous muscle length (L_M) from the instantaneous force on muscle (F_M) through Eq. (A2). Brady used an elaborate on-line computorized feedback system to give the proper amount of pull. A similar relation between L_M and F_M can be derived for constant CE length in the case of the three element models. The method is very much dependent on the model selected. A typical response is shown in Fig. 9. It is seen that in comparison to isometric twitch, the active state occurs earlier when CE length is fixed.

REFERENCES

1. Abbott, B.C. and D.G. Gordon, A commentary on muscle mechanics, Cir. Res. 36: 1, 1975.

2. Abbott, B.C. and W.H.F.M. Mommaerts, A study of inotropic mechanisms in the papillary muscle preparation, J. Gen. Physiol. 42: 533, 1959.

3. Aidley, D.J., The Physiology of Excitable Cells, Cambridge, 1971.

4. Armour, J.A. and W.C. Randall, Structural basis for cardiac function, Am. J. Physiol. 218: 1517, 1970.

5. Aubert, X., La relation entre la force et la vitesse d'allongement et de raccourcissement du muscle strié, Arch. Int. Physiol. Biochim. 64: 121, 1956.

6. Bergel, D.H., ed., Cardiovascular Fluid Dynamics, vol. 1, Academic Press, London, 1972.

7. Berne, R.M. and M.N. Levy, Cardiovascular Physiology, Mosby Co., St. Louis, 1972.

8. Bishop, V.S., L.D. Horwitz, H.L. Stone, H.F. Stegall and E J. Engelken, Left ventricular internal diameter and cardiac function in conscious dogs, J. Appl. Physiol. 27: 619, 1969.

9. Blinks, J.R., Factors influencing the prolongation of active state by stretch in isolated mammalian heart muscle, Fed. Proc. 29: 611, 1970.

10. Bove, A.A. and P.R. Lynch, Measurement of canine left vectricular performance by cineradiography of the heart, J. Appl. Physiol. 29: 877, 1970a.

11. Bove, A.A. and P.R. Lynch, Radiographic determination of force-velocity-length relationship in the intact dog heart, J. Appl. Physiol. 29: 884, 1970b.

12. Brady, A.J., Time and displacement dependence of cardiac contractility: problems in defining the active state and force-velocity relations, Fed. Proc. 24: 1410, 1965.

13. Brady, A.J., The three element model of muscle mechanics: its applicability to cardiac muscle, Physiologist 10: 75, 1967.

14. Brady, A.J., Active state in cardiac muscle, Physiol. Reviews 48: 570, 1968.

15. Braunwald, E., J. Ross Jr. and E.H. Sonnenblick, Mechanics of Contraction of the Normal and Failing Heart, Little, Brown Co., Boston, 1968.

16. Briller, S.A. Ed., The Myocardial Cell, Univ. Penn. Press, 1966.

17. Brutsaert, D.L., V.A. Claes and J.J.H. Donders, Effects of controlling the velocity of shortening on force-velocity-length and time relations in cat papillary muscle: velocity clamping, Cir. Res. 30: 310, 1972.

18. Brutsaert, D.L., V.A. Claes and E.H. Sonnenblick, Effect of abrupt load alternations on force-velocity, length and time relations during isotonic contractions in heart muscle: load clamping, J. Physiol. (London) 216: 319, 1971b.

19. Brutsaert, D.L., V.A. Claes, E.H. Sonnenblick, Velocity of shortening of unloaded heart muscle and the length-tension relation, Cir. Res. 29: 63, 1971b.

20. Brutsaert, D.L. and E.H. Sonnenblick, Force-velocity-length-time relations of the contractile elements in heart muscle of the cat, Cir. Rec. 24: 137, 1969.

21. Brutsaert, D.L. and E.H. Sonnenblick, Early onset of maximum velocity of shortening in the heart muscle of the cat, Pfuegers Arch. 324: 91, 1971.

22. Bugge-Asperheim, B., S. Leraand and F. Kiil, Local dimensional changes of the myocardium measured by ultrasonic techniques, Scand. J. Clin. Lab. Invest. 24: 361, 1969.

23. Burns, J.W., J.W. Covell and J. Ross, Jr., Mechanics of isotonic left ventricular contractions, Am. J. Physiol. 224: 725, 1973.

24. CIBA Foundation, The Physiological Basis of Starling's Law of the Heart, Symposium 24 (new series). Associated Scientific Publishers, Amsterdam 1974.

25. Civan, M.M. and R.J. Podolsky, Contraction kinetics of striated muscle fibres following quick changes in load, J. Physiol. 180: 511, 1966.

26. Close, R.I., The relations between sarcomere length and characteristics of isometric twitch contractions of frog sartorius muscle, J. Physiol. (London) 220: 745, 1972.

27. Covell, J.W., J. Ross, E.H. Sonnenblick and E. Braunwald, Comparison of the force-velocity relation and the ventricular function curve as measures of the contractile state of the intact heart, Cir. Res. 19: 364, 1966.

28. Covell, J.W., R.R. Taylor and J. Ross, Series elasticity in the intact left ventricle determined by a quick release method, Fed. Proc. 26: 382, 1967.

29. Denef, B., H. DeGeest and H. Kesteloot, Influence of changes in myocardial contractility on the height and slope of the calibrated apex cardiogram, Am. J. Cardiol. 32: 662, 1973.

30. Donald, T.C., K. Unnoppetchara, D. Peterson and L.L. Hefner, Effect of initial muscle length on Vmax in isotonic contraction of cardiac muscle, Am. J. Physiol. 223: 262, 1972.

31. Downing, S.E. and E.H. Sonnenblick, Cardiac muscle mechanics and ventricular performance: force and time parameters, Am. J. Physiol. 207: 705, 1964.

32. Edman, K.A.P. and E. Nilsson, The mechanical parameters of myocardial contraction studied at a constant length of the contractile element, Acta Physiol. Scand. 72: 205, 1968.

33. Escudero, E., A. Moreyra, C. Iveli, H. Lardani and H.E. Cingolani, Contractilidad miocardica: analisis experiimental de diversos indices propuestos, Acta Physiol. Latino. Am. 23: 259, 1973.

34. Falsetti, H.L., R.E. Mates, D.G. Greene and I.L. Bunnel, Vmax as an index of contractile state in man, Circulation 43: 467, 1971.

35. Feigenbaum, H., Echocardiography, Lea and Febiger, Philadelphia, 1972.

36. Feigl, E.O. G.A. Simon and D.L. Fry, Auxotonic and isometric cardial force transtucers, J. Appl. Physiol. 23: 597, 1967.

37. Fenn, W.O. and B.S. Marsh, Muscular force at different speeds of shortening, J. Physiol. (London) 85: 277, 1935.

38. Folkow, B. and E. Neil, Circulation, Oxford University Press, New York, 1971.

39. Ford, L.E. and R. Forman, Tetanized cardiac muscle. In the Physiological Basis of Starling's Law of the Heart, pp.137-154, CIBA Foundation Symposium No. 24, Associated Scientific Publishers, Amsterdam, 1974.

40. Forrester, J.S., G. Diamond, W.W. Parmley and H.J.C. Swan, Early increase in left ventricular compliance after myocardial infarction, J. Clin. Invest. 51: 598, 1972.

41. Forward, S.A., K.M. McIntyre, J.G. Lipana and J.J. Lefine, Active stiffness of the intact canine left ventricle, Cir. Res. 19: 970, 1966.

42. Frank, O., Zur Dynamik des Herzmuskels, Z. Biol. 32: 370, 1895.

43. Fry, D.L., D.M. Griggs Jr. and J.C. Greenfield Jr., Myocardial mechanics: tension-velocity-length relationships of heart muscle, Cir. Res. 14: 73, 1964.

44. Fung, Y.C., A necessary modification of Hill's equation for cardiac muscle, Fed. Proc. 29: 839, 1970.

45. Fung, Y.C., N. Perrone and M. Anlikev, eds., Biomechanics, Prentice-Hall, New Jersey, 1972.

46. Fung, Y.C., Comparison of different models of the heart muscle, J. Biomech. 4: 289, 1971.

47. Furnival, C.M., R.J. Linden and H.M. Snow, Inotropic changes in the left ventricle: the effect of changes in heart rate, aortic pressure and end-diastolic pressure, J. Physiol. (London) 211: 359, 1970.

48. Gasser, H.S. and A.V. Hill, The dynamics of muscular contraction, Proc. Roy. Soc. (London) B96: 398, 1924.

49. Gay, W.A. and E.A. Johnson, An anatomical evaluation of the myocardial length-tension diagram, Cir. Res. 21: 33, 1967.

50. Gleason, W.L. and E. Braunwald, Studies on the first derivative of the ventricular pressure pulse in man, J. Clin. Invest. 41: 80, 1962.

51. Gordon, A.M., A.F. Huxley and F.G. Julian, Variation in isometric tension with sarcomere length in vertebrate muscle fibers, J. Physiol. (London) 184: 170, 1966.

52. Grant, R.P., Notes on muscular architecture of the left ventricle, Circulation 32: 301, 1965.

53. Grimm, A.F., K.V. Katele, R. Kubta and W.V. Whitehorn, Relation of sarcomere length and muscle length in resting myocardium, Am. J. Physiol. 218: 1412, 1970.

54. Grossman, W., H. Brooks, S. Meister, H. Sherman and L. Dexter, New technique for determining instantaneous force-velocity relations in the intact heart, Cir. Res. 28: 290, 1971.

55. Grossman, W., F. Haynes, J.A. Paraskos, S. Saltz, F. Dalen and L. Dexter, Alternations in preload and myocardial mechanics in the dog and in man, Cir. Res. 31: 83, 1972.

56. Grossman, W., L.P. McLaurin, S.B. Saltz, J.A. Paraskos, J.E. Dalen and L. Dexter, Changes in the inotropic state of the left ventricle during isometric exercise, Brit. Heart J. 35: 697, 1973.

57. Guyton, A.C. and C.E. Jones, Eds., Cardiovascular Physiology, MTP International Review of Science, Physiology Series 1 vol. 1, Butterworths, London, 1975.

58. Hanson, J. and H.E. Huxley, Structural basis of contraction in striated muscle. In The Fibrous Proteins and Their Biological Significance: pp.228-264. Society for Experimental Biology Symposium No. 9, Academic Press, New York, 1955.

59. Hanson, J. and J. Lowy, Molecular basis of contractility in muscle, Brit. M. Bull. 21: 264, 1965.

60. Hefner, L.L. and T.E. Bowen, Elastic components of cat papillary muscle, Am. J. Physiol. 212: 1221, 1967.

61. Hill, A.V., The heat of shortening and the dynamical constants of muscle, Proc. Roy. Soc. London, ser. B. 126: 136, 1938.

62. Hill, A.V., The abrupt transition from rest to activity in muscle, Proc. Roy. Soc. (London) B136: 399, 1949.

63. Hill, A.V., The series elastic component of muscle, Proc. Roy Soc. London Ser. B. 137: 272, 1950.

64. Hill, A.V., The mechanics of active muscle, Proc. Roy Soc. London Ser. B. 141: 104, 1953.

65. Hill, A.V., The effect of load on the heat of shortening of muscles, Proc. Royal Soc. B159: 297, 1964.

66. Hisada, S., Myocardial contractility and pumping function of the ventricle, Jap. Circ. J. 33: 1557, 1969.

67. Hisada, S. M. Normura, S. Takeuchi, K. Ando and Y. Mizuno, Maximal velocity of contractile element shortening (Vmax) as an index of contractile state in the intact ventricle, Jap. Cir. J. 37: 713, 1973.

68. Howell, W.H. and F. Donaldson, Experiments upon the heart of a dog with reference to the maximum volume of blood sent out by the left ventricle in a single beat, and the influence of variations in venous pressure, arterial pressure, and the pulse rate upon the work done by the heart, Phil. Trans. Roy. Soc. London 175: 139, 1884.

69. Huxley, H.E., Muscle structure and theories of contraction, Prog. Biophys. and Biophys. Chem. 7: 257A, 1957.

70. Huxley, H.E., The contraction of muscle, Scient. Am. 199: 67, 1958.

71. Huxley, H.E., The contractile structure of cardiac and skeletal muscle, Circulation 24: 328, 1961.

72. Huxley, H.E., The mechanism of muscular contraction, Science 164: 1356, 1969.

73. Huxley, H.E. and J. Hanson, Changes in the cross-striations of muscle during contraction and stretch and their structural interpretation, Nature 173: 973, 1954.

74. Huxley, A.F. and L.D. Peachey, The maximum length for contraction in vertebrate striated muscle, J. Physiol. (London) 156: 150, 1961.

75. Jewell, B.R. and J.R. Blinks, Drugs and the mechanical properties of heart muscle, Ann. Rev. Physiol. 8: 113, 1968.

76. Jewell, B.R. and D.R. Wilkie, An analysis of the mechanical components in frog striated muscle, J. Physiol. (London) 143: 515, 1958.

77. Jewell, B.R. and D.R. Wilkie, The mechanical properties of relaxing muscle, J. Physiol. 152: 30, 1960.

78. Karliner, J.S., J.H. Gault, D. Eckberg, C.B. Mullins and J. Ross, Jr., Mean velocity of fiber shortening: A simplified measure of left ventricular myocardial contractility, Circulation 44: 323, 1971.

79. Knowlton, F.P. and E.H. Starling, The influence of variations in temperature and blood pressure on the performance of the isolated mammalian heart, J. Physiol. (London) 44: 206, 1912.

80. Krayenbuehl, H.P., W. Rutshauser, P. Wirz, I. Amende and H. Mehmel, High-fidelity left ventricular pressure measurements for the assessment of cardiac contractility in man, Am. J. Cardiol. 31: 415, 1973.

81. Krueger, J.W. and G.H. Pollack, Myocardial sarcomere dynamics during isometric contraction, J. Phsyiol. (London) 251: 627, 1975.

82. Kumade, T., T. Yaginuma, A. Sakai, M. Motomura, T. Konishi, A. Wakabayashi and M. Watanabe, An index (dP/dt)/(P/t) for the assessment of the left ventricular function, Jap. Cir. J. 37: 1445, 1973.

83. Langer, G.A. and A.J. Brady, eds., The Mammalian Myocardium, Wiley, 1974.

84. Levine, H.J. and N.A. Britman, Force-velocity relations in intact dog heart, J. Clin. Invest. 43: 1383, 1964.

85. Little, R.C. and W.B. Wead, Diastolic viscoelastic properties of active and quiescent heart muscle, Am. J. Physiol. 221: 1120, 1971.

86. Marshall, R.J. and J.T. Shepherd, Cardiac Function in Health and Disease, Saunders, Philadelphia, 1968.

87. Mason, D.T., E.H. Sonnenblick, J. Ross, Jr., J.W. Covell and E. Braunwald, Time to peak dP/dt: a useful measurement for evaluating the contractile state of the human heart, Circulation Suppl. 32: 145, 1965.

88. Mason, D.T., J.F. Spann and R. Zelis, Quantification of the contractile state of the intact human heart, Am. J. Card. 26: 248, 1970.

89. Mehmel, H., H.P. Krayenbuehl and W. Rutishauser, Peak measured velocity of shortening in the canine left ventricle, J. Appl. Physiol. 29: 637, 1970.

90. Meijler, F.L. and D.L. Brutsaert, eds., Contractile Behavior of Heart Muscle, British Medical Assoc., 1971.

91. Mirsky, I., Left ventricular stress in the intact human heart, Biophys. J. 9: 189, 1969.

92. Mirsky, I., A critical review of cardiac function parameters, Circulation Suppl. 39: III-147, 1969.

93. Mirsky, I., R.C. Ellison and P.G. Hugenholtz, Assessment of myocardial contractility in man from ventricular pressure recordings, Clin. Res. 17: 255, 1969.

94. Mirsky, I., R.C. Ellison and P.G. Hugenholtz, Assessment of myocardial contractility in children and young adults from ventricular pressure recordings, Am. J. Cardiol. 27: 359, 1971.

95. Mirsky, I. and D.N. Ghista, A critical evaluation of force-velocity analysis, J. Asso. Adv. Med. Instr. 6: 374, 1972.

96. Mirsky, I., D.N. Ghista and H. Sandler, eds., Cardiac Mechanics, Wiley, 1974.

97. Mirsky, I., A. Pasternac and R.C. Ellison, General index for the assessment of cardiac function, Am. J. Cardiol. 30: 483, 1972.

98. Mirsky, I. and W.W. Parmley, Evaluation of passive elastic stiffness for the left ventricle and isolated heart muscle. In Cardiac Mechanics: Physiological, Clinical and Mathematical Considerations. Ed. by I. Mirsky, D.N. Ghista and H. Sandler. Wiley, New York, 1974.

99. Mitchell, J.H., K. Wildenthal and C.B. Mullins. Geometrical studies of the left ventricle utilizing biplane cireflourography, Fed. Proc. 28: 1334, 1969.

100. Morgenstern, C., G. Arnold, U. Höljes and W. Lochner, Die Druckanstiegsgeschwindigkeit im linken Ventrikel als Mass für die Kontraktilität unter verschiedenen hämodynamischen Bedingungen, Pflügers Arch. 315: 173, 1970.

101. Monroe, R.G., W.J. Gamble, C.G. LaFarge, A. Edaljikumar and F.J. Manasek, Left ventricular performance at high end-diastolic pressure in isolated perfused dog hearts, Cir. Res. 26: 85, 1970.

102. Monroe, K.G., C.G. LaFarge, W.J. Gamble, R.P. Hammond and C.L. Morgan, Norepinephrine release and left ventricular pressure in isolated heart, Cir. Res. 19: 774, 1966.

103. Montcastle, V.B., Ed., Medical Physiology, 13th Ed., Mosby Co., St. Louis, 1974.

104. Motomura, M., M. Omae, H. Uehata, T. Kumata, T. Yaginuma, A. Wakabayashi and T. Konishi, An apex cardiographic index "(peak dA/dT)/A" for the assessment of left ventricular function, Jap. Cir. J. 37: 1355, 1973.

105. Nejad, N.S., M.D. Klein, I. Mirsky and B. Lown, Assessment of contractile state of the heart utilizing the maximum value of (dP/dt)/P, Physiologist 12: 313, 1969.

106. Nejad, N.S., M.D. Klein, I. Mirsky and B. Lown, Assessment of myocardial contractility from ventricular pressure recordings, Cardiovas. Res. 5: 15, 1971.

107. Nejad, N.S., E.F. Uretz, H.G. Tobin and M.P. Kaye, Simultaneous assessment of seven indices of myocardial contractility, Physiologist 16: 408, 1973.

108. Ninomiya, I. and M.F. Wilson, Analysis of ventricular dimension in the unanethetized dog, Cir. Res. 16: 249, 1965.

109. Noble, M.I.M., Problems concerning the application of concepts of muscle mechanics to the determination of the contractile state of the heart, Circulation 45: 252, 1972.

110. Noble, M.I.M., T.E. Bowen and L.L. Hefner, Force velocity relationships of cat cardiac muscle, studied by isotonic and quick-release techniques, Cir. Res. 24: 821, 1969.

111. Noble, M.I.M. and W. Else, Re-examination of the applicability of the Hill model of muscle to cat myocardium, Cir. Res. 31: 580, 1972.

112. Noble, M.I.M., D. Trenchard and A. Guz, Left ventricular ejection in conscious dogs: II, determinants of stroke volume, Cir. Res. 19: 148, 1966.

113. Parmley, W.W., L. Chuck, S. Clark and A. Matthews, Effects of added compliance on force-velocity relations calculated from isometric tension records, Am. J. Physiol. 225: 1271, 1973.

114. Parmley, W.W., L. Chuck and E.H. Sonnenblick, Relation of Vmax to different models of cardiac muscle, Cir. Res. 30: 34, 1972.

115. Parmley, W.W. and E.H. Sonnenblick, Series elasticity in heart muscle: Its relation to contractile element velocity and proposed muscle models, Cir. Res. 20: 112, 1967.

116. Parmley, W.W. and E.H. Sonnenblick, Re-evaluation of Vmax as an index of contractile state: an analysis of different muscle models, Circulation suppl. 42: III-115, 1970.

117. Patterson, S.W. and E.H. Starling, On the mechanical factors which determine the output of the ventricles, J. Physiol. (London) 48: 357, 1914.

118. Peskin, C.S., Mathematical Aspects of Heart Physiology, New York University, 1975.

119. Peterson, K.L., D. Skloven, P. Ludbrook, J.B. Uther and J. Ross, Comparison of isovolumic and ejection phase indices of myocardial performance in man, Circulation 49: 1088, 1974.

120. Pollack, G.H., Maximum velocity as an index of contractility in cardiac muscle: a critical evaluation, Cir. Res. 26: 11, 1970.

121. Pollack, G.H., L.L. Huntsman and P. Verdugo, Cardiac muscle models. An overextension of series elasticity? Cir. Res. 31: 569, 1972.

122. Pollisar, M., Physical chemistry of contractile process in muscle, Am. J. Physiol. 168: 766, 1952.

123. Reeves, T.J., L.L. Hefner, W.B. Jones, C. Coghlan, G. Prieto and J. Carroll, The hemodynamic determinants of the rate of change in pressure in the left ventricle during isometric contraction, Am. Heart J. 60: 745, 1960.

124. Ross, J., Jr., J.W. Covell, E.H. Sonnenblick and E. Braunwald, Contractile state of the heart characterized by force-velocity reactions in variably afterloaded and isovolume beats, Cir. Res. 18: 149, 1966.

125. Ross, J., Jr. and B.E. Sobel, Regulation of cardiac contraction, Annu. Rev. Physiol. 34: 47, 1972.

126. Ross, J., Jr., E.H. Sonnenblick, J.W. Covell, G.A. Kaiser and D. Spiro, The architechture of the heart in systole and diastole. Technique of rapid fixation and analysis of left ventricular geometry, Cir. Res. 21: 409, 1967.

127. Ross, J., Jr. and R.L. Peterson, On the assessment of cardiac inotropic state, Circulation 47: 435, 1973.

128. Roy, C.S., On the influences which modify the work of the heart, J. Physiol. (London) 1: 452, 1879.

129. Rüdel, R. and S.R. Taylor, Striated muscle fibers: facilitation of contraction a short lengths by caffeine, Science 172: 387, 1971.

130. Rushmer, R.F., Effects of nerve stimulation and hormones on heart: role of heart in general circulatory regulation. In Handbook of Physiology, Edited by W.F. Hamilton and P. Dow 1: 533, 1962.

131. Rushmer, R.F., Initial ventricular impulse, a potential key to cardiac evaluation, Circulation 29: 268, 1964.

132. Rushmer, R.F., Cardiovascular Dynamics, 3rd Ed., Saunders, Philadelphia, 1970.

133. Sandler, H. and H.T. Dodge, Left ventricular tension and stress in man, Cir. Res. 13: 91, 1963.

134. Sarnoff, S.J. and J.H. Mitchel, Control of function of the heart. In Handbook of Physiology; Circulation Vol. 1, W.F. Hamilton and P. Dow, Eds. Am. Physiol. Soc. 503, 1962.

135. Siegel, J.H. and E.H. Sonnenblick, Isometric time-tension relationships as an index of myocardial contractility, Cir. Res. 12: 597, 1963.

136. Sonnenblick, E.H., Force-velocity relations in mammalian heart muscle, Am. J. Physiol. 202: 931, 1962.

137. Sonnenblick, E.H., Series elastic and contractile elements in heart muscle: changes in muscle length, Am. J. Physiol. 207: 330, 1964.

138. Sonnenblick, E.H., Determinants of active state in heart muscle: force, velocity instaneous muscle length, time, Fed. Proc. 24: 1396, 1965.

139. Sonnenblick, E.H., The delayed onset and prolonged maintenance of maximum active state in heart muscle, Proc. 8th Int. Cong. Physiol. Sci. 174, 1965.

140. Sonnenblick, E.H., Active state in heart muscle: its delayed onset and modification by inotropic agents, J. General Physiol. 50: 661, 1967.

141. Sonnenblick, E.H., Contractility of Cardiac Muscle (Letters to Editor), Cir. Res. 27: 479, 1970.

142. Sonnenblick, E.H. and Z.T. McCallum, Active state, force-velocity relationships and inotropic mechanisms in mammalian heart muscle, Fed. Proc. 20: 126, 1961.

143. Sonnenblick, E.H. J. Ross, Jr., J.W. Covell and E. Braunwald, Alternations in resting length-tension relations of cardiac muscle induced by changes in contractile force, Cir. Res. 19: 980, 1966.

144. Sonnenblick, E.H., D. Spiro and T.S. Cottrell, Fine structural changes in heart muscle in relation to length-tension curve, Proc. Nat. Acad. Sci. 49: 193, 1963.

145. Spiro, D. and E.H. Sonnenblick, Comparison of ultrastructural basis of contractile process in heart and skeletal muscle, Cir. Res. (Suppl. 2) 15: 14, 1964.

146. Starling, E.H., The Linacre Lecture on the Law of the Heart, Longmans Green and Co. London, 1918.

147. Streeter, D.D., Jr. and D.L. Bassett, An engineering analysis of myocardial fiber orientation in pig's left ventricle in systole, Anat. Rec. 155: 503, 1966.

148. Streeter, D.D., Jr., H.M. Spotnitz, D.J. Patel, J. Ross, Jr. and E.H. Sonnenblick, Fiber orientation in the canine left ventricle during diastole and systole, Cir. Res. 24: 339, 1969.

149. Stenger, R.J. and D. Spiro, Ultrastructure of mammalian cardiac muscle, J. Biophys. and Biochem. Cytol. 9: 325, 1961.

150. Tanz, R.D. F. Kavaler and J. Roberts, eds., Factors Influencing Myocardial Contractility, Academic Press, London, 1967.

151. Taylor, R.R., Theoretical analysis of the isovolumic phase of left ventricular contraction in terms of cardiac muscle mechanics, Card. Res. 4: 429, 1970.

152. Taylor, R.R., J. Ross, Jr., J.W. Covell and E.H. Sonnenblick, A quantitation analysis of left ventricular myocardial function in the intact sedated dog, Cir. Res. 21: 99 1967.

153. Templeton, G.H., R.R. Ecker and J.H. Mitchell, Left ventricular stiffness during diastole and systole: the influence of changes in volume and inotropic state, Cardiovasc. Res. 6: 95, 1972.

154. Tsakiris, A.G., D.E. Donald, R.E. Sturm and E.H. Wood, Volume, ejection fraction and internal dimensions of left ventricle determined by biplane videometry, Fed. Proc. 28: 1358, 1969.

155. Urschel, C.W., A.H. Henderson and E.H. Sonnenblick, Model dependency of ventricular force-velocity relations: importance of developed pressure, Fed. Proc. 29: 719, 1970a.

156. Urschel, C.W., P.S. Vokonas, A.H. Henderson, A.J. Liedtke, L.D. Horwitz and E.H. Sonnenblick, A comparison of indices of contractility derived from isovolumic force-velocity relation, Circulation Suppl. 42: III-115, 1970b.

157. Van Den Bos, G.C., G. Elzinga, N. Westerhof and M.I.M. Noble, Problems in the use of indices of myocardial contractility, Card. Res. 7: 834, 1973.

158. Vetter, W.R., R.W. Sullivan and K.H. Hyatt, Assessment of quantitative apex cardiography, J. Appl. Physiol. 29: 667, 1972.

159. Wallace, A.G., N.S. Skinner, Jr. and J.H. Mitchell, Hemodynamic determinants of the maximal rate of rise of left ventricular pressure, Am. J. Physiol. 205: 30, 1963.

160. Wildenthal, K., C.L. Skelton and H.N. Coleman, Cardiac muscle mechanics in hypertonic solutions, Am. J. Physiol. 217: 302, 1969.

161. Wolk, M.J., J.F. Keefe, O.H.L. Bing, L.J. Findelstein and H.J. Levine, Estimation of Vmax in auxotonic stystoles from the rate of relative increase of isovolumic pressure: (dP/dt)/kP, J. Clin. Invest. 50: 1276, 1971.

162. Yeatman, L.A., W.W. Parmely and E.H. Sonnenblick, Effects of temperature on series elasticity and contractile element motion in heart muscle, Am. J. Physiol. 217: 1030, 1969.

163. Yeatman, L.A., Jr., W.W. Parmley, C.W. Urschel and E.H. Sonnenblick, Dynamics of contractile elements in isometric contractions of cardiac muscle. Am. J. Physiol. 220: 534, 1971.