DRUGS AND THE MECHANICAL PROPERTIES OF HEART MUSCLE[1,2]

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It can no longer be considered sufficient to describe the action of a drug on myocardial contractility simply as a positive or negative inotropic effect. Far more comprehensive descriptions of changes in the performance of heart muscle are possible, and are probably required if progress is to be made in understanding the modes of action of inotropic drugs. In this review we have attempted a critical appraisal of how techniques and concepts, developed for the study of skeletal muscle, have been used, and can be used, for this purpose. We have limited our consideration almost entirely to work done with preparations of isolated heart muscle (mainly papillary muscles) because we feel that they are best suited to this approach. In many respects, this review is an extension of an earlier and more comprehensive one (8), but it is not an exhaustive survey of the literature for the intervening period; only the references most pertinent to the discussion have been listed.

The study of the mechanical properties of skeletal muscle is oriented around a conceptual model; this contains a contractile component and two elastic components, one in series with the contractile component and one in parallel with it (39). The analysis of tension and length changes that take place in the muscle during simple isometric and isotonic contractions is based on the assumption that these changes result from the interaction of the three components. The properties of an individual component can be determined from measurements made on the muscle under conditions so contrived that interference from the other components is eliminated. This conceptual framework is being applied increasingly to the study of the mechanical properties of cardiac muscle. The component of special interest with respect to the actions of inotropic drugs and other agents is the contractile component. Its properties can be described in terms of the relations among the following variables: the tension in the contractile component (active tension), its velocity of shortening, the muscle length (the length of the contractile component cannot be measured) and the time after excitation. [A change in myocardial contractility may be defined as a change in the performance of the heart that results from a change in these relations (8).] Various combinations

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of two- and three-dimensional diagrams can be used to display the relations among the four variables, but for most purposes we feel these relations are most conveniently described by: (*a*) the relation between muscle length and developed tension; (*b*) the force-velocity relation, which shows how the velocity of shortening is related to the force opposing shortening (i.e. the tension in the contractile component); and (*c*) the time course of activity, which describes how the ability of the contractile component to shorten or bear tension varies with time after excitation. These fundamental relations are familiar from long usage in the field of muscle mechanics, and the nature of each has a very direct relevance to the function of striated muscle as it is now understood (44, 45, 47, 85, 109). Clearly, precise information about these relations and the way in which they may be changed will figure significantly in the development of an understanding of the molecular events involved in contraction, and of the mechanism of action of inotropic drugs. However, the general nature of the relations is also of great importance for understanding the gross behavior of heart muscle.

The Study of the Mechanical Properties of Heart Muscle

Preparations.—The majority of studies on the mechanical properties of isolated heart muscle have been carried out on the papillary muscle of the cat. Other preparations have been used, however, and information on their relative merits is needed. Clark (21) has compared the rate at which the peak tension developed by atrial strips and papillary muscles from a number of commonly used species deteriorated with time under identical experimental conditions. She found that preparations from kittens (0.5 to 1.0 kg) deteriorated far less rapidly than those from rats, guinea pigs, and rabbits. In all the species, papillary muscles deteriorated less rapidly than atrial strips. Preparations made from the atria of larger kittens (>1.5 kg) and cats were rarely satisfactory; they tended to be excessively thick, and often developed conduction blocks.

Although atrial muscle is used commonly in various types of pharmacological studies, it has been used very little in the more refined studies of muscle mechanics. One obvious reason for this is that it is difficult to obtain strips of atrial muscle in which the fibers are uniformly oriented. Another problem is the very prominent parallel elastic component in atrial muscle. However, detailed mechanical studies should certainly not be neglected on the assumption that the properties of atrial muscle will be similar to those of ventricular muscle from the same species, for the two types of muscle differ in the durations of their electrical and mechanical responses, in their interval-strength relations (62), and in their responses to drugs (17, 53). In addition, in some species at least, the cell sizes and transverse tubular systems differ in the two types of muscle (68).

The question of how thick a preparation of isolated heart muscle can be and still function normally was considered in detail in an earlier review (8). The indirect evidence on this point was conflicting, and it was concluded

that there was still not enough information on which to base reliable calculations of critical thickness. The situation has not changed in this respect, though further conflicting indirect evidence has been presented in two recent papers, one suggesting that the critical thickness of cat papillary muscle is rather large (77), the other suggesting that it is very small (30). There seem to be no grounds for believing that the critical thickness of a working muscle may be increased by cooling it (8, 69, 77). Clearly, the critical thickness must depend to some extent on the experimental conditions, but prudence dictates that the thinnest preparations feasible should always be used.

Efforts have been made recently to develop particularly thin preparations of heart muscle. Brady (12, 15) has worked with a thin trabecula (100 μ) of frog atrium, and this preparation does not appear to suffer from the defects found in some larger preparations of atrial muscle. It produces about as much tension per unit cross-sectional area as the best papillary muscles. Gay & Johnson (31) have studied equally thin trabeculae taken from the right ventricle of the rabbit, but these probably consist largely of Purkinje fibers (89), so they are of limited interest from the point of view of contractile behavior. The tension developed by this preparation was not reported.

Stimulation.—The need to drive preparations of isolated heart muscle with electrical stimuli confronts the experimenter with a difficult choice. In order to ensure synchronous excitation of all parts of the muscle, it is desirable to deliver intense stimuli through massive or multiple electrodes, but such stimuli liberate substantial amounts of acetylcholine and norepinephrine from autonomic nerves within the myocardium (e.g. 3, 6, 8, 56, 58, 64, 105, 106). The extent to which these substances accumulate in the muscle will depend on the frequency of stimulation (6, 58), but it can be kept to a minimum by applying threshold stimuli through a small punctate cathode in contact with one edge of the tissue (6). The effects of the liberated acetylcholine are readily prevented by atropine, but very high concentrations of propranolol are required to antagonize the liberated norepinephrine (6). Norepinephrine release can usually be prevented in kittens (but not in guinea pigs) by large doses of reserpine, and it can be prevented by complete extrinsic denervation of the heart (6), though this is scarcely a practical procedure for routine use.

For most purposes, the complications introduced by massive stimulation are more troublesome than the slight asynchrony that results from punctate stimulation. If the conduction velocity is taken as 1 m/sec (42), the time required for the action potential to traverse a normal papillary muscle preparation cannot be more than five to ten msec. Furthermore, the time course of the first isometric contraction after a switch from punctate to massive stimulation is scarcely distinguishable from that of preceding beats (except in preparations that have an abnormally low conduction velocity) (7). Subsequent contractions are, of course, influenced as the liberated neurotransmitters accumulate.

The practice of stimulating preparations with near-threshold stimuli ap-

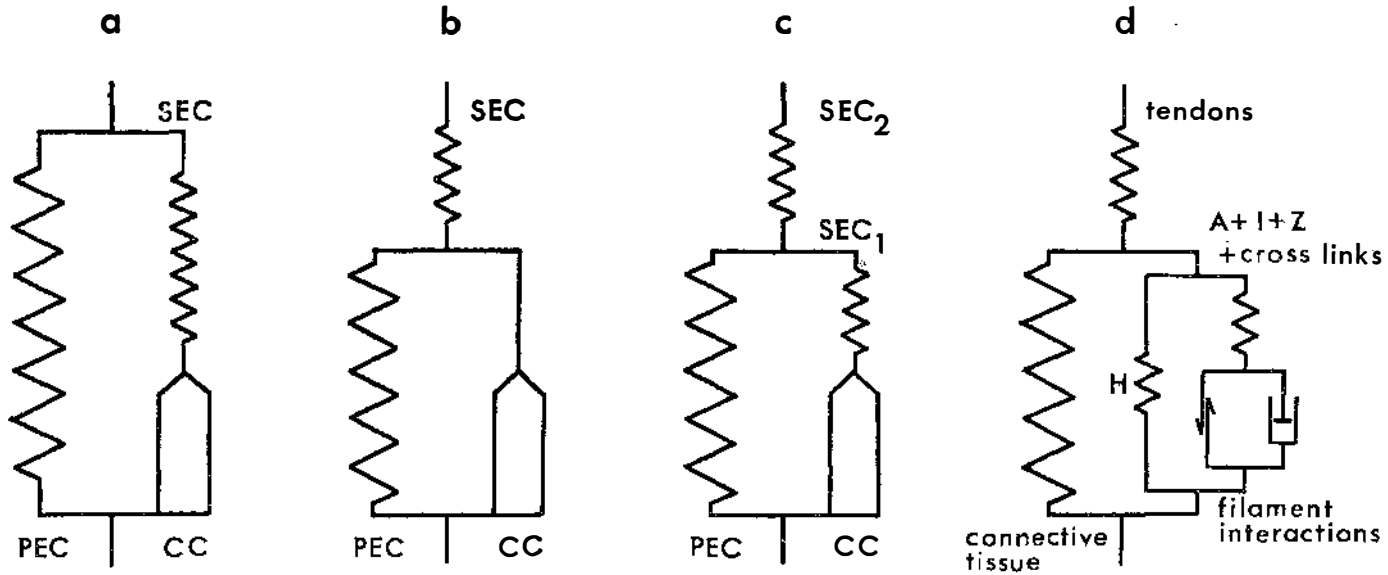

FIGURE 1. Models of muscle. CC = contractile component, SEC = series elastic component, and PEC = parallel elastic component. (a) Three-component model I (39); (b) Three-component model II (4). (c) A four-component model (76). (d) Model with structural identification of components (79). (H = possible connections between actin filaments in the H zone.)

plied through massive electrodes (e.g. 76) combines the worst features of both forms of stimulation. It does not guarantee synchronous excitation because near-threshold stimuli cannot be assumed to excite the tissue at more than one point; however, experiments in which a muscle is stimulated with threshold pulses delivered through either a punctate cathode or massive electrodes have shown that substantially greater amounts of neurotransmitters are liberated by the latter method (7).

Although cardiac muscle normally cannot be made to produce a tetanic contraction when stimulated with repetitive electrical pulses, it resembles frog skeletal muscle (24, 50, 101) and mammalian smooth muscle (22, 23) in that it gives a sustained contraction when placed in an intense field of alternating current of the appropriate frequency and orientation; this is true of both amphibian (34) and mammalian heart muscle (7). It is not yet clear whether AC field stimulation produces its effect simply by depolarizing the cell membrane, or whether more complicated mechanisms are involved. However, this technique holds considerable promise for investigations in which a steady state of activity is desirable.

Long-lasting contractions (generally referred to as contractures) can be evoked in heart muscle by prolonged depolarization of the membrane; this can be accomplished by passing direct current through the tissue (54, 110) or by the application of potassium-rich solutions (9, 73, 75). However, various other interventions that would not be expected to depolarize the cell membrane have also been reported to cause contractures in amphibian heart muscle. Among these are exposure to solutions low in sodium (35, 65) or low in potassium (35, 103), and to solutions containing extremely high concentrations of nicotine (19, 70, 72) or caffeine (37, 71). The action of high concentrations of cardiac glycosides in this respect is well known, though in this case (and perhaps in others) the change produced might better be described as rigor than as contracture (8, 85).

Models of muscle.—The three-component model proposed for skeletal muscle by Hill (39) has been used extensively in the study of cardiac muscle (94). The two possible arrangements of the three components are shown in Figure 1a and 1b. Pringle (79), in a valuable appraisal of the status of models in the study of muscle, emphasized the ambiguous position now occupied by the three-component model. It was originally conceived as a conceptual model or analogue of muscle–that is, a model in which the choice of elements, the number of elements, and their arrangement are determined solely by the requirement that the model should accurately simulate the behavior of the whole muscle–but attempts have been made since to identify components of the model with actual structures in the muscle (48, 76). This approach leads inevitably to the inclusion of additional components that are required in a homologue of muscle, but not necessarily in an analogue (see Fig. 1d). Model-building of this sort is interesting, but the models are too complex to be of much use in the quantitative analysis of the mechanical properties of muscle. In this respect the simple analogue is of great value, and it is impor-

tant to decide what model best simulates the properties of the muscle in which one is interested.

There is no problem in most studies of skeletal muscle because the parallel elastic component can be ignored over the wide range of lengths where the resting tension is zero, and Models I and II then become indistinguishable. However, the choice of the correct model is important in cardiac muscle where problems arise in both isometric and isotonic studies because of the presence of resting tension. In isometric studies, the problem is whether the tension developed by the contractile component (i.e. active tension) can be obtained simply by subtracting the resting tension from the total tension during a contraction. In isotonic studies, where a preload is required to hold the muscle at a given initial length, the problem is whether the force opposing shortening of the contractile component when the muscle begins to shorten can be equated with the afterload on the muscle.

Several independent attempts have been made recently (13, 38, 76) to decide whether either version of the three-component model simulates the behavior of resting and active cardiac muscle during quick releases. The results obtained (38, 76) appear to exclude Model II, but not Model I. (We disagree with the conclusion of Parmley & Sonnenblick (76) that Model I can also be excluded, because the procedure that they used in analyzing their results is inappropriate for a system consisting of non-linear elastic elements.) However, even if we assume that Model I provides a suitable analogue of the muscle, it is clear that in any experimental situation one or more additional components must be present in the position of SEC_2 in Figure 1c in order to account for the properties of the damaged end of the preparation, the connections, and the apparatus. With care, the last two items can be made very small, but the problem of the damaged end of the preparation remains. There is reason to believe that intact heart muscle includes a highly damped elastic component that bears both resting and active tension (8, 29, 32, 97). (In preparations of isolated heart muscle, it seems possible that the damaged end of the preparation, and thread in the connections, might contribute to this.) The fact that this elastic component is highly damped means that it should not interfere greatly in events that take place during a quick release or a single contraction. Therefore, it seems reasonable to use Model I as an analogue of the preparation under these circumstances, provided care is taken to ensure that the stray compliance introduced by the apparatus and the connections (SEC_2 in Fig. 1c) is small compared with that of the series elastic component of the muscle (SEC_1 in Fig. 1c). It follows then that the tension developed by the contractile component can be taken as the difference between the total tension during contraction and the resting tension; similarly, the force opposing shortening of the contractile component at the beginning of an afterloaded isotonic contraction can be taken as the afterload on the muscle.

Force-velocity relation.—The properties of the contractile component vary throughout a contraction, and the general inverse relation that pertains at all

times between the velocity at which it can shorten and the force opposing shortening cannot be described by a single force-velocity curve. However, a single curve (an 'instantaneous' force-velocity curve or IFVC) can be used to define the properties of the contractile component at a given instant during a contraction: its intercept on the velocity axis (V_i) is the velocity at which the contractile component could shorten against zero force; and its intercept on the force axis (P_i) is the tension that the contractile component could bear at constant length [i.e. the 'intensity of the active state' as defined by Hill (39)].

The approach that has been used most commonly in the study of the force-velocity relation of heart muscle is to measure the velocity of shortening of the muscle in a series of afterloaded isotonic contractions against different loads (66, 90–92, 94, 104). If the results obtained are analyzed in terms of Model I (Fig. 1a), the force-velocity curve of the contractile component is obtained by plotting the velocity of shortening against the afterload on the muscle. However, it must be remembered (8) that as the load is increased, it is lifted progressively later after excitation, so each velocity measurement refers to a different time after excitation. The intercept on the velocity axis is the velocity of shortening against zero load, measured about 40 msec after stimulation, and the intercept on the force axis is the peak tension reached in an isometric contraction, measured about 400 msec after stimulation (91). Each point can, therefore, be regarded as belonging to a different IFVC, and the curve joining the points will cut across the family of IFVCs that shows how the force-velocity relation changes with time after excitation. The exact shape of the curve will be critically dependent on the time course of activity, and very misleading results must be expected if a comparison is made between the curves obtained in the presence and absence of an inotropic intervention that alters the time course of activity. We therefore feel very strongly that this method of studying the force-velocity relation has no place in the investigation of the effects of drugs on heart muscle.

A much more satisfactory approach would be to determine instantaneous force-velocity curves at different times during a contraction, and then to examine the effects of drugs or other inotropic interventions on this family of IFVCs. Force-velocity curves that are closely akin to IFVCs can be obtained at different times after stimulation by means of the 'isotonic quick release technique' (48, 49). The essential feature of the technique is that at a predetermined moment during an isometric contraction, the muscle is suddenly allowed to shorten against an afterload which is changed from one release to the next. The muscle first shortens rapidly as a result of the recoil of the stretched series elastic elements, and then more slowly as the contractile component shortens under isotonic conditions. Contrary to the original assumption (48), the velocity of shortening of the contractile component does not settle down to its final steady value immediately after the release, at least in frog skeletal muscle (20, 46, 78). When the records are analyzed in the way described by Jewell & Wilkie (48), the velocity of shortening measured is

the final steady value, so the force-velocity curve describes the properties of the contractile component a short time after the release, rather than at the time of the release. This technique does not allow a direct measurement of P_1, but an estimate of this can be made by an extrapolation from the experimental data (49). The force-velocity curve obtained in this way is the closest approach possible to the measurement of an IFVC with the techniques currently available. Measurements of this type have been made on heart muscle in the last few years (27, 92, 95), but there has been only one report (92) of the effect of an inotropic drug on cardiac muscle in which IFVCs have been determined. The reason the force-velocity curve, obtained by the isotonic quick release technique, is not strictly an IFVC is that the velocity measurements are made at slightly different contractile component lengths. The release records can, of course, be analyzed so that all the velocity measurements refer to the same length (27), but the curve obtained is still not an IFVC because the contractile component reaches the same length at different times after the release.

Time course of activity.—The family of IFVCs that can be obtained by releasing the muscle at different times during an isometric contraction gives a good indication of how the ability of the contractile component to shorten or bear tension varies with time after excitation. If the IFVCs in such a family are similar in shape, as they are in frog skeletal muscle (49), then the way in which they change with time can be described fairly accurately by two graphs showing how P_i (the force intercept) and V_i (the velocity intercept) vary with time. Conflicting reports have appeared regarding the way in which the IFVCs change with time in cat papillary muscle. Sonnenblick (92) found that the shape of the IFVC remained unchanged–the curve simply expanded and then collapsed symmetrically with respect to the origin. However, in a later paper (95), he has shown a family of IFVCs in which the shape of the curves varied with time after excitation; in fact when releases were made 250 msec or more after excitation (27° C), the curves obtained were S-shaped. Unfortunately, the author has not related this finding to the results reported in his earlier paper. Independent measurements by Edman, Grieve & Nilsson (27) on rabbit papillary muscle have been interpreted by them as showing that the IFVC did not change in shape when releases were made at different times after stimulation, but close inspection of these results shows that they can be construed as supporting Sonnenblick's (95) finding that the IFVC becomes S-shaped when releases are made 200 msec or more after excitation.

In several recent papers (11, 27, 28, 92, 95), the isotonic quick release technique has been used to determine how the 'post-release velocity' (11) varies with time after excitation when the force opposing shortening is constant. The post-release velocity of shortening against a small load has been taken as an approximation of V_i, and it has been argued (27, 92) that changes in this measurement reflect changes in the 'intensity of the active state,' which Hill (39) defined as the tension that the contractile component

can just bear at a given instant without lengthening or shortening (note that P_i is the same thing). However, if the IFVC changes its shape with time after excitation, then it is clear that the post-release velocity of shortening against a small load may give a very poor indication of what is happening to P_i, and there is certainly no justification for using the expression 'intensity of active state' in referring to such a measurement. Nevertheless, it does provide a valid index of the activity of the muscle, and the way in which it has been shown to vary with time after excitation indicates that activity is slow in onset in cardiac muscle (11, 27, 28, 92, 95). This has been confirmed by Brady (11), who has studied the onset of activity (he has used the term 'contractility' in this sense) by means of the Hill 'quick stretch' technique (39) and a modified version of the Ritchie 'quick release' technique (84). Brady (14) has also developed an elegant modification of the 'quick stretch' method which involves 'clamping' the length of the contractile component in the active muscle; this has enabled him to determine the variation of P_i with time during a single contraction. The results of all these studies show that activity in the papillary muscle does not reach its maximum until shortly before the peak of an isometric contraction, and that it then declines without any intervening plateau of maximum activity.

In our opinion, graphs showing how V_i and P_i vary with time after excitation would provide a useful, though admittedly incomplete, picture of the way in which the IFVCs change with time. At a given instant after excitation, the activity of the muscle would be indicated by the corresponding values of P_i and V_i, and the effects of various inotropic interventions on the time course of activity could be described in terms of the changes in maximum P_i and maximum V_i, time to maximum P_i and time to maximum V_i, and the total duration of activity. The isotonic quick release technique allows accurate determination of the high velocity end of the IFVC and V_i but it is less reliable at the high force end. It is not clear how the experimental data should be extrapolated to obtain a value for P_i if the IFVC is S-shaped (as it may be when measured 200 msec or more after excitation). The answer to this problem may be provided by Brady's new method (14), which can be used to determine how P_i varies during a single contraction.

The Influence of Muscle Length

Resting muscle.—The subject of the extensibility of heart muscle at rest was considered in detail in an earlier review (8), in which it was concluded that there was no convincing evidence that any drug alters resting extensibility without producing rigor. There seems to be no reason to alter that conclusion, but because recent reports of 'variable diastolic compliance' (5, 41, 59, 86) have been the subject of heated debate at various meetings, and have stimulated a series of rebuttals (29, 32, 96, 97), some comment on the matter is in order here.

The controversy seems to have arisen largely because of differences in the

interpretation of the terms "diastolic" and "compliance" which have been used freely without adequate definition. It is crucial for this discussion to distinguish clearly between diastole and rest. Diastole is a period defined by hemodynamic events (107); it begins with the closure of the outlet valve of the ventricle, and it always includes a period in which activity in the ventricular muscle is still waning. If the heart rate is low, the muscle may be completely relaxed in the latter part of diastole, but if partial fusion of contractions occurs, there will be no time at which the muscle is fully relaxed, and any intervention that alters the degree of fusion will alter the end-diastolic length-tension relation of the muscle. The term "diastolic" has been used by many workers in connection with studies on preparations of isolated heart muscle, a context in which it is not very meaningful because the hemodynamic events defining the onset of diastole do not occur. However, it is reasonable and convenient to use the term "end-diastolic" to refer to the moment just before the onset of contraction, provided that the distinction between end-diastolic and relaxed or resting is always kept in mind. The term "compliance" has also been used very differently by various workers. In some cases (59, 86), it appears to have been used to refer to the relation between length and tension at any given moment; whereas in others (97), it seems to have been applied to this relation solely under equilibrium conditions. [Feigl (29) has used extensibility in this sense.] The difference between these interpretations is crucial in that under the first, the compliance of the muscle would be considered to change as a result of stress relaxation or creep, whereas under the second, it would not.

These semantic problems make it pointless to debate the question of whether diastolic compliance is variable. No one would deny that nerve stimulation, the administration of various drugs, and other similar interventions change the end-diastolic length-tension relation of heart muscle, but there is no convincing evidence that these interventions change the mechanical properties of resting heart muscle. As Feigl (29) has pointed out, the observations that have been claimed to demonstrate variations in diastolic compliance can be accounted for in terms of the operation of four well-established factors: (*a*) partial fusion of contractions; (*b*) alterations in the shape of intact cardiac chambers (e.g., due to the influence of the pressure in one ventricle on the shape of the other); (*c*) viscous effects (stress relaxation and creep); and (*d*) aftercontractions in preparations of isolated heart muscle. The subject of aftercontractions is a fascinating one of great relevance to theories of excitation-contraction coupling, but a detailed examination of the recent literature (16, 51, 52, 54, 80–83, 87) on this subject is beyond the scope of this review. The other three factors were discussed in detail in an earlier review (8); however, we feel that there are some additional points worth noting regarding viscous effects in heart muscle.

It has commonly been observed (8, 29, 32, 63, 97) that under isometric (or isochoric) conditions, large increases in the strength of contraction,

whatever their cause, are accompanied by slight decreases in end-diastolic tension (or pressure). If the inotropic intervention is withdrawn the end-diastolic tension returns to its original level after a few beats, and if contractions are stopped the resting tension creeps up toward an equilibrium level. These observations suggest that there is a damped elastic component that bears both resting and active tension; they do not indicate that the inotropic intervention alters the properties of that component or of any other in the resting muscle (63). Similarly, damping of part of the parallel elastic component leads to alterations in the end-diastolic length-tension relation when the properties of the muscle are examined under freeloaded isotonic conditions. After each contraction the muscle creeps the last small fraction of the way toward its equilibrium length (29), and it does not reach this length unless the interval between contractions is very long. Presumably, this creep takes place in part of the parallel elastic component that is highly damped, and agents that increase the amount of unloading of this component during contraction (by increasing the amount of shortening of the contractile component) may increase the time required for the muscle to regain its equilibrium length during relaxation [for an illustration, see (29) Fig. 7]. Unless the interval between contractions is very long, there will be an alteration in the end-diastolic length-tension relation, but again this need not signify any alteration in the properties of the resting muscle. A given agent with a positive inotropic effect may decrease the end-diastolic tension in a muscle contracting isometrically (apparently increasing diastolic compliance), yet decrease the end-diastolic length when the same muscle is lightly loaded and allowed to contract isotonically (apparently decreasing diastolic compliance). This seeming paradox is readily understandable in terms of the existence of damped elastic components, but it is difficult to explain otherwise.

Active muscle.—Spiro & Sonnenblick (98, 100) have attempted to relate tension development in cat papillary muscle to sarcomere length by first defining the length of a muscle with respect to L_{max}, the length at which maximum tension development occurs, and then fixing it in the resting state. (Note that sarcomere length in resting muscle provides an unreliable guide to the sarcomere length during activity.) In muscles fixed at L_{max}, the sarcomere length was about 2.2 μ, and it changed in proportion to the change in muscle length over the range 1.7 to 2.2 μ. However, when muscles were stretched beyond L_{max}, the sarcomere length did not increase in proportion to the change in muscle length, and the maximum sarcomere length that could be obtained was 2.6 μ (99). Although slippage of columns of cells might explain the lack of correlation between increases of muscle length and increases of sarcomere spacing (99), it would not necessarily explain the decline in active tension observed under these circumstances. Clearly, this is a point that needs to be explored further before it can be assumed that in cardiac muscle the relation between active tension and muscle length can be explained simply in terms of the sliding filament mechanism.

Gay & Johnson (31) have obtained evidence that the situation is even more complicated in preparations from the rabbit ventricle. They used a high-power optical system to determine the relation between sarcomere length and muscle length in living trabeculae carnae. Many of the fibers in the preparation were buckled, even in the presence of resting tension, and they found a wide variation in the sarcomere spacing in different parts of the muscle. Furthermore, they could find no predictable relation between the overall length of the strand and the length of a given sarcomere. Rabbit papillary muscles fixed at known muscle lengths with respect to L_{max} also showed buckling of fibers in the center of the preparation at lengths below L_{max}.

The influence of muscle length on the force-velocity curves obtained from simple afterloaded isotonic contractions was studied by Sonnenblick (90, 91). He assumed that the force opposing shortening of the contractile component was the total load on the muscle [an assumption that has been justifiably criticized by Ullrick (104) and by Hefner & Bowen (38)] and arrived at the conclusion that the maximum velocity of shortening against zero force was unaltered by a change of muscle length. However, if his results are interpreted according to Model I (Fig. 1a), they indicate that the maximum velocity of shortening is decreased when the length of the muscle is decreased below L_{max}, as it is in frog skeletal muscle (2, 33, 67). Sonnenblick (92, 93) has also obtained families of force-velocity curves for various muscle lengths, each curve determined by measuring the velocity of shortening of the muscle at a specific length during a series of simple afterloaded contractions against various loads. He referred to these as 'instantaneous' curves; however, it is important to note that this use of the word 'instantaneous' refers to the length of the muscle, and not to time.. The points on each curve were obtained at widely different times after stimulation, so these curves are quite different from the IFVCs described previously. Sonnenblick (93) has claimed that the way in which these curves are affected by changes of muscle length supports his earlier conclusion (90, 91) that the maximum velocity of shortening is unchanged, but his results lead to the opposite conclusion if they are interpreted in terms of Model I.

The effect of muscle length on the time course of activity has not been studied specifically. It has been widely reported that stretching the muscle has no effect on the time course of an isometric contraction (26, 88, 90), but there is evidence that it prolongs the contraction in cardiac muscle (7, 8, 11, 82) as it does in skeletal muscle (36, 49). Brady (11) has shown that the effect of stretching the muscle on the peak tension and time-to-peak is the same when the muscle is stretched before stimulation or during the early part of the tension rise that follows stimulation. This interesting observation shows that the tension developed by the muscle is a function of the muscle length at the time when activity reaches its maximum, not the length at which the muscle is stimulated.

The Influence of Inotropic Interventions

Although detailed information about the effects of inotropic interventions on isolated heart muscle can be obtained only through the use of fairly sophisticated techniques such as those discussed earlier, it is possible to deduce a good deal about these effects from studies of simple isometric contractions. Unfortunately, we must still rely very heavily on such qualitative deductions. None of the inotropic interventions examined so far has an appreciable influence on the properties of the passive elastic components of heart muscle (1, 28, 29, 63, 76, 91). Therefore, it seems reasonable to attribute changes in the isometric myogram to alterations in the properties of the contractile component until proven otherwise. The effects of an intervention on the following features are worth noting:

(*a*) Rise of tension. If the tension rises faster in the early part of an isometric contraction, the contractile component must be shortening faster. This indicates that V_i increases more rapidly after excitation, but it does not follow that maximum V_i (which is not reached until shortly before the peak of the isometric contraction) is necessarily increased as well.

(*b*) Peak tension. The peak tension is less than maximum P_i and it is reached later after excitation (14). Small changes in peak tension are difficult to interpret, but a large increase signifies an increase in maximum P_i.

(*c*) Time-to-peak and total duration of contraction. Small changes are again difficult to interpret, but large changes indicate similar alterations in the time to maximum activity and the duration of activity.

Interval between contractions.—The interval-strength relation of heart muscle has been reviewed in detail elsewhere (62). In most types of ventricular muscle, the effects of reducing the interval between contractions on the form of the isometric myogram are similar: the peak tension and the rate of rise of tension are increased, and the time-to-peak and the total duration of the contraction are reduced. These effects are seen when the interval between contractions is varied over a wide range, and the effects on the time course are particularly marked when the interval is made very short. (The interval-strength relation is very different in most types of mammalian atrial muscle, and the influence of frequency on the duration of contraction is much less pronounced.) Edman & Nilsson (28) have shown that when the frequency of contraction of the rabbit papillary muscle (30° C) was increased from 30 to 75 per min, the post-release velocity of shortening against a small load (which approximates V_i) reached its maximum value earlier, and then declined sooner. Since their measurements have been converted into percentages in a way that makes the original numbers irretrievable, it is not clear whether maximum V_i is increased; however, measurements of the maximum velocity of shortening in simple isotonic contractions with zero afterload indicate that it is (1, 28, 90, 91). The large increases in isometric tension development imply that maximum P_i must increase with frequency over a wide range. At very high frequencies, tension development may be limited by an abbrevia-

tion of the active state despite a continued increase in V_i in the early part of contraction. It seems likely that P_i increases concomitantly with V_i under these conditions, though there is no direct information on this point. (The force-velocity curves determined by Sonnenblick (91) with simple afterloaded contractions led him to differentiate between a 'force Treppe' and a 'velocity Treppe,' but these terms have no relevance when instantaneous force-velocity curves are considered.)

Change of temperature.—At stimulus frequencies within the range commonly used, the effect of raising the temperature of preparations of isolated heart muscle is to increase the rate of rise of tension in an isometric contraction, but to decrease the peak tension, the time-to-peak, and the total duration of the contraction (8, 66, 102). The force-velocity curves obtained from simple afterloaded isotonic contractions change in three respects (66, 92) when the temperature is raised: the curve intersects the axes at a higher velocity (suggesting an increase in maximum V_i) and at a lower force (because of the reduction in peak tension), and the curve tends to become concave towards the origin. Mashima & Matsumura (66), who made detailed studies of the influence of temperature on frog ventricular muscle strips, have shown that the duration of activity, as determined by the Ritchie method (84), is decreased when the temperature is raised, but with a much greater temperature coefficient than that of the action potential duration. These workers also found that the tension developed in a potassium contracture, which they used as a measure of maximum P_i, had a temperature coefficient similar to that of the peak tension. This suggests that the decrease in peak tension produced by raising the temperature is not due simply to the reduction in time available for tension development, as it appears to be in frog skeletal muscle (40).

Catecholamines.—Under most circumstances norepinephrine and other catecholamines increase the rate of rise of tension in isometric contractions of heart muscle, and reduce both the time to peak tension and the total duration of the contraction. (The latter effects are less prominent in atrial than in ventricular muscle.) Detailed information on the individual dose-response relations of the various effects would be useful. The peak tension is usually greatly increased by catecholamines, but under certain experimental conditions it may be unchanged (10, 12) or even decreased (55), because the increase in the rate of tension development is offset or even outweighed by the abbreviation of the active state. This is most likely to occur when catecholamines are studied in the presence of another inotropic intervention (e.g., raised calcium concentration). Measurements of the post-release velocity of shortening against a small load (95) indicate that in cat papillary muscle, norepinephrine increases maximum V_i, and decreases both the time to maximum V_i and the total duration of activity. The marked increases in peak tension usually produced by catecholamines make it seem virtually certain that maximum P_i is increased as well. Force-velocity curves obtained from simple afterloaded contractions (90–92) provide no additional information on

this point, because the intercepts on the force axis are the corresponding peak tensions produced in isometric contractions. Sonnenblick (92) has used the isotonic quick release technique to obtain IFVCs in the presence and the absence of norepinephrine, but the curves that have been plotted do not show the effect of the drug on P_i at the time of measurement, nor do they give an indication of the effect on maximum P_i.

Cardiac glycosides.—Most workers have found that cardiac glycosides cause very little change in the time to peak tension or the total duration of the isometric contraction curve (26, 60, 61, 88, 95). There is some suggestion, however, that large degrees of glycoside effect may be associated with an appreciable abbreviation of the contraction (26, 61). Sonnenblick (95) measured the post-release velocity of shortening against a small load at various times after excitation, and the results suggest that in cat papillary muscle 2.5×10^{-6} *M* strophanthidin increased the maximum V_i, while decreasing slightly the time to maximum V_i and prolonging slightly the total duration of activity. Rather different results were obtained by Edman & Nilsson (28), who studied the effect of 5×10^{-7} *M* ouabain on the rabbit papillary muscle. They measured the post-release velocity of shortening against a very small load, so their results can be taken as a good estimate of V_i. They found that this concentration of ouabain substantially reduced the time to peak tension of the isometric contraction, the time to maximum V_i, and the total duration of activity. (The effect on the maximum value of V_i is not clear from their paper, because all measurements of V_i are expressed as percentages of the maximum V_i under given conditions.) To what extent the differences in the effects reported in these papers (28, 95) may be due to the differences in preparation and drug used, the force opposing shortening during the isotonic releases, and concentration and time of exposure to the drug is not clear, but this important point needs to be settled. The fact that the cardiac glycosides increase the tension developed in an isometric twitch without much alteration in the time-to-peak indicates that they probably increase maximum P_i. However, there is no direct evidence on this point.

Calcium and sodium concentrations.—Raising the calcium concentration in the solution bathing a preparation of isolated heart muscle increases the tension developed in an isometric contraction. In amphibian heart muscle, the tension developed depends on the ratio of the calcium concentration to the square of the sodium concentration (65, 108). Changes in peak tension brought about by altering the calcium concentration are not accompanied by any marked changes in the time-to-peak or in the total duration of the contraction; Reiter (82) reported that in guinea pig papillary muscle the time-to-peak may be increased or decreased slightly, depending on the range of calcium concentrations examined and on other experimental details. Sonnenblick (90) has shown that the maximum velocity of shortening of the cat papillary muscle against zero afterload is increased when the calcium concentration is raised, so V_i is increased in the early part of the contraction. The effect on maximum V_i is not known (the isotonic quick release technique

has not yet been used to obtain information on this). The increase in peak tension in the absence of any appreciable change in peak time suggests that maximum P_i is increased, especially when the change in peak tension is large. Quantitative investigations of the effect of altering the calcium concentration (or the Ca^{++}:Na^{+} ratio mentioned above) on the force-velocity relation of heart muscle would be most valuable.

Other interventions.—There is a need for quantitative studies of the effects on the mechanical properties of heart muscle of many other interventions known to alter the form of the isometric myogram in interesting ways. For example, caffeine and other xanthine derivatives greatly prolong the time course of activity in cardiac muscle (25, 74). They also increase the maximum rate of rise of tension in isometric contractions, but unlike most agents with this action they delay the attainment of that maximum (74). Strontium ions have effects very much like those of caffeine (82). Choline esters and adenosine, agents that markedly abbreviate the action potential in atrial muscle, may decrease the time to peak tension somewhat, but at body temperature their main effects on the isometric myogram are to decrease the peak tension and the rate of rise of tension (25, 43, 60). At reduced temperatures, the effects of acetylcholine on the time-to-peak are more pronounced (18). Progressive increases in osmotic pressure first increase the rate of rise of tension without much change in peak time, and then decrease the rate of rise with a prolongation of the time to peak (57). The possibility that changes in the properties of the series elastic component may result from changes in osmotic pressure, as has been shown to be the case in skeletal muscle (48), must be taken into account in further studies of these effects.

LITERATURE CITED

1. Abbott, B. C., Mommaerts, W. F. H. M., *J. Gen. Physiol.*, **42**, 533–51 (1959)
2. Abbott, B. C., Wilkie, D. R., *J. Physiol. (London)*, **120**, 214–23 (1953)
3. Amory, D. W., West, T. C., *J. Pharmacol.*, **137**, 14–23 (1962)
4. Aubert, X., *Le couplage énergétique de la contraction musculaire* (Thèse d'agrégation, Université Catholique de Louvain, Editions Ascia, Brussels, 1956)
5. Bartlestone, H. J., Scherlag, B. J., Hoffman, B. F., Cranefield, P. F., *Bull. N. Y. Acad. Med.*, **41**, 616–45 (1965)
6. Blinks, J. R., *J. Pharmacol. Exptl. Therap.*, **151**, 221–35 (1966)
7. Blinks, J. R. (Unpublished observations)
8. Blinks, J. R., Koch-Weser, J., *Pharmacol. Rev.*, **15**, 531–99 (1963)
9. Bommert, C., *Z. Biol.*, **113**, 58–64 (1961)
10. Brady, A. J., *Proc. Intern. Pharmacol. Meeting, 2nd, Prague, 1963*, Vol. 5, 15–23 (Pergamon Press, Oxford, 1964)
11. Brady, A. J., *J. Physiol. (London)*, **184**, 560–80 (1966)
12. Brady, A. J., *Ann. N. Y. Acad. Sci.*, **139**, 661–72 (1967)
13. Brady, A. J., *Physiologist*, **10**, 75–86 (1967)
14. Brady, A. J., *Physiologist*, **10**, 130 (1967)
15. Brady, A. J., Tan, S. T., *J. Gen. Physiol.*, **49**, 781–91 (1966)
16. Braveny, P., Šumbera, J., Kruta, V., *Arch. Intern. Physiol.*, **74**, 169–78 (1966)
17. Buccino, R. A., Sonnenblick, E. H., Cooper, T., Braunwald, E., *Circulation Res.*, **19**, 1097–1108 (1966)

18. Burgen, A. S. V., Terroux, K. G., *J. Physiol.* (*London*), **120**, 449–64 (1953)
19. Cheney, R. H., *J. Pharmacol.*, **54**, 42–52 (1935)
20. Civan, M. M., Podolsky, R. J., *J. Physiol.* (*London*), **184**, 511–34 (1966)
21. Clark, A. (Unpublished)
22. Csapo, A., *Am. J. Physiol.*, **177**, 348–54 (1964)
23. Csapo, A., Goodall, M. C., *J. Physiol.* (*London*), **126**, 384–95 (1954)
24. Csapo, A., Wilkie, D. R., *J. Physiol.* (*London*), **134**, 497–514 (1956)
25. De Gubareff, T., Sleator, W., Jr., *J. Pharmacol. Exptl. Therap.*, **148**, 202–14 (1965)
26. Dudel, J., Trautwein, W., *Cardiologia*, **25**, 344–62 (1954)
27. Edman, K. A. P., Grieve, D. W., Nilsson, E., *Pflügers Arch. Ges. Physiol.*, **290**, 320–34 (1966)
28. Edman, K. A. P., Nilsson, E., *Acta Physiol. Scand.*, **63**, 507–8 (1965)
29. Feigl, E., *Circulation Res.*, **20**, 447–58 (1967)
30. Fisher, V., Lee, R. J., Marlon, A. M., Kavaler, F., *Circulation Res.*, **20**, 520–33 (1967)
31. Gay, W. A., Johnson, E. A., *Circulation Res.*, **21**, 33–43 (1967)
32. Gilmore, J. P., Cingolani, H. E., Taylor, R. R., Powell, W. J., *Am. J. Physiol.*, **211**, 1227–31 (1966)
33. Gordon, A. M., Huxley, A. F., Julian, F. J., *J. Physiol.* (*London*), **184**, 170–92 (1966)
34. Goto, M., Kawata, H., Ozono, I., Hamasaki, B., Sakamoto, C., *Japan. J. Physiol.*, **17**, 348–63 (1967)
35. Hajdu, S., *Am. J. Physiol.*, **174**, 371–80 (1953)
36. Hartree, W., Hill, A. V., *J. Physiol.* (*London*), **55**, 389–411 (1921)
37. Heathcote, R. St. A., *J. Pharmacol.*, **16**, 327–44 (1920)
38. Hefner, L. L., Bowen, T. E., *Am. J. Physiol.*, **212**, 1221–27 (1967)
39. Hill, A. V., *Proc. Roy. Soc.* (*London*) *Ser. B*, **136**, 399–420 (1949)
40. Hill, A. V., *Proc. Roy. Soc.* (*London*) *Ser. B*, **138**, 349–54 (1951)
41. Hoffman, B. F., Bartlestone, H. J., Cranefield, P. F., *Bull. N. Y. Acad. Med.*, **41**, 616–45 (1965)
42. Hoffman, B. F., Cranefield, P. F., *Electrophysiology of the Heart* (McGraw-Hill, New York, 323 pp., 1960)
43. Hollander, P. B., Webb, J. L., *Circulation Res.*, **5**, 349–53 (1957)
44. Huxley, A. F., *Progr. Biophys.*, **7**, 255–318 (1957)
45. Huxley, A. F., *Ann. Rev. Physiol.*, **26**, 131–52 (1964)
46. Huxley, A. F., Armstrong, C. M., Julian, F. J., *J. Physiol.* (*London*), **186**, 26P (1966)
47. Huxley, H. E., in *The Cell*, 365–481 (Brachet, J., Mirsky, A. E., Eds., Academic Press, New York, 511 pp., 1960)
48. Jewell, B. R., Wilkie, D. R., *J. Physiol.* (*London*), **143**, 515–40 (1958)
49. Jewell, B. R., Wilkie, D. R., *J. Physiol.* (*London*), **152**, 30–47 (1960)
50. Katz, B., Lou, C. H., *J. Physiol.* (*London*), **106**, 30P (1947)
51. Katzung, B., *J. Cellular Comp. Physiol.*, **64**, 103–14 (1964)
52. Kaufmann, R., Fleckenstein, A., Antoni, H., *Arch. Ges. Physiol.*, **278**, 435–46 (1963)
53. Kaumann, A. J., Blinks, J. R., *Pharmacologist*, **9**, 248 (1967)
54. Kavaler, F., *Am. J. Physiol.*, **197**, 968–70 (1959)
55. Kavaler, F., Morad, M., *Circulation Res.*, **18**, 492–501 (1966)
56. Kennedy, B. L., West, T. C., *J. Pharmacol. Exptl. Therap.*, **157**, 149–58 (1967)
57. Koch-Weser, J., *Am. J. Physiol.*, **204**, 957–62 (1963)
58. Koch-Weser, J., *J. Pharmacol. Exptl. Therap.*, **150**, 184–89 (1965)
59. Koch-Weser, J., *Circulation Res.*, **18**, 330–43 (1966)
60. Koch-Weser, J., Berlin, C. M., Jr., Blinks, J. R., *Proc. Intern. Pharmacol. Meeting, 2nd, Prague*, 1963, Vol. 5, 63–72 (Pergamon Press, Oxford, 1964)
61. Koch-Weser, J., Blinks, J. R., *J. Pharmacol.*, **136**, 305–17 (1962)
62. Koch-Weser, J., Blinks, J. R., *Pharmacol. Rev.*, **15**, 601–52 (1963)
63. Leach, J. K., Alexander, R. S., *Am. J. Physiol.*, **209**, 935–40 (1965)
64. Lewartowski, B., *Nature* (*London*), **199**, 76–77 (1963)
65. Luttgau, H. C., Niedergerke, R., *J. Physiol.* (*London*), **143**, 486–505 (1958)
66. Mashima, H., Matsumura, M., *Japan. J. Physiol.*, **14**, 423–38 (1964)
67. Matsumoto, Y., *J. Gen. Physiol.*, **50**, 1125–37 (1967)
68. McNutt, N. S., Fawcett, D. W., *J. Cell Biol.* **35**, 90A (1967)
69. Monroe, R. G., Strang, R. H. La-

Farge, C. G., Levy, J., *Am. J. Physiol.*, 67–73 (1964)
70. Nayler, W. G., *Am. J. Physiol.*, **205**, 890–96 (1963)
71. Nayler, W. G., *Am. J. Pnysiol.*, **204**, 969–74 (1963)
72. Nayler, W. G., Emery, P. F., *Arch. Intern. Pharmacodyn.*, **153**, 283–89 (1965)
73. Niedergerke, R., *J. Physiol. (London)*, **134**, 584–99 (1956)
74. Olson, C. B., Bravený, P., Blinks, J. R., *Pharmacologist*, **9**, 223 (1967)
75. Otsuka, M., Nonomura, Y., *J.Pharmacol.*, **141**, 1–5 (1963)
76. Parmley, W. W., Sonnenblick, E. H., *Circulation Res.*, **20**, 112–23 (1967)
77. Pool, P. E., Chandler, B., Sonnenblick, E. H., Braunwald, E., *Pharmacologist*, **9**, 212 (1967)
78. Podolsky, R. J., *Nature* **188**, 666–68 (1960)
79. Pringle, J. W. S., *Symp. Soc. Exptl. Biol.*, **14**, 41–68 (1960)
80. Reiter, M., *Arch. Exptl. Pathol. Pharmakol.*, **242**, 497–507 (1962)
81. Reiter, M., *Proc. Intern. Pharmacol. Meeting, 1st, Stockholm, 1961*, Vol. 3, 265–79 (Pergamon Press, Oxford, 1963)
82. Reiter, M., *Proc. Intern. Pharmacol. Meeting, 2nd, Prague*, 1963, Vol. 5, 25–42 (Pergamon Press, Oxford, 1964)
83. Reiter, M., Schöber, H. G., *Arch. Exptl. Pathol. Pharmakol.*, **250** 21–34 (1965)
84. Ritchie, J. M., *J. Physiol. (London)*, **126**, 155–68 (1954)
85. Sandow, A., *Physiol. Rev.*, **17**, 265–320 (1965)
86. Scherlag, B. J., Bartlestone, H. J., Wyte, S. R., Hoffman, B. F., *Nature*, **209**, 1246–48 (1966)
87. Schmidt, R. F., Chang, J. J., *Arch. Ges. Physiol.*, **272**, 393–99 (1961)
88. Siegel, J. H., Sonnenblick, E. H., *Circulation Res.*, **12**, 597–610 (1963)
89. Sommer, J. R., Johnson, E. A., *J. Cell Biol.*, **33**, 103–29 (1967)
90. Sonnenblick, E. H., *Am. J. Physiol.*, **202**, 931–39 (1962)
91. Sonnenblick, E. H., *Federation Proc.*, **21**, 975–90 (1962)
92. Sonnenblick, E. H., *Federation Proc.*, **24**, 1396–1409 (1965)
93. Sonnenblick, E. H., *Circulation Res.*, **16**, 441–51 (1965)
94. Sonnenblick, E. H., in *The Myocardial Cell*, 173–250 (Briller, S. A., Conn, H. L., Eds., Univ. Pennsylavnia Press, Philadelphia, 374 pp., 1966)
95. Sonnenblick, E. H., *J. Gen. Physiol.*, **50**, 661–76 (1967)
96. Sonnenblick, E. H., Frommer, P. L., Braunwald, E., *Bull. N. Y. Acad. Med.*, **41**, 554–59 (1965)
97. Sonnenblick, E. H., Ross, J., Covell, J. W., Braunwald, E., *Circulation Res.*, **19**, 980–88 (1966)
98. Sonnenblick, E. H., Spiro, D., Cottrell, T. S., *Proc. Natl. Acad. Sci. U.S.*, **49**, 193–200 (1963)
99. Spiro, D., in *The Myocardial Cell*, 13–61 (Briller, S. A., Conn, H. L., Eds., Univ. Pennsylvania Press, Philadelphia, 374 pp., 1966)
100. Spiro, D., Sonnenblick, E. H., *Symp. Structure and Function of Heart Muscle, Circulation Res.*, Suppl. II, **15**, 14–36 (1964)
101. Sten-Knudsen, O., *J. Physiol. (London)*, **125**, 396–404 (1954)
102. Šumbera, J., Bravený, P., Kruta, V., *Arch. Intern. Physiol. Biochim.*, **75**, 261–76 (1967)
103. Thomas, L. J., Jr., *J. Gen. Physiol.*, **43**, 1193–1206 (1960)
104. Ullrick, W. C., *Am J. Physiol.*, **206**, 1285–90 (1964)
105. Vincenzi, F. F., West, T. C., *J. Pharmacol.*, **141**, 185–94 (1963)
106. West, T. C., in *The Specialised Tissues of the Heart*, 81–94 (Elsevier Publ. Co., Amsterdam, 1961)
107. Wiggers, C. J., *Am. J. Physiol.*, **56**, 415–59 (1921)
108. Wilbrandt, W., Koller, H., *Helv. Physiol. Acta*, **6**, 208–21 (1948)
109. Wilkie, D. R., *Ann. Rev. Physiol.*, **28**, 17–38 (1966)
110. Wood, E. H., Heppner, R. L., Weidmann, S., *Federation Proc.*, **26**, 381 (1967)

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