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Functional comparison of the right anterior papillary muscle in isolated failing and normal canine hearts.

LeRoy D. Claycomb
Iowa State University

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by

LeRoy D. Claycomb

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ABSTRACT

Force-velocity relations were studied in the right anterior papillary muscle from acutely failing and normal canine hearts. Acute failure resulted from attempts to isolate a working canine heart having a normal flow pattern, i.e. from right heart to left and exiting through an "aorta." The examination of the contractile state of the failing myocardium was conducted in order to determine if a decrease in contractility or a deficiency in the perfusion system was responsible for failure. The results of this study indicated there were no significant differences in the responses of failing and non-failing cardiac muscle. The responses to afterload, preload, increased frequency, and l-norepinephrine were similar and comparisions of the initial velocities of shortening and the time intervals of contraction were not statistically significant. The importance of these results and their relevance to changes in V_{MAX} are also discussed.

INTRODUCTION

The force-velocity relation or the dependence of contractile force on the velocity of isotonic shortening is the most characteristic property of active muscle. It provides an accurate and reproducible index of a muscle's ability to develop force and shorten and, in addition, relates the initial velocity of shortening (the constant velocity attained early in contraction) to the internal force produced by a given load (26, 42).

This relation was identified and confirmed in studies using skeletal muscle (17, 26) but similar studies with cardiac tissue were not conducted at that time because a suitable isolated tissue preparation was not available. The development of the papillary muscle technique by Cattell and Gold (6) corrected this situation, however, and subsequent investigators (1, 49) were able to illustrate the characteristic dependence of force on velocity in mammalian heart muscle. These findings, coupled with the observation that papillary muscle possesses the intrinsic peculiarities of cardiac tissue (46), have provided a means of evaluating contractility in mammalian heart muscle.

The extrapolation of an afterloaded velocity of isotonic shortening curve to zero load yields the maximal velocity of shortening (V_{MAX}). V_{MAX} is unique for a given contractile state and provides an extremely sensitive indication of change in contractility (49, 54). This sensitivity is obvious upon examination of the effects of increased frequency of contraction (1) and l-norepinephrine (49). Both of these inotropic agents effect a significant change in V_{MAX}. Changes in force

development, on the other hand, do not exhibit this consistency, and therefore, cannot be related to changes in the contractile state of the muscle (1, 40, 49, 50).

These observations have resulted in the following characterization of heart muscle (50):

1) When initial muscle length is increased, force development increases and V_{MAX} remains constant.
2) Inotropic interventions increase V_{MAX} with or without altering force development.

Application of the force-velocity relation to isolated, supported canine hearts has produced results analogous to those obtained with the papillary muscle (44, 46). Subsequent studies in unanesthetized man confirmed these observations (21). Similar investigations involving both the intact heart and papillary muscle have shown a significant depression of myocardial contractility following chronic heart failure (44, 55, 57). This depression was characterized by a marked decrease in V_{MAX} and a distinct difference in the effects of inotropic interventions (55).

The initial purpose of this study involved the isolation of a working canine heart having a normal flow pattern, i.e. from right heart to left and exiting through an "aorta". However, an inability to maintain adequate coronary perfusion pressure in the system resulted in a high incidence of acute failure. It was, therefore, logical to examine the contractile state of the myocardium in order to determine if a decrease in contractility was, in part, responsible for this

deficiency. This determination would answer two questions:

1) Is there any difference in contractility when comparing non-failing heart muscle and muscle from hearts in acute failure?
2) Was the heart still a viable muscle capable of active contractions if the system had been adequate or had it deteriorated to the point that no system would have been adequate?

LITERATURE REVIEW

Essentials of the Force-Velocity Relation

Doi (14), Hill (27), Lupton (37), Gasser and Hill (20), Long and Lupton (36), and Fenn and Marsh (17) derived a conceptual base for the force-velocity relation from studies involving human, cat, and frog striated muscle. The results of these investigations defined the relation between the speed of shortening of a muscular contraction, the amount of work done, and the force generated.

Doi (14) demonstrated that at a constant temperature the maximal work done by a muscle (frog sartorius) subjected to a single shock has a maximal value with moderate initial extension. It was also determined that the absolute work increases as the optimal extension is approached and decreases with increasing extension beyond this point.

Hill (27) and Lupton (37) observed a linear relation between the speed of shortening of a muscular contraction and the amount of work performed in studies involving the flexion muscles of the human arm. The decrease in external work with increased speed of shortening was attributed to viscosity or internal friction. Long and Lupton (36) confirmed these results and further demonstrated that this relation was not seriously influenced by fatigue.

Gasser and Hill (20), in reporting on the influence of speed of shortening on force and work in the frog sartorius muscle, noted a decrease in both of these parameters with increased speed. These observations resulted in the proposal of a two component visco-elastic system of muscular contraction in an attempt to explain the results.

The linear nature of these relations was challenged by Fenn and Marsh (17), however, when further investigation resulted in the derivation of an exponential relation from velocity of shortening and force data. These results were obtained by measuring the rate of shortening of muscles contracting isotonically at varying loads. Increases in the speed of shortening resulted in a decrease in force but not in a linear fashion as would be the case if simple viscosity alone were involved. The exponential nature of these observations was ascribed to the development of extra energy for the work of shortening.

Hill (26, 29), in determining the precise nature of the force-velocity relation, reported the relation expresses the initial velocity of isotonic shortening as a function of developed force under afterloaded conditions. The derivation of a "characteristic" equation relating speed (V) and load (P) during isotonic shortening provided an accurate and reproducible index of muscle contractility. The equation, $(P + a)(V + b) = \text{constant}$, represents a rectangular hyperbola with asymptotes at $P = -a$ and $V = -b$. The dynamic constants, a and b, have respective dimensions of force and velocity and may be determined by either thermal measurements or by fitting the equation to observations of P and V obtained during isotonic shortening. At a given temperature the values of a and b were found to be very constant.

Subsequent studies by Hill (25, 28, 29) and Wilkie (63) confirmed the validity of the "characteristic" equation and suggested first, a

two component and finally, a three component system to explain the properties of contracting muscle. These properties were described in terms of the following constituents:

1) A main contractile portion or element (CE) which is assumed to be freely extensible at rest, but which shortens and develops force with activation.
2) A passive elastic element in series (SE) with the contractile element. The existence of the SE was proven from evidence obtained by calculating the rate of rise of isometric tension. This method assumed the "characteristic" equation to be true at every instant during contraction and the results indicated this was true.
3) A passive parallel elastic (PE) element in parallel with both the CE and SE serves to sustain resting tension. At less than rest length the mechanical system consists solely of the SE and CE.

It was also noted, by definition, that during isotonic shortening there is a constant force (load) acting on the SE which results in a constant length. Since the PE served only to sustain resting tension and the SE remained at a constant length, the course of isotonic shortening was found to be totally dependent on the properties of the CE. Therefore, by studying afterloaded isotonic contractions it was possible to acquire information about the contractile components

independent of the elastic components. The most fundamental mechanical property of muscle, the relation between the initial velocity of shortening and force, must, as a consequence of these observations, result from CE activity.

The dependency of the force-velocity relation on the CE was further demonstrated by Wilkie (61, 62) who reported the existence of a series elastic component which had constant properties throughout a muscle twitch. Jewell and Wilkie (30), in agreeing with these observations, suggested that series elasticity may be distributed along the muscle fibers as well as in the tendons and tendon bundles. Parallel elasticity, on the other hand, probably resides in the connective tissue sheath and is the same in resting or active muscle.

Abbott and Wilkie (2) found that isotonic records must be corrected for the effect of the inert elastic component if isotonic contractions at different tensions (initial lengths) are to be compared. The effect of this correction was small and thought to be due to extra shortening not visible externally. It was also observed in this study that the force-velocity relation applies to muscles from toads, cats, tortoises, mussels, and rays as well as frogs and man.

Podolsky (41, 42) agreed that the dependence of contractile force on shortening velocity is the most characteristic property of muscle and, in doing so, suggested a mechanochemical cycle characterized by the force-velocity relation. This cycle involves the conversion of chemical energy into mechanical energy. The absolute rate of this force generating chemical process may be measured experimentally by

determining the maximum velocity of shortening (V_{MAX}). The mechanical response of the muscle is dependent on the supply of substrate, the speed of the chemical process for a given amount of substrate, and the mechanical loading since substrate utilization increases with velocity. This response involves the shortening of the muscle and this occurs when the force generated by the muscle just exceeds the load. The decrease in force per unit distance when the contractile mechanism shortens very rapidly results from the chemical processes being out paced. When this occurs the fall in force with distance is independent of the shortening speed. Therefore, the shape of the force-velocity curve for a given muscle would depend on the number of myofilaments activated, the rate at which chemical energy is supplied to each myofilament, and the efficiency with which it is converted to work. It was further stated that consideration of these factors would provide clues about how various interventions affect the contractile process.

Determination of Myocardial Contractility in Normal Heart Muscle

Cattell and Gold (6), in studies designed to determine the effect of digitalis glucosides on myocardial contractility, found that papillary muscle survived better and provided the most consistent results of any cardiac tissue preparation used. The advantages of the papillary muscle included the ease of isolation without damage to the tissue and the uniformity of the preparation. It was also sufficiently thin to preclude problems with oxygenation. Hill (28), in a previously cited report, pointed out that with shorter muscles

the absolute acceleration of their free ends was less and the effect of inertia was reduced.

One problem in investigating contractility in cardiac tissue is the fact that it cannot be tetanized with a resultant decline in the active state and contractile force before the load is lifted. Abbott and Mommaerts (1) found that the full value of the active state corresponding to isometric tension (occurs when V = 0) cannot be determined with heavier afterloads (force encountered during shortening only) for this reason. The velocities at lower loads were not influenced, however, and could be accurately extrapolated to the maximum velocity of shortening (V_{MAX}). The purpose of afterloading was to study the relation between shortening and load over as wide a range as possible. This was done at negligible resting tension in order to eliminate parallel elasticity and because the principle of afterloading implies the load exceeds resting tension. The fact that diastolic pressure is low indicated a relationship with physiological conditions. Preloaded (force establishing initial length) conditions were also studied and this was not considered arbitrary in cardiac muscle since myocardial fibers do not have a well defined resting or maximal length. Both preloaded and afterloaded force-velocity curves extrapolated to the same velocity at zero force. It was also observed that changes in contractility were characterized by changes in the intrinsic initial velocity of shortening.

Sonnenblick (49, 50) observed that the heart functions in a manner analogous to an afterloaded muscle. It has an initial muscle length

established by a small preload (ventricular end-diastolic pressure) and upon activation develops a force equal to the afterload (aortic pressure) after which shortening (ejection) occurs. For this reason, the papillary muscle preparation of Cattell and Gold (6) was used by Sonnenblick (49, 50) to determine the nature of the force-velocity relation in mammalian heart muscle. A small preload was used to establish an initial length that would produce significant contractions. By using a stop, it was then possible to add additional loads (afterloads), which would be encountered only during shortening, and maintain a constant initial length. When the muscle developed adequate force to lift the load, isotonic shortening began. Initially this shortening occurs at a constant velocity, the initial velocity of shortening. Since the force applied during shortening was constant, the length of the elastic components remained constant and the course of isotonic shortening was totally dependent on the contractile elements of the muscle. With increasing load, the initial velocity and the extent of shortening (ΔL) rapidly decreased. This dependence of contractile force on the initial velocity of shortening (the force-velocity relation) had been previously observed in skeletal muscle by Hill (26). Sonnenblick and Parmley (53) found little difference in the strength of heart and skeletal muscle. The lesser force of contraction produced by cardiac muscle was due to the fact that the contractility of the muscle is less than maximal normally and it contains a large amount of non-contractile material, primarily mitochondria. Therefore, the potential for force generation in skeletal and cardiac muscle may be considered similar and this

study (49) verified the similarity by confirming the force-velocity relation in cardiac muscle.

The effects of various inotropic interventions were also investigated by Sonnenblick (49) and Sonnenblick et al. (54) and resulted in the following characterization of heart muscle:

1) An increase in muscle length results in an increase in the force of contraction. This was reflected by an increase in isometric tension without a change in V_{MAX}. The contractility of cardiac muscle may, therefore, be defined and quantified by this parameter; V_{MAX}.
2) At any given muscle length (preload) and temperature, increasing the frequency of contraction or changing the chemical environment by the addition of calcium or l-norepinephrine may alter the rate of force development with or without a change in isometric tension. By altering V_{MAX} these interventions induce a change in the basic state of the muscle and thereby, alter contractility.

Parmley et al. (40) also noted changes in isometric tension with increasing length and the addition of catecholamines. The change in V_{MAX} with inotropic influences was again offered as evidence of this parameter's peculiar ability to serve as an index of contractility.

Podolsky (42) had considered V_{MAX} an experimental measure of the force generating process of the muscle. Isometric tension, on the other

hand, reflected the number of active tension-generating sites. Activation of the contractile unit results in the release of a fixed amount of activating substance which is consumed at a rate dependent on V_{MAX}. Therefore, the increase in isometric tension with increasing muscle length without a change in V_{MAX} occurs because there are more sites available for interaction without a change in the rate of interaction. In contrast, the increase in V_{MAX} accompanying an inotropic intervention results from an increase in the rate determining process. An accompanying change in isometric tension, whether by activation of additional sites or further activation of the same sites, aids in defining the form of the intervention.

Sonnenblick (52), in attempting to explain the increase in isometric tension with increasing initial muscle length, suggested that the stiffness of the SE component might increase with increasing initial length. Since an increase in length would imply an increase in the number of CE effectively arranged in parallel, an increase in series elasticity might explain the constant nature of V_{MAX} under these conditions.

Instantaneous determination of force, velocity, and length by Sonnenblick (51) added another dimension to the relation between force and velocity. This study suggested that within broad limits, the velocity of shortening at any instant is a function of muscle length at that instant and not the length at which shortening began. Therefore, the decline in velocity with shortening would necessarily depend on the muscle length at that point. The existence of the relatively constant

velocity during the initial period of shortening was once again confirmed, however. Augmentation of the contractile state by l-norepinephrine and increased frequency were observed again and confirmed by the fact that the instantaneous velocity at any muscle length was increased as was V_{MAX}.

Sonnenblick (51) also postulated that the duration of the active state in cardiac muscle was important in fitting force-velocity data to the Hill ("characteristic") equation. It was suggested that the lack of fit or the inability to obtain hyperbolic curves was due to the fact that a decline in the active state occurred before maximal force development could be manifest externally. Brady (3), in agreeing with this theory, noted that relative to intermediate loads, the velocities at which heavy loads are lifted are too low to fit a hyperbolic relation. Additionally, in afterloaded contractions where heavier loads are lifted at shorter CE lengths, a plot of the force-velocity relation will not fit.

Brutsaert and Sonnenblick (4) and Brutsaert et al. (5) suggested the force-velocity curve deviates from a true hyperbola at high loads because of CE shortening during isometric contraction. This was related to the presence of a series elastic component which reduces the length of the CE and hence, force and velocity at high loads and not the limitation of time. The latter investigation (6) also pointed out that peak velocities of shortening with increasing afterload occur at almost the same length. Therefore, the use of peak velocities with increasing

load still provides the most useful method of obtaining force-velocity relations and evaluating cardiac contractility.

Siegel and Sonnenblick (46) confirmed the validity of the force-velocity relation in the intact heart by comparing the data from an isolated, supported canine heart with that obtained from cat papillary muscles. The analogous nature of the results suggested the properties observed were intrinsic to cardiac muscle. Glick et al. (21) used cineradiography to study the force-velocity relation in intact unanesthetized man and found the results comparable to those obtained in isolated tissues.

The extent of isotonic shortening (ΔL) and the time to maximal ΔL were found to be related to the contractility of the papillary muscle as defined by V_{MAX}. This observation was made by Downing and Sonnenblick (15) in a study comparing isolated muscle contractility with that of the intact heart of cats. The latter parameter, time to maximal ΔL, was found to be an inverse function of V_{MAX}. By correlating this time parameter with the time to maximal pressure development in the ventricle, it was possible to estimate relative changes in V_{MAX} in the intact heart. The observation that V_{MAX} was independent of ventricular end-diastolic pressure and aortic pressure agreed with the effects of preload and afterload on the papillary muscle preparation. Similarly, since these interventions (preload and afterload) do not exert an influence on the inotropic state of the heart, it was noted that they had no effect on the time intervals of contraction. Norepinephrine and increased

frequency, on the other hand, decreased the time to maximal Δ L and increased V_{MAX} in both the isolated muscle preparation and the intact heart. The decrease in time to maximal Δ L in papillary muscle may be compared to a reduction in peak pressure time in the intact heart. The results of this study support the suggestion that characterization of both the intact heart and isolated papillary muscle is dependent on both force and velocity parameters.

The Effect of Heart Failure on Myocardial Contractility

Prinzmetal et al. (43) found that acute ischemia of myocardial tissue resulted in a marked decrease in contractility. The ischemia was precipitated by ligation of a coronary artery.

Heart tissue obtained at autopsy by Kako and Bing (31) yielded actomyosin bands whose contractility remained undiminished for six hours after death. Those prepared from failing human hearts showed a pronounced decrease in contractility. Digoxin alone failed to correct this defect but a combination of calcium and digoxin restored the shortening of the bands to normal. Neither had an effect when used alone with normals.

Complete physical-chemical characterization of myosin isolated from normal and failing dog hearts by Ellenbogen et al. (16) indicated that irreversible changes had occurred in the cardiac myosin from failing hearts. These changes were related to the chronic stretch of the myocardium which resulted from congestive heart failure.

Ross et al. (44) examined the force-velocity relation of the intact left ventricle of the dog in a manner analogous to that used with the isolated muscle preparation, e.g. by variation in afterload from a constant end-diastolic volume. The induction of failure by barbiturates or deterioration resulted in a significant decrease in the initial velocity of shortening at any tension. Similar results were observed by Spann et al. (55) in studies involving the papillary muscle from cats with experimentally produced ventricular hypertrophy and congestive heart failure. The depression of the contractile state was characterized by a substantial and significant reduction in V_{MAX}. The absolute response to increased frequency was also less in failing hearts.

Spann et al. (56) produced chronic right ventricular hypertrophy and heart failure in cats by pulmonary artery constriction. The contractile properties of the intact ventricle and papillary muscles isolated from these hearts were then compared with normal hearts. In failure both force and velocity were depressed in the isolated muscle. V_{MAX}, not force, was depressed in the intact ventricle. These findings provided a quantitative analysis of a depressed intrinsic contractile state in the intact, failing heart and indicated the rate of interaction of the contractile sites was reduced.

The Effect of Inotropic Influences on Contractility

Increased Frequency of Contraction. Cattell and Gold (8) observed a several fold increase in the force of contraction when the rate of stimulation was accelerated. Conversely, a decrease in force was noted

when the rate was slowed. Changes in rhythm, as opposed to increased activity, were reported as the cause. Garb and Penna (19) confirmed these findings and agreed that the cause for the increase in force was the spacing between stimuli.

Subsequent investigations by Cattell and Gold (7) provided additional evidence that a direct relationship between force and frequency of contraction existed. There was also some evidence indicating that as a muscle fails the increase in force with increased frequency becomes more marked.

Abbott and Mommaerts (1) characterized the change by application of the force-velocity relation. Increased frequency effected a change in the intrinsic initial velocity of the papillary muscle and this indicated a change in the contractile state of the muscle. These results implied that at greater frequencies of contraction the heart shifts its optimal efficiency to greater velocities of shortening.

Sonnenblick (49) also observed a change in the force-velocity relation with increased frequency. This change was reflected in a change in V_{MAX}. Since V_{MAX} is considered a sensitive indicator of the contractile state of the muscle, it was concluded that an altered state of contractility existed. Additionally, it was observed that the increase in V_{MAX} occurred without an increase in isometric tension.

Glick et al. (21) and Downing and Sonnenblick (15) observed the same relationship between increased frequency and the contractile state of the muscle in intact hearts. In both studies it was shown

that the intact heart displays the same force-velocity relations as the isolated papillary muscle and a change in the contractile state of the myocardium is characterized by a change in the force-velocity relation.

Podolsky (42) theorized that an inotropic intervention such as increased frequency accelerates the rate determining processes of the muscle and, the increase in V_{MAX} may result from increasing the rate of interaction of the contractile units.

Catecholamines. Garb (18), in studies using the cat papillary muscle, found that epinephrine, norepinephrine, and n-isopropyl-norepinephrine (ISP) all produced an increase in the force of muscular contraction. The degree of increase was variable, and a quantitative comparison was impossible. It was reported, however, that both norepinephrine and ISP exerted an inotropic action at least as great as epinephrine. Lee (33) observed that both epinephrine and norepinephrine produced an immediate increase in 0_2 consumption accompanied by a simultaneous increase in the force of contraction. The two amines were indistinguishable in their effects on force of contraction, 0_2 consumption, and speed of action. It was concluded that their activity as measured by alterations in muscular contractility is about the same.

Goldberg et al. (22), Cotten and Pincus (11), and West and Rushmer (60) observed similar pronounced positive inotropic effects with epinephrine and norepinephrine in both conscious and anesthetized dogs. The effect on ventricular contractility was such that the amines were considered to have a qualitatively and quantitatively comparable action.

In attempting to characterize the role of myocardial catecholamines in cardiac contractility, Lee and Shideman (34) found that papillary muscles depleted of norepinephrine by pretreatment with reserpine or bilateral sympathectomy exhibited a marked decrease in contractility when compared with normals.

Sarnoff et al. (45) noted that norepinephrine augments the strength of contraction in isolated canine hearts. This change in contractility was effected by stellate ganglia stimulation or the infusion of the amine and was measured while end-diastolic pressure and fiber length remained constant.

Spann et al. (56) found a reduction of norepinephrine stores in guinea pigs with experimentally induced ventricular hypertrophy and congestive heart failure. Both the concentration and content of the ventricles were reduced and the extent of the reduction was related to the degree of failure. Chidsey et al. (9) made similar observations in the dog. The papillary muscles from failures treated with tyramine responded significantly less than normals. It was concluded that norepinephrine depletion occurring in congestive heart failure may interfere with sympathetic activity in the failing heart and thereby adversely affect contractility.

Papillary muscles removed at the time of mitral valve replacement in human hearts responded similarly to the sympathomimetic norepinephrine-releasing amine, tyramine. Chidsey et al. (10) reported a decrease in norepinephrine concentration in these muscles.

The inotropic influence of norepinephrine on myocardial contractility was quantified by Sonnenblick (48, 49, 50) who reported an increase in V_{MAX} accompanied by an increase in isometric tension. These changes in the force-velocity relation indicated a change in the basic contractile state of the muscle. The amine was also observed to shorten the latency period from electrical stimulus to mechanical response, accelerate the onset of maximal active state, increase the intensity of the active state, and shorten its duration. The effect of shortening the duration of contraction while increasing the velocity of contraction was an increase in the force of contraction.

Spann et al. (55) found the response to norepinephrine in failing heart muscle exceeded that in normal hearts. The papillary muscle removed from hypertrophied or congestively failing hearts also exhibited depletion of catecholamine stores.

Mediation of the Catecholamine Response. In studying the action of sympathomimetic amines on isometric tension and phosphorylase activity in isolated rat hearts, Kukovetz et al. (32) noted an increase in both enzyme activity and contractility. The order of potency of the drugs used was: epinephrine < norepinephrine < n-isopropyl-norepinephrine. There was a definite correlation between drug concentration, increased systolic isometric tension, and increased phosphorylase activity.

Haugaard and Hess (23, 24) reported an increase in cyclic 3', 5'-AMP accompanied the use of catecholamines. The most important action of this compound seemed to be the activation of phosphorylase which

in turn stimulated glycogenolysis and the production of high-energy phosphate bonds. It was also pointed out, however, that cyclic 3', 5'-AMP may stimulate glycogenolysis and cardiac contraction by two entirely separate mechanisms.

Sutherland and Robison (38) used the isolated perfused working rat heart to compare the time course of the cyclic 3', 5'-AMP response with that of the inotropic response. The advantage of using the rat heart was that an increase rate leads to a decrease in contractile force. Therefore, when positive inotropic effects were noted with agents which also increase rate, it was obvious that a direct effect of the agent was being observed. These studies indicated the activation of cyclic 3', 5'-AMP by catecholamines was an extremely rapid process. The level of cyclic 3', 5'-AMP was increased approximately fourfold within three seconds after the injection of a sub-maximal dose of epinephrine. Contractile force peaked twenty seconds after the injection and phosphorylase activation was maximal at forty five seconds. Both cyclic 3', 5'-AMP levels and phosphorylase activity were observed to remain elevated after muscular response had returned to control levels. Skelton et al. (47) used dibutyryl cyclic 3', 5'-AMP to study the positive inotropic effects of cyclic 3', 5'-AMP since cardiac cells are not readily permeable to the latter. Additionally, the dibutyryl derivative is resistant to enzymic degradation by phosphodiesterase. The compound was found to increase both isometric tension and the rate of tension development. It also shifted the force velocity curve in a

positive direction. These changes were similar to those observed at peak norepinephrine concentrations. Propranolol depressed the effect of the amine but had no effect on dibutyryl cyclic 3', 5'-AMP.

Cutting (13) reported that norepinephrine may also produce a decreasing effect, possibly by being fixed to, and occluding the receptor.

The effect of catecholamines on the tissue levels of calcium in the dog papillary muscle was reported by Nayler (38). The amines were observed to positively affect the rate at which the tissue accumulated calcium and this effect was partially antagonized by propranolol. It was suggested that this positive effect on calcium exchangability may, therefore, contribute to the positive inotropic effect of norepinephrine. The fact that propranolol did not completely block the effect of calcium alone indicated there may be several mechanisms of exchange involved.

Isolation of Artificially Oxygenated Hearts

Levy et al. (35) found a method by which viable and uninjured mammalian hearts may be removed. Cannulation of one of the brachiocephalic arteries and the left pulmonary artery effect a cardiopulmonary bypass. Subsequent ligation and division of the remaining vessels of the heart permitted isolation and removal. These hearts were found to be viable for approximately two hours.

An oxygenator simple in design and operation was described by Cuss et al. (12). It was used over a wide range of flow rates without requiring excessive blood for priming. The report indicated it had proved satisfactory in both clinical and laboratory applications.

MATERIALS AND METHODS

Canine Papillary Muscle Preparation from Non-failing Hearts

Five mongrel dogs (11.3-16.3 kg) were anesthetized with sodium pentobarbital (30 mg/kg). Following a left sided anterior thoracotomy, the heart was rapidly excised, the right ventricle opened and the right anterior papillary muscle (59) carefully dissected free. The individual muscles varied in weight (dry muscle weight: 0.027-0.062 g) and stability (Table 1). Attempts to correlate weight with performance were not significant. Muscles were oven-dried at 100°C for 24 hours.

The muscle was immediately placed in a modified Krebs-Henseleit solution (Na^+ 143.5 mEq/l, K^+ 5.4 mEq/l, Ca^{++} 5.1 mEq/l, Mg^{++} 2.4 mEq/l, Cl^- 128.0 mEq/l, $H_2PO_4^-$ 2.2 mEq/l, HCO_3^- 24.9 mEq/l, $SO_4^=$ 2.4 mEq/l, glucose 10 mEq/l), pH 7.4, through which a mixture of O_2:CO_2 (95%:5%) was being bubbled. A ligature was placed around the base of the muscle to secure the muscle to a muscle holder. Another ligature was placed around the chordae tendineae near the attachment to the remnants of the valve. The entire preparation was then placed in a muscle bath containing oxygenated Krebs-Henseleit at 27°C (39) and the free ligature was attached to an isotonic (Fig. 1) muscle lever. Bath temperature was maintained at a constant value with a controlled temperature circulating pump.

The muscle lever consisted of a balsa beam 10 cm (5 cm each side of the fulcrum) in length attached to a Brush isotonic muscle transducer (Model No. 33-03-981). The lower moment of inertia of the light-weight

balsa avoids any reaction force and its section modulus negates the effect of beam deflection. It also provides a means of precisely setting the counter movement. The error involved in measuring linear displacement with a rotary transducer was insignificant since the correction for non-linearity is $\pm$ 0.15% of full scale. A compass mounted on the transducer was used to correlate recorder pen deflection with beam deflection.

Initial length of the muscle was determined by a small preload. A stop was set which maintained this length at a constant prior to contraction. Additional loads (afterloads) could then be added to the preload and encountered only during contraction (50). Tension adjustment was simplified by mounting the muscle transducer on a rack-and-pinion clamp stand.

The muscle was stimulated by a Grass impulse stimulator (Model S4). Two silver-silver chloride electrodes placed laterally along the parallel aspect of the muscle provided transverse field stimulation. A bipolar stimulus 10% above threshold voltage with a duration of 10 msec and frequency of 30 per minute was used (39).

Linear displacement, tension development and stimulation artifact were recorded simultaneously on a dual-trace Brush direct-writing oscillograph (Mark 220). Recordings were made at a paper speed of 25 mm/sec. The initial velocity of shortening was calculated from the slope of the initial course of shortening.

Canine Papillary Muscle Preparation from Failing Hearts

Five mongrel dogs (12.7-16.3 kg) were anesthetized with sodium pentobarbital (30 mg/kg) and ventilated with 0_2 using a Bird automatic respirator (Mark 7). The initial purpose of this phase of the experiment was to develop a method for isolating a working canine heart having a normal flow pattern, i.e. from right heart to left and exiting through an "aorta."

A bilateral anterior thoracotomy was performed at the fourth intercostal space. The right thoracic cavity was entered and both vena cava and the azygous vein were isolated. The azygous was then ligated and divided. The right auricle was exposed, the tip of the auricle removed, and a stoppered cannula inserted and secured. This would later serve as both vena cava in returning perfusate to the right side of the heart. The left thoracic cavity was then entered and the brachiocephalic artery, the left subclavian artery, the aorta, and the left pulmonary artery were isolated. The brachiocephalic artery was then ligated and divided. The left auricle was exposed, the tip removed, and a stoppered cannula inserted and secured. This would later serve as the pulmonary veins and form part of a right-to-left shunt. Sodium heparin (6 mg/kg) was administered intravenously and the left subclavian artery was cannulated for the infusion of oxygenated perfusate to the coronaries. The perfusate was a mixture of blood and modified Krebs-Henseleit solution, pH 7.4. Arterial pressure was allowed to stabilize and the left pulmonary artery was cannulated. The cannula was inserted through the left pulmonary artery into the

pulmonary artery and secured in this position. Cardiopulmonary bypass was then instituted using a roller pump at an infusion rate sufficient to maintain mean arterial pressure (MAP) of 60 mm Hg (35). Pressures were measured with Statham physiological pressure transducers (Model P23Dc) and recorded on a Grass direct-writing oscillograph (Model 7). The perfusate-blood mixture was oxygenated with 0_2 using an Esmond Lexan polycarbonate convoluted disc plastic oxygenator (12). Perfusate-blood temperature was maintained at 27°C. Following the institution of bypass, dissection was continued by ligating and dividing the pulmonary veins and arteries on the left side. The aorta was clamped and the venae cavae were ligated and divided as were the pulmonary arteries and veins on the right side. Flow rate was reduced following clamping of the aorta in order to maintain MAP at 60 mm Hg. A right to left shunt was then instituted by connecting the cannula in the left auricle to a Y-tube which formed part of the pulmonary artery cannula. Care was exercised in order to prevent leakage of air into the Penrose tubing forming the shunt. Penrose tubing was used because of its flexibility and this precluded the possibility of high resistance to flow, right heart distension and failure. The aorta was then divided and cannulated. Flow rate was again adjusted to maintain a MAP of 60 mm Hg. The cannula in the right auricle was connected to a second pump and flow was started at a rate which allowed the heart to maintain a mean pulmonary arterial pressure of 25 mm Hg. This was augmented by varying the flow out of the external circuit of the Y-tube. The heart was then removed to a chamber of modified Krebs-Henseleit at 37°C. A constant

temperature was maintained by a controlled temperature circulating pump. A platinum electrode in the bottom of the chamber combined with a second electrode placed on the surface of the heart provided an epicardial EKG (See Figs. 2 and 3 for a description of the apparatus).

Of the five animals studied, all hearts failed soon after bypass was initiated (0:00-0:50 hrs). Four of the five began fibrillating because the system was unable to maintain a MAP above 40 mm Hg. One heart simply stopped without any apparent cause.

Immediately following failure the papillary muscles were excised and treated in the same manner as those from non-failing hearts.

Inotropic Interventions

The papillary muscles were subjected to increased frequency (30 per minute to 60 per minute) and the results noted.

L-norepinephrine ($0.3X10^{-7}M$) was added to the bathing medium and the effects noted. Agonist contact time was 30 seconds with a stimulation period of 15 seconds. Control values were obtained prior to the addition of l-norepinephrine at each succeeding afterload.

RESULTS

The Force-Velocity Relation and Isotonic Shortening

The Effects of Increasing Afterload. The initial length of the isotonically contracting muscle is set by a small load (preload) on the muscle prior to contraction. By setting a stop on the muscle lever it is possible to maintain this length and add additional loads (afterloads) which are encountered only during contraction. Tables 2 and 3 contain the initial velocities of contraction of failing (FH) and non-failing (NFH) heart muscle. A variety of preloads are listed but the effect of increasing afterload can be observed with each preload. Figure 4 is a plot of the same data averaged across all preloads at each afterload. The plot of force versus velocity describes the force-velocity relation (26). As the afterload increases, the initial velocity of shortening decreases. An analysis of variance (Table 4) indicated this effect was significant. There was not, however, a significant difference between the papillary muscles from failing and non-failing hearts.

The velocity of shortening with no load on the muscle is maximal (V_{MAX}). In heart muscle, this value is obtained by using the smallest preload which produces a significant contraction and extrapolating the force-velocity curve to zero load (65). The resulting curve, according to the Hill equation, is hyperbolic (26). The data from this study, when subjected to an analysis of variance, did not deviate significantly from a straight line, however. Because of the linear nature of the relation, the large increments (0.5 g) in preload used, and the lack of

significance in comparing failing and non-failing heart muscle, V_{MAX} was obtained by extrapolation to zero afterload. This resulted in a quantitative, not a qualitative difference.

The Effect of Increasing Initial Length. Figure 5 illustrates the effect of increasing initial length (preload) on the force-velocity relation. The initial velocity of shortening increased until optimal length was attained and then decreased with increasing length. This effect was significant but there was no significant difference between failing and non-failing heart muscle. This increase in initial velocity with increasing length is characterized by an increase in isometric tension without an accompanying increase in V_{MAX} (67).

The Effect of Inotropic Interventions. Control data were obtained prior to the addition of norepinephrine to the bath at each succeeding afterload, i.e. the initial velocity of shortening was obtained prior to and after the addition of norepinephrine to the bath at each succeeding afterload (0.5-3.0 g). Tables 5 and 6 indicate a drug effect in the control data after the initial afterload (0.5 g). The initial velocity at the next increment in afterloading (1.0 g) increases in direct opposition to the force-velocity relation. Subsequent data from increasing afterloads (1.5-3.0 g) indicate a return to the expected relation. No significant difference was found in comparing failing and non-failing heart muscle data over a range including the initial afterload (0.5-2.5 g) or over an abbreviated range (1.5-3.0 g) which did not include the afterloads in the control data lacking a drug effect (Tables 7 and 8). V_{MAX} determinations (Figs. 6, 7, 8, and 9), both

including and excluding the unaffected control afterload, yielded quantitatively different but qualitatively similar results with one exception; in comparing Figs. 6 and 8, there is a shift in the force-velocity relation favoring control data when the abbreviated range (1.0-2.5 g) is used.

A significant mean difference was found between treated and untreated muscles as a whole (Table 7) after norepinephrine was added to the bath. Table 8 contains comparisons of treated and non-treated muscles of failing and non-failing hearts. Both in-group and between-group comparisions are indicated. A significant difference is noted between control and pretreatment response in failing muscle and a similar, but non-significant trend, is indicated for non-failing muscle. A comparison of relative amplitudes of contraction (Fig. 10) shows no significant difference between treated and untreated and failing and non-failing heart muscle.

Tables 8 and 9 indicate there were no differences between the response of papillary muscles of failing and non-failing hearts with increased frequency of contraction and, as with the addition of norepinephrine to the bath, mean differences were non-significant. Table 10 contains the data used in these comparisions. Figures 6, 7, 8, and 9 illustrate V_{MAX} comparisons for all interventions.

Table 11 contains the initial velocities of shortening of muscles from failing and non-failing hearts at optimal preload and over a range of afterloads. These results were used in making statistical comparisons of initial velocities.

The effect of norepinephrine and increased frequency on the time intervals of contraction were analyzed (Fig. 11). Comparisons of the differences between failing and non-failing hearts were non-significant as were in-group comparisons. Both interventions positively affected the time from stimulus to mechanical response and the time from initiation of contraction to peak amplitude (Table 12).

The Effect of Acute Failure on the Force-Velocity Relation of Mammalian Heart Muscle. No significant difference was found between the performance of failing and non-failing heart muscle when subjected to the various interventions, e.g. increasing preload, increasing afterload, increased frequency of contraction, and norepinephrine. A difference in V_{MAX} is evident but due to variability, no statistically significant difference is present.

DISCUSSION

The contractile state of isolated skeletal or cardiac muscle has been previously described in terms of the force-velocity relation (17, 26, 49, 54). A basic difference between skeletal and cardiac muscle is the ability of the latter to alter its force-velocity relations with increased frequency or the addition of l-norepinephrine (50). The hyperbolic relation between the velocity of shortening and developed force is considered the most basic property of an isotonically contracting muscle (17, 26). Changes in contractility result in an alteration of this relation and are characterized by a change in the intrinsic velocity of shortening (V_{MAX}). Changes in force development are not consistent and, for this reason, cannot be used as an index of contractility (1, 40, 49, 50).

An analysis of variance of the data obtained in this study indicated the existence of a linear relation between force (load) and initial velocities of shortening. Previous investigations (3, 4, 5, 51) have reported difficulty in obtaining a hyperbolic fit. This has been related to a decline in the active state and the presence of a series elastic component in the muscle. Because of the linear nature of the force-velocity relation in this study, V_{MAX} was determined by extrapolation to zero afterload. This resulted in a difference in the value of V_{MAX} without altering the slope of the line.

The validity of using the papillary muscle preparation has been confirmed in previous studies (15, 21, 46) where comparisons of the force-velocity relations of intact hearts have been made with those

observed in isolated tissue preparations.

An analysis of the data obtained in this study confirms the previously reported (49, 50) effects of norepinephrine and increased frequency. These interventions significantly altered the inotropic state of the muscle. The significance of the effects of preload, afterload, and norepinephrine was confirmed by statistical analysis and changes in V_{MAX}. Significant changes in the time intervals of contraction and alterations of V_{MAX} confirmed the inotropic effect of increased frequency. The inability to consistently find a statistically significant difference between treatment, control, and pretreatment data was related to the magnitude of the variance.

Downing and Sonnenblick (15) have suggested that changes in the time intervals of contraction may be as reliable in determining cardiac contractility as changes in V_{MAX}. Changes in the inotropic state of the papillary muscle from failing and non-failing hearts were characterized by decreases in the time intervals of contraction and increases in V_{MAX}. This would further substantiate the hypothesis that the lack of a consistent statistical difference between treatment, control, and pretreatment values may be due to variance in the data.

The presence of a drug effect in the control data also added to the problem of analysis. This may have been the result of receptor occlusion, calcium flux, or mediation of the catecholamine response. Norepinephrine, like other receptor-active agents, may produce a decreasing effect by occluding the receptor (13). Partial occlusion and subsequent activation by washing could have resulted in the observed

effect. The amine has also been shown to produce an increase in the rate at which calcium is accumulated by the cell. The resultant increase in intracellular calcium could have resulted in the observed increase in contractility in the control group. Norepinephrine also increases the level of cyclic 3', 5'-AMP and active phosphorylase in cardiac tissue. The time course of this increase is such that these agents may be responsible for the drug effects noted in the control group.

Previous studies have shown that ischemia (43) and chronic heart failure (44, 55, 56) significantly reduce contractility in myocardial tissue. The effect of failure on the force-velocity relation was confirmed by determining V_{MAX} and developed force. Both of these parameters were depressed.

A comparison of the initial velocities of contraction and the effects of inotropic interventions on the papillary muscle from non-failing and acutely failing hearts produced no significant difference. A difference in V_{MAX} was noted with or without interventions but a comparison of initial velocities and the time intervals of contraction was not significant.

Cattell and Gold (7) observed a difference in the effect of increased frequency on failing and non-failing tissue. The failing tissue was more responsive than normal. Similar results (55) were obtained with norepinephrine and failing cardiac muscle. The response in failing tissue was significantly greater than that in normal muscle.

The results of this study did not indicate a significant difference in the response of failing and non-failing cardiac muscle to any intervention. The responses to preload, afterload, increased frequency, and norepinephrine were similar. A comparison of initial velocities of contraction and the time intervals of contraction produced no statistically significant difference. Differences in V_{MAX} were noted, but the dependence of this value on initial velocity and the time intervals of contraction make these results suspect. Therefore, the present study suggests that at the time of acute failure, the myocardium was still viable and capable of effective contractions had the system been adequate.

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APPENDIX

Figure 1. Diagram of isolated muscle preparation. Muscle chamber is suspended in a constant temperature (27°C) bath. O_2:CO_2 (95%:5%) is bubbled through a modified Krebs-Henseleit solution in the chamber (AL: afterload; PL: preload).

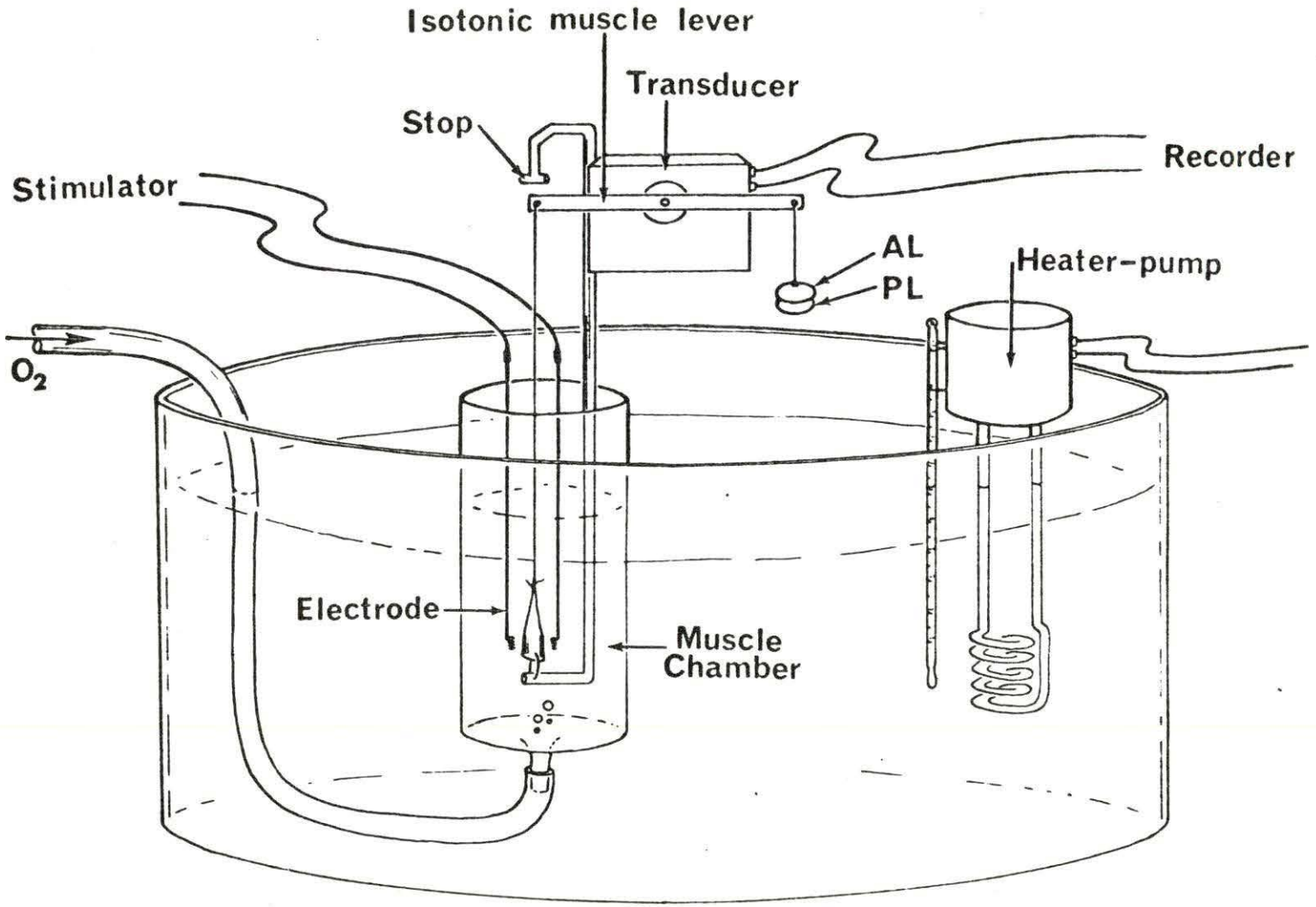
Isotonic muscle lever
Transducer
Stop
Recorder
Stimulator
AL
PL
Heater-pump
O_2
Electrode
Muscle
Chamber

Figure 2. Diagram of isolated, working canine heart apparatus.

a - Blood-perfusate mixture is pumped (Pump A) from oxygenator to right heart.

b - Blood-perfusate mixture exits oxygenator and then is delivered to either the right heart (Pump A) or the subclavian artery (Pump B).

c - Blood-perfusate mixture exits pulmonary artery and enters the oxygenator or the left heart (d).

d - This forms the right-to-left shunt and c is the external portion of the circuit.

e - Blood-perfusate mixture exits aorta and enters the oxygenator.

f - Blood-perfusate mixture is pumped (Pump B) from the oxygenator to the aorta via the subclavian artery. This maintains coronary perfusion pressure.

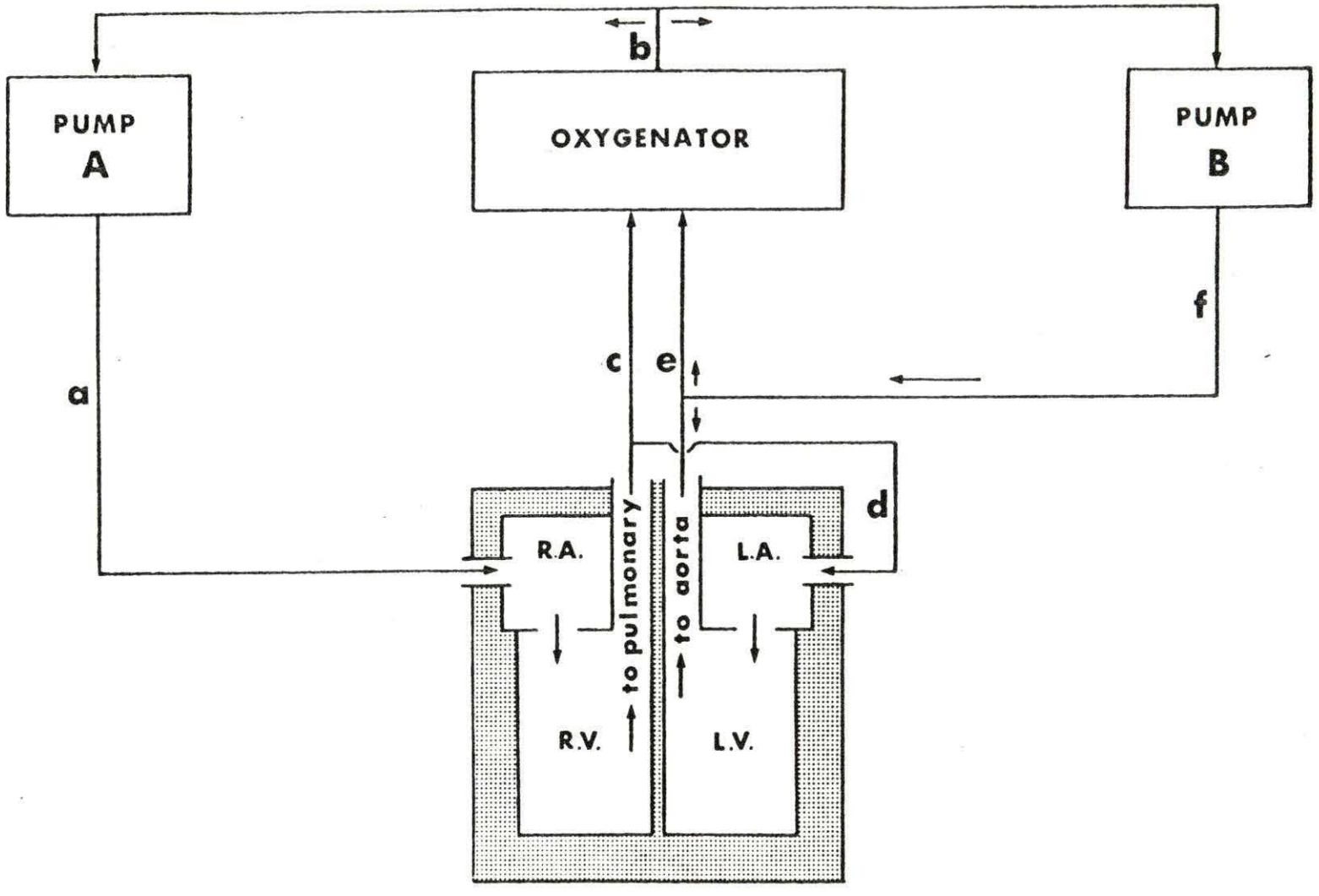
PUMP
A
OXYGENATOR
PUMP
B
b
a
c
e
f
d
R.A.
L.A.
R.V.
L.V.
to pulmonary
to aorta

Figure 3. Diagram of the isolated, working canine heart.

A - From pump to right auricle which is now serving as both venae cavae.

B - From pump to aorta via the subclavian artery.

C - Aortic exit to oxygenator.

D - Right-to-left shunt external circuit to oxygenator.

a - Aorta

b - Ligated and divided brachiocephalic artery.

c - Subclavian artery.

d - Right auricle.

e - Right ventricle.

f - Left auricle.

g - Left ventricle.

h - Pulmonary artery.

i - Left pulmonary artery.

j - Aortic valve.

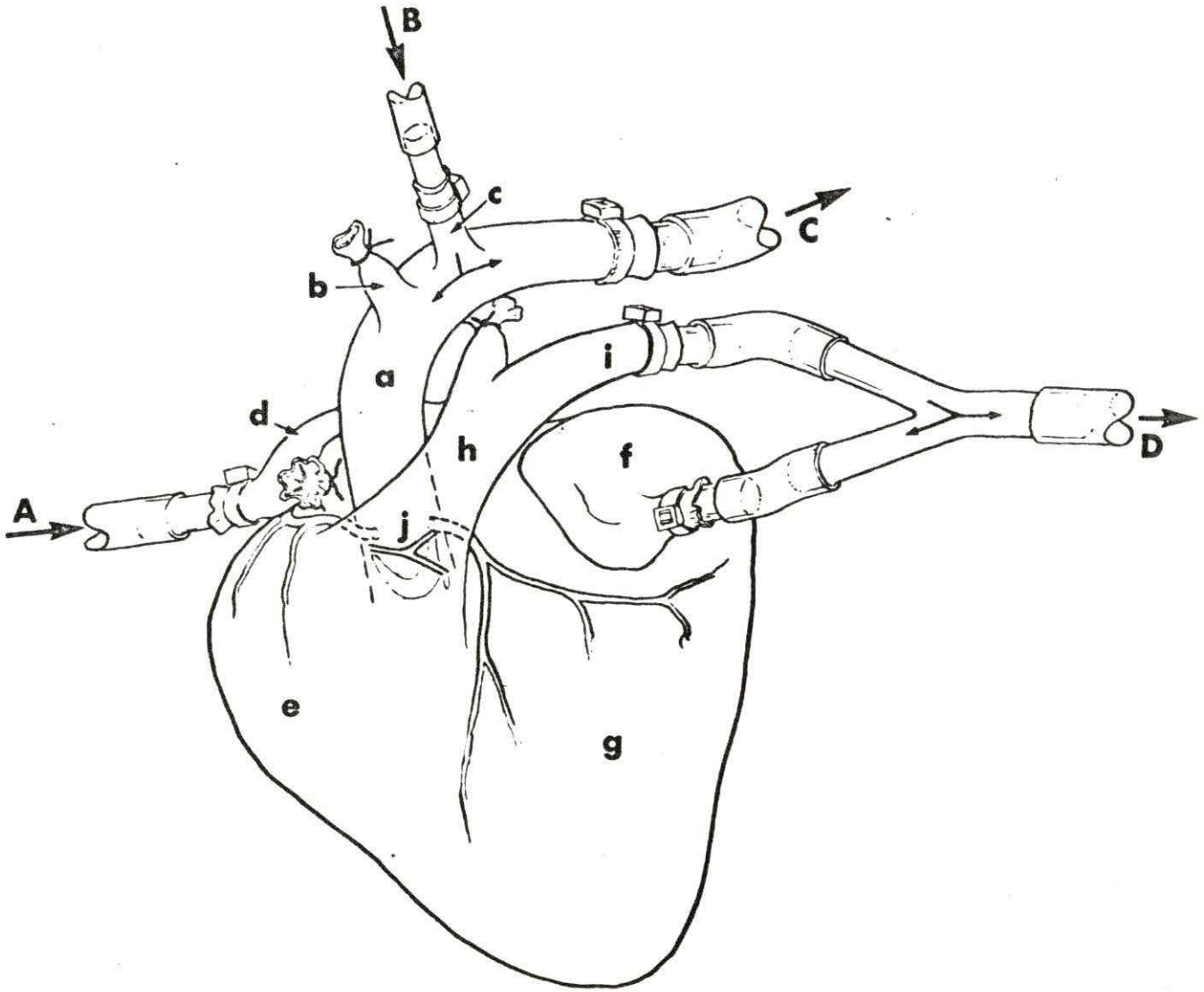
B
c
C
b
a
i
d
h
f
D
A
j
e
g

Figure 4. Effect of increasing afterload. Temperature: 27°C. Stimulus frequency: 30 per minute. Ordinate: Mean initial velocity. Abscissa: Afterload. Force-velocity curve representing a mean preload (range: 0.5-3.0 g) over a range of afterloads (0.5-2.0 g). Velocity of shortening has been extrapolated to zero afterload in order to approximate V_{MAX} (shaded area). Best fitting line: $Y = \overline{Y} + b\ (X-\overline{X})$.

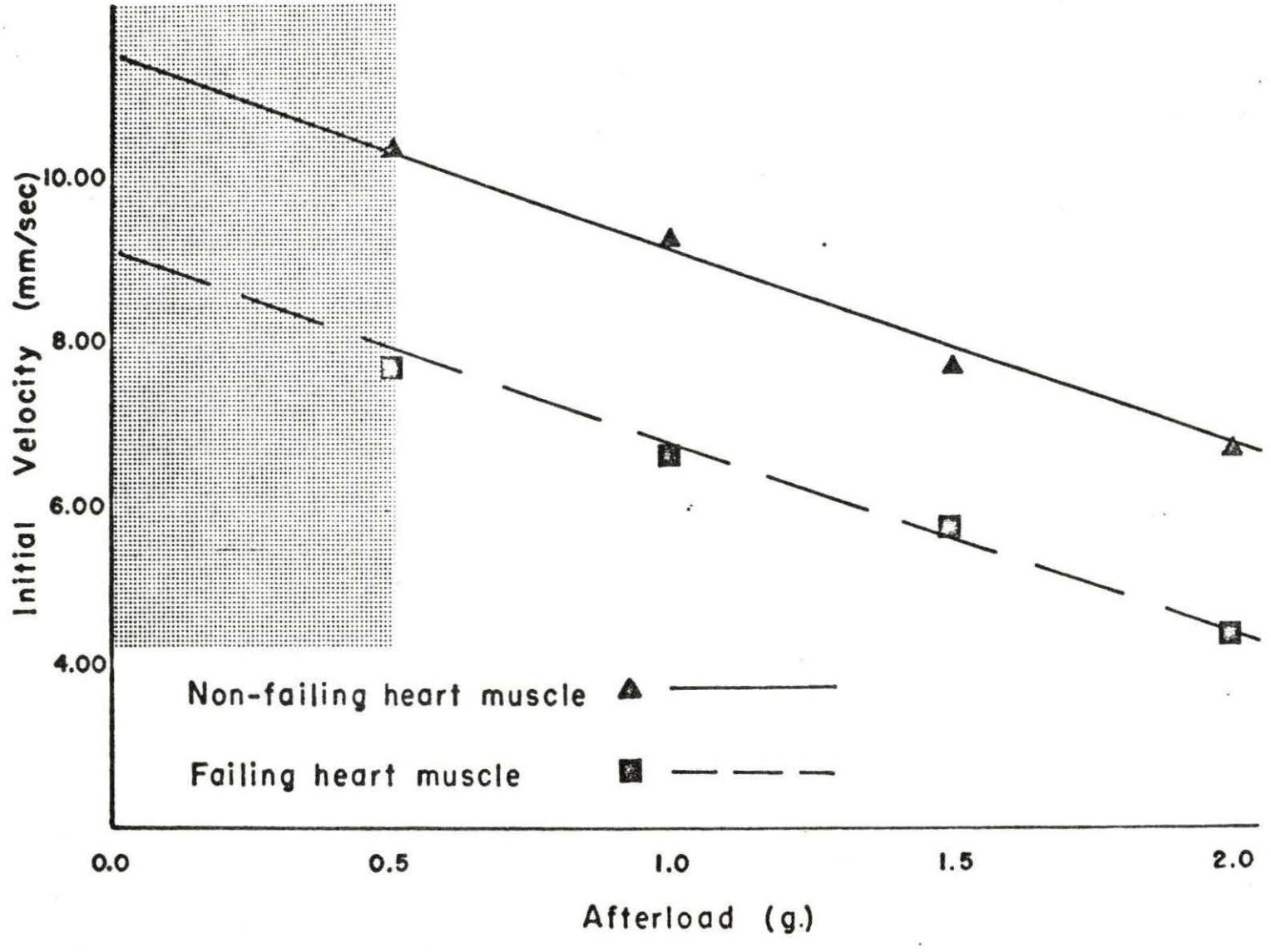
Initial Velocity (mm/sec)
10.00
8.00
6.00
4.00
Non-failing heart muscle
Failing heart muscle
0.0
0.5
1.0
1.5
2.0
Afterload (g.)

Figure 5. Effect of increasing preload. Temperature: 27°C. Stimulus frequency: 30 per minute. Ordinate: Mean initial velocity. Abscissa: Preload. Best fitting line: $Y = \bar{Y} + b_1 (X-\bar{X}) + b_2 (X^2-\bar{X}^2)$.

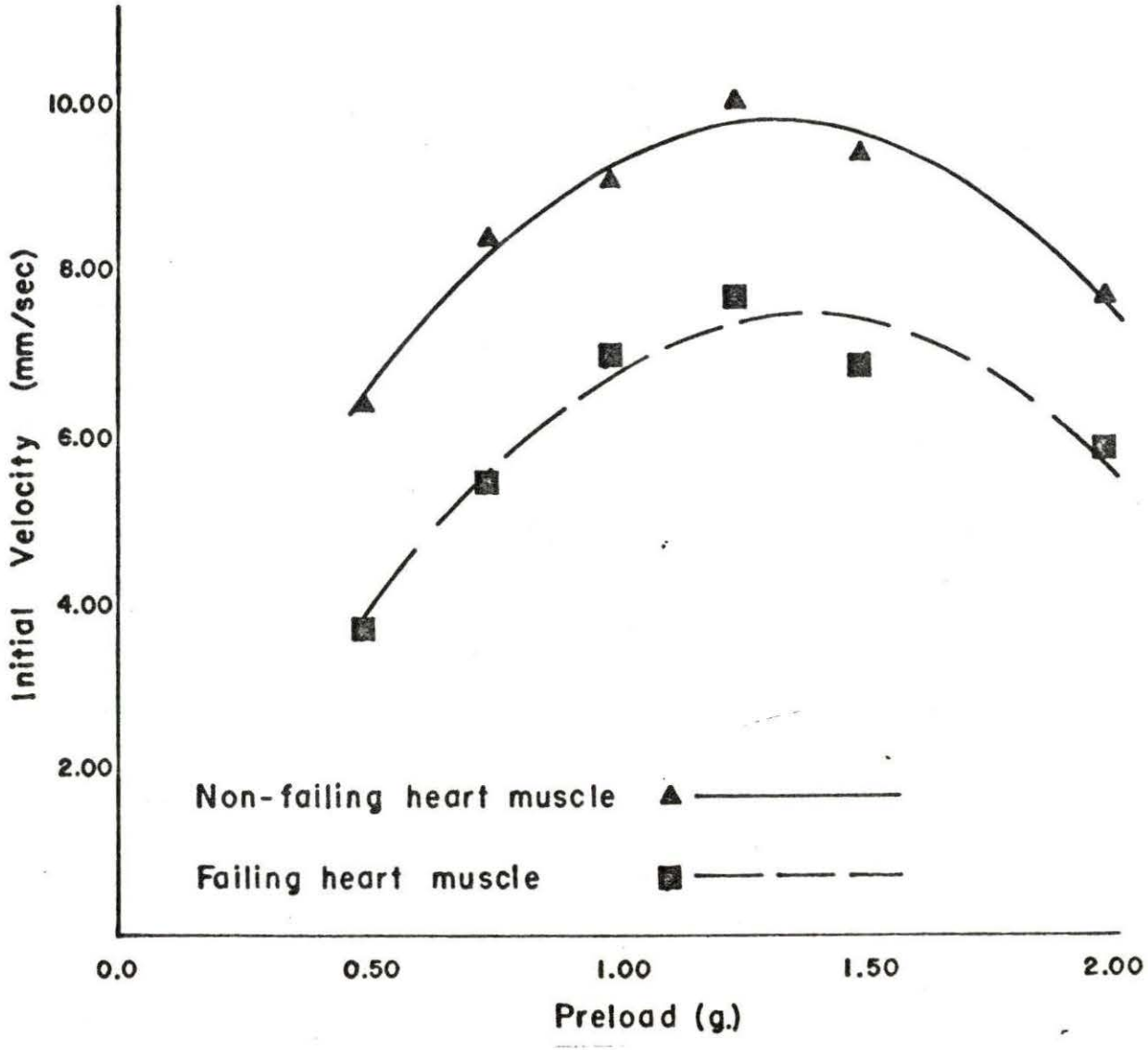
10.00
8.00
6.00
4.00
2.00
Initial Velocity (mm/sec)
Non-failing heart muscle
Failing heart muscle
0.0
0.50
1.00
1.50
2.00
Preload (g.)

Figure 6. Force-velocity relations of the right anterior papillary muscle from failing (FH) hearts following the indicated interventions. Temperature: 27°C. Stimulus frequency: 30 per minute. Ordinate: Mean initial velocity of shortening. Abscissa: Afterload. Velocity of shortening has been extrapolated to zero afterload in order to approximate V_{MAX} (shaded area). Best fitting line: $Y = \overline{Y} + b\ (X-\overline{X})$.

c: Controls accompanying interventions.

ne: Treated with norepinephrine.

60: Stimulus frequency increased from 30 per minute to 60 per minute.

FH: Pretreatment values.

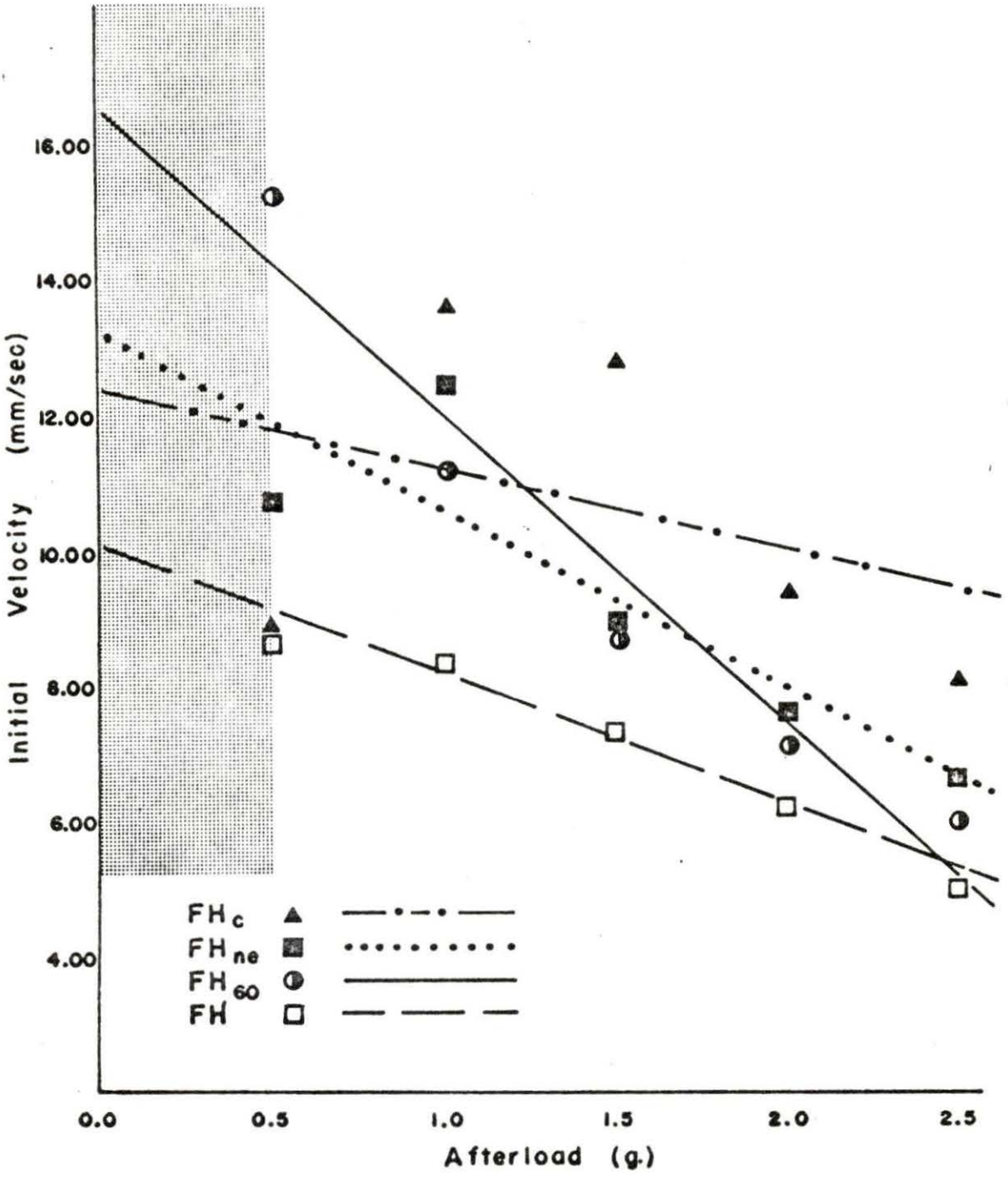
16.00
14.00
12.00
10.00
8.00
6.00
4.00
Initial Velocity (mm/sec)
FHc
FHne
FH60
FH
0.0
0.5
1.0
1.5
2.0
2.5
Afterload (g.)

Figure 7. Force-velocity relations of the right anterior papillary muscle from non-failing (NFH) hearts following the indicated interventions. Temperature: 27°C. Stimulus frequency: 30 per minute. Ordinate: Mean initial velocity of shortening. Abscissa: Afterload. Velocity of shortening has been extrapolated to zero afterload in order to approximate V_{MAX} (shaded area). Best fitting line: $Y = \overline{Y} + b\ (X-\overline{X})$.

c: Controls accompanying interventions.

ne: Treated with norepinephrine.

60: Stimulus frequency increased from 30 per minute to 60 per minute.

NFH: Pretreatment values.

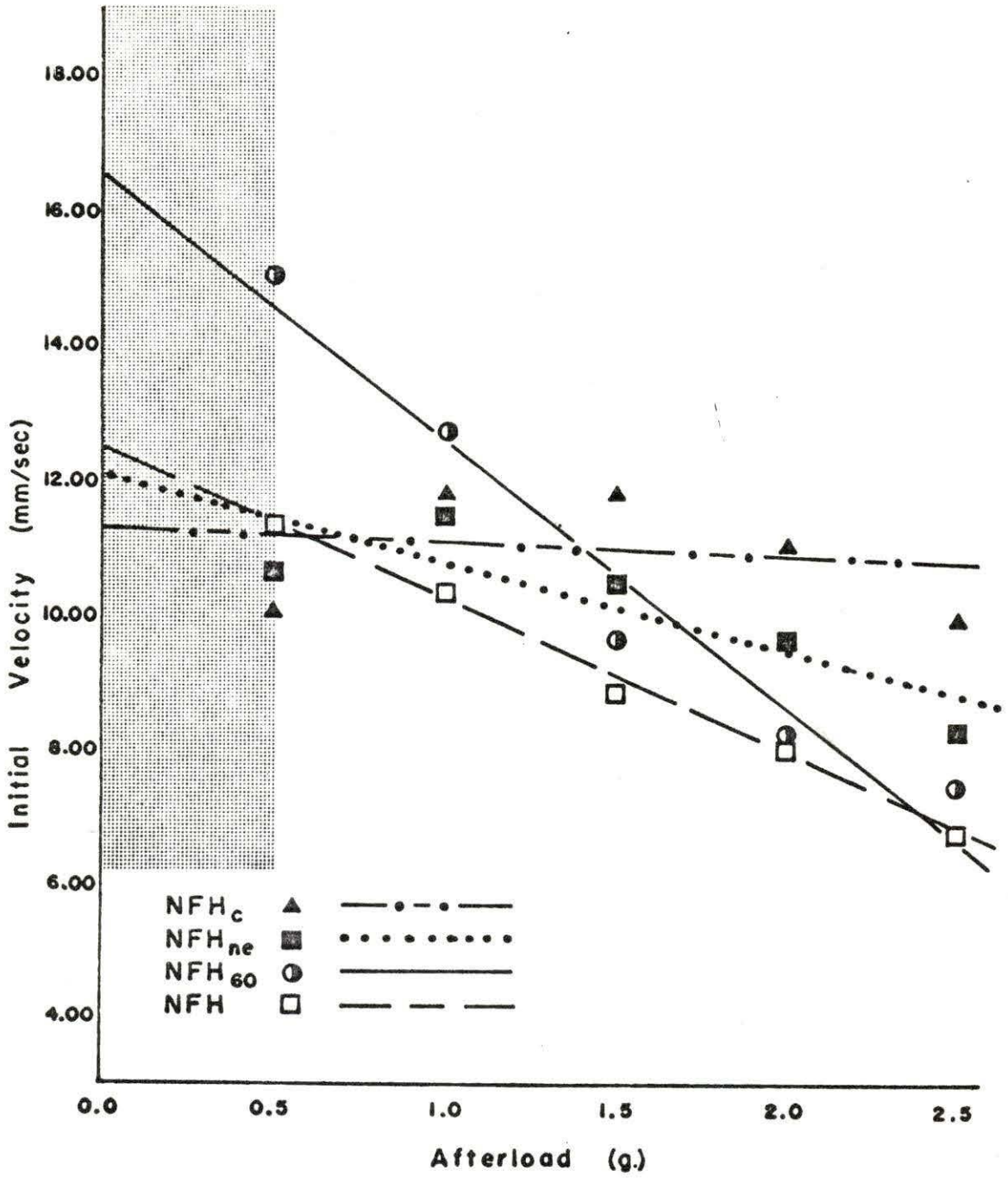
18.00
16.00
14.00
12.00
10.00
8.00
6.00
4.00
Initial Velocity (mm/sec)
0.0
0.5
1.0
1.5
2.0
2.5
Afterload (g.)
NFH$_c$
NFH$_{ne}$
NFH$_{60}$
NFH

Figure 8. Force-velocity relations of the right anterior papillary muscle from failing (FH) hearts over an abbreviated range of afterloads following the indicated interventions. Temperature: $27^{\circ}C$. Stimulus frequency: 30 per minute. Ordinate: Mean initial velocity of shortening. Abscissa: Afterload. Velocity of shortening has been extrapolated to zero afterload in order to approximate V_{MAX} (shaded area). Best fitting line: $Y = \bar{Y} + b\ (X-\bar{X})$.

c: Controls accompanying interventions.

ne: Treated with norepinephrine.

60: Stimulus frequency increased from 30 per minute to 60 per minute.

FH: Pretreatment values.

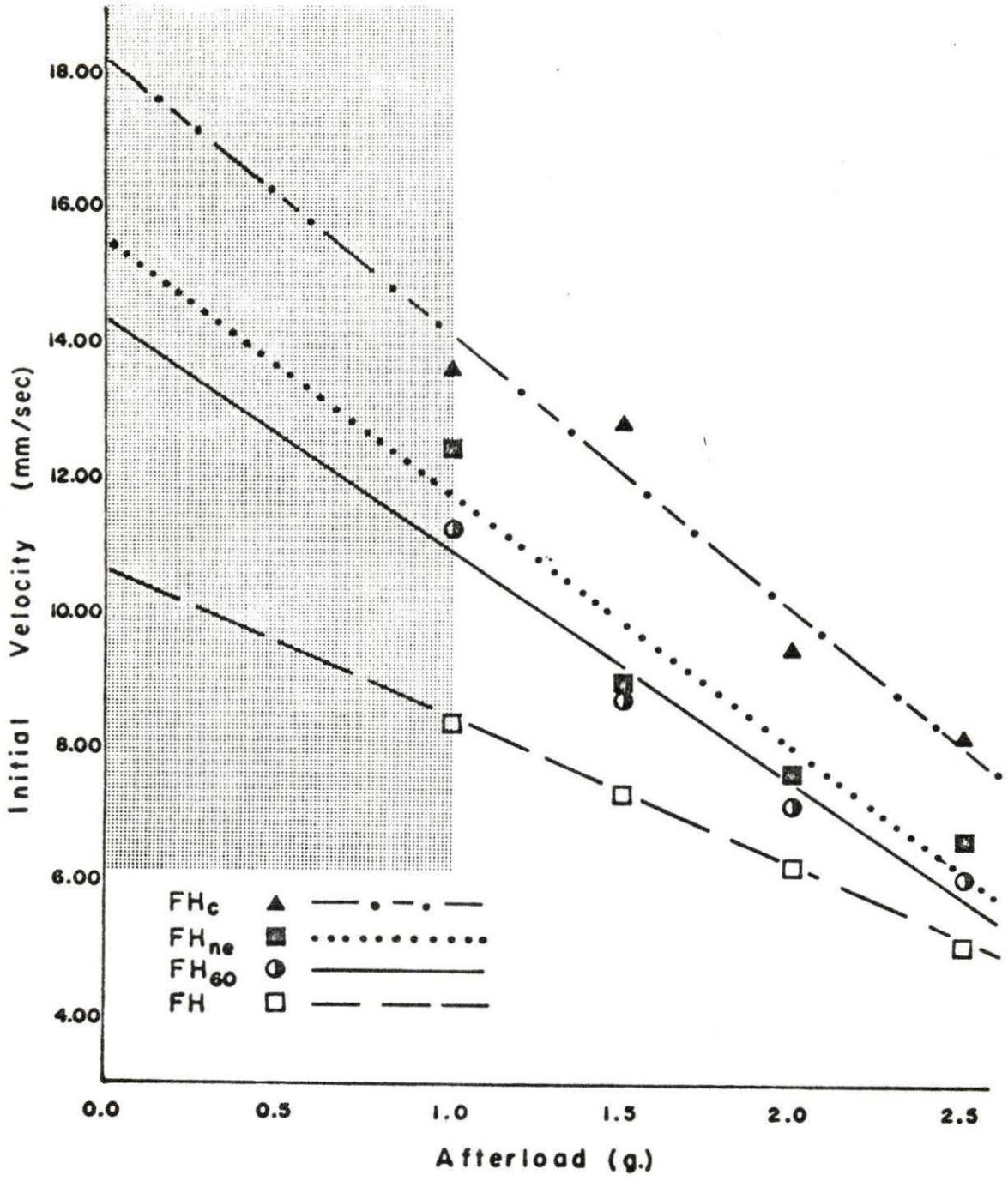
18.00
16.00
14.00
12.00
10.00
8.00
6.00
4.00
Initial Velocity (mm/sec)
FHc
FHne
FH60
FH
0.0
0.5
1.0
1.5
2.0
2.5
Afterload (g.)

Figure 9. Force-velocity relations of the right anterior papillary muscle from non-failing (NFH) hearts over an abbreviated range of afterloads following the indicated interventions. Temperature: 27°C. Stimulus frequency: 30 per minute. Ordinate: Mean initial velocity of shortening. Abscissa: Afterload. Velocity of shortening has been extrapolated to zero afterload in order to approximate V_{MAX} (shaded area). Best fitting line: $Y = \overline{Y} + b\ (X-\overline{X})$.

c: Controls accompanying interventions.

ne: Treated with norepinephrine.

60: Stimulus frequency increased from 30 per minute to 60 per minute.

NFH: Pretreatment values.

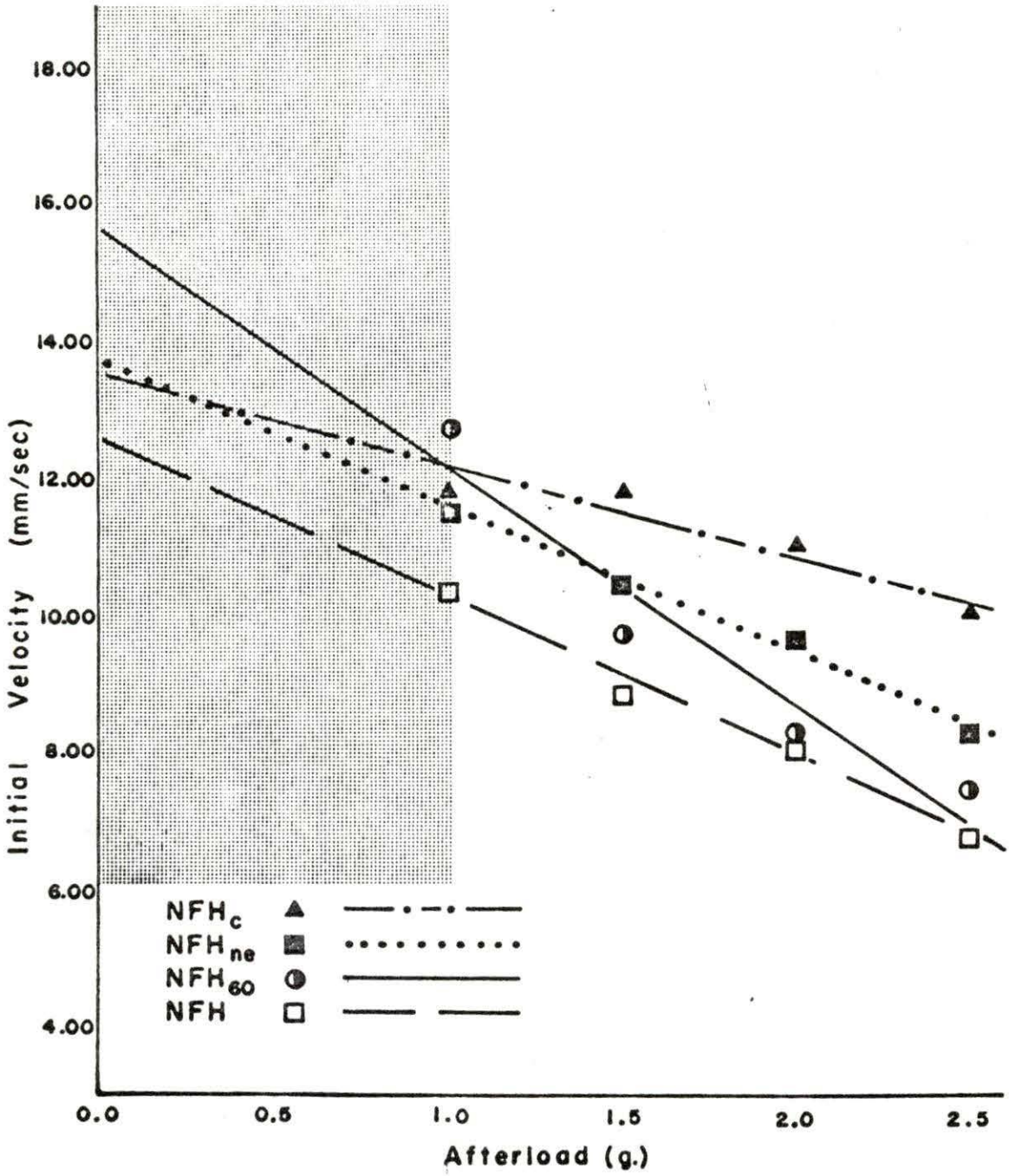
18.00
16.00
14.00
12.00
10.00
8.00
6.00
4.00
Initial Velocity (mm/sec)
0.0
0.5
1.0
1.5
2.0
2.5
Afterload (g.)
NFH$_c$
NFH$_{ne}$
NFH$_{60}$
NFH

Figure 10. The relative amplitude of contraction (mm) of the right anterior papillary muscle from failing (FH) and non-failing (NFH) hearts treated with norepinephrine (ne). Values are mean values $\pm$ standard deviation.

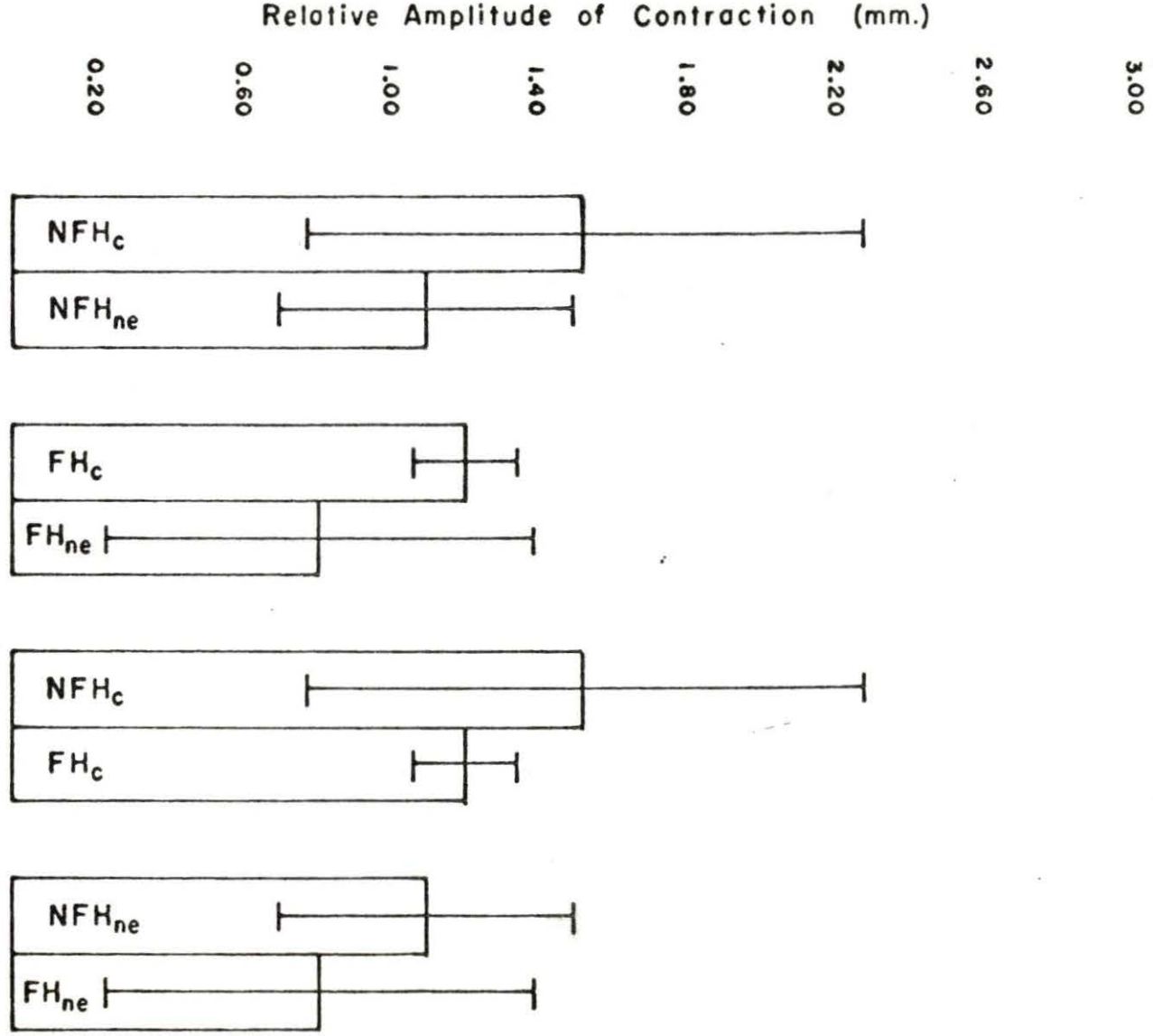
Relative Amplitude of Contraction (mm.)
0.20
0.60
1.00
1.40
1.80
2.20
2.60
3.00
NFHc
NFHne
FHc
FHne
NFHc
FHc
NFHne
FHne

Figure 11. A comparison of the effect of various interventions on the time intervals of contraction in failing (FH) and non-failing (NFH) heart muscle. Temperature: 27°C. Stimulus frequency: 30 per minute.

t_1: Time (sec) from stimulus to mechanical response.

t_2: Time (sec) from mechanical response to peak amplitude.

T: $t_1 + t_2$.

c: Controls accompanying interventions.

ne: Treated with norepinephrine.

60: Stimulus frequency increased from 30 per minute to 60 per minute in order to observe the effects of increased frequency on contractility.

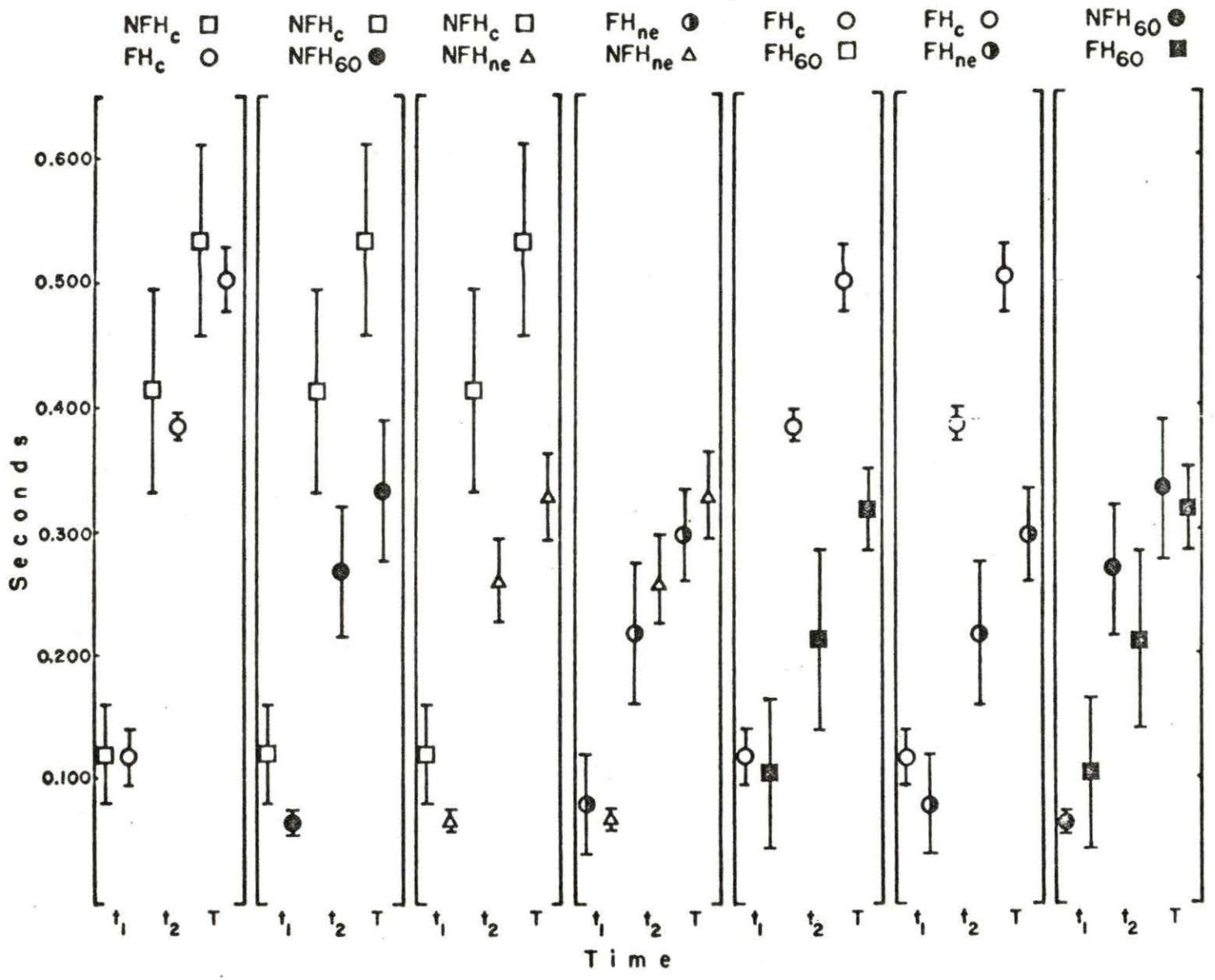
NFH$_c$ □
FH$_c$ ○
NFH$_c$ □
NFH$_{60}$ ●
NFH$_c$ □
NFH$_{ne}$ △
FH$_{ne}$ ◑
NFH$_{ne}$ △
FH$_c$ ○
FH$_{60}$ □
FH$_c$ ○
FH$_{ne}$ ◑
NFH$_{60}$ ●
FH$_{60}$ ■
0.600
0.500
0.400
0.300
0.200
0.100
Seconds
t$_1$ t$_2$ T
Time

TABLE 1. The determination of the degree of fatigue suffered by the right anterior papillary muscle from failing (FH) and non-failing hearts (NFH) during the course of the experimental procedure*

Heart	Initial+ Run	Control‡ Run	%
NFH 2	14.40	12.51	-13
3	11.93	9.27	-22
4	8.88	5.74	-38
5	15.37	9.54	-38
6	5.96	4.22	-29
		$\bar{X} \pm$ S.D.:	-28±10.75
FH 2	9.31	8.81	- 5
3	8.61	7.22	-16
4	9.83	8.06	-18
5	6.34	6.45	+ 1
6	10.27	6.04	-41
		$\bar{X} \pm$ S.D.:	-16±16.11
Overall mean ± S.D.: -22±14.42		P 0.05: N.S.	

* Values listed are initial velocities of shortening (mm/sec) at optimal preload and 0.5 g afterload.

\+ Initial run: Represents values collected during the pretreatment phase of the experimental procedure.

‡ Control run: Run accompanying interventions.

TABLE 2 . Initial velocity (mm/sec) of shortening of the right anterior papillary muscle from non-failing hearts (NFH)

	Preload-Afterload (g)					
Heart	0.5-0.5	0.5-1.0	0.5-1.5	0.5-2.0	0.5-2.5	0.5-3.0
NFH 2	12.24	9.31	5.54	3.27	*	*
NFH 3	9.74	7.48	4.75	2.47		
NFH 4	11.45	9.05	6.32	4.62		
NFH 5	8.58	6.52	6.60	6.32		
NFH 6	6.45	4.71	2.83	1.57		
Heart	0.75-0.5	0.75-1.0	0.75-1.5	0.75-2.0	0.75-2.5	0.75-3.0
NFH 2	14.68	12.79	8.81	8.00	5.57	*
NFH 3	10.41	9.42	7.66	5.64	4.10	
NFH 4	8.88	8.81	5.08	4.74	3.65	
NFH 5	11.06	10.85	10.00	9.96	9.16	
NFH 6	7.22	5.53	4.49	3.13	2.11	
Heart	1.0-0.5	1.0-1.0	1.0-1.5	1.0-2.0	1.0-2.5	1.0-3.0
NFH 2	14.68	13.31	10.55	9.42	6.92	*
NFH 3	10.96	10.80	9.05	7.95	5.46	
NFH 4	8.24	7.74	5.52	4.55	3.74	
NFH 5	13.88	12.72	12.31	11.93	10.41	
NFH 6	5.96	5.25	4.32	3.50	2.69	

TABLE 2 . (Continued)

	Preload-Afterload (g)					
Heart	1.25-0.5	1.25-1.0	1.25-1.5	1.25-2.0	1.25-2.5	1.25-3.0
NFH 2	16.84	16.01	13.71	11.99	9.20	7.61
NFH 3	11.93	10.90	9.54	8.42	5.48	3.21
NFH 4	7.53	7.16	6.14	5.53	3.91	2.94
NFH 5	15.37	13.80	13.88	12.72	12.38	11.22
NFH 6	5.53	4.95	4.44	3.68	2.92	1.93
Heart	1.5-0.5	1.5-1.0	1.5-1.5	1.5-2.0	1.5-2.5	1.5-3.0
NFH 2	14.40	13.08	11.68	11.68	9.79	8.81
NFH 3	12.05	11.01	8.74	6.74	7.02	5.43
NFH 4	7.27	6.38	6.52	5.35	4.54	3.78
NFH 5	15.27	15.06	13.47	11.99	10.04	9.62
NFH 6	5.16	4.54	3.92	3.30	2.94	2.09
Heart	2.0-0.5	2.0-1.0	2.0-1.5	2.0-2.0	2.0-2.5	2.0-3.0
NFH 2	13.96	12.05	11.68	10.09	9.35	8.27
NFH 3	10.18	8.98	6.84	4.74	2.92	1.30
NFH 4	6.17	5.96	5.22	4.61	3.97	3.15
NFH 5	10.65	9.87	8.88	8.48	7.92	7.63
NFH 6	4.62	4.04	3.77	3.28	2.63	2.15

* Note: Missing values are a result of zero response or a poorly defined curve. Stimulus frequency: 30 per minute.

TABLE 3 . Initial velocity (mm/sec) of shortening of the right anterior papillary muscle from failing hearts (FH)

	Preload-Afterload (g)					
Heart	0.5-0.5	0.5-1.0	0.5-1.5	0.5-2.0	0.5-2.5	0.5-3.0
FH 2	5.54	4.37	3.45	1.35	*	*
FH 3	6.80	5.49	4.15	2.88		
FH 4	5.49	4.82	3.32	1.93		
FH 5	6.90	4.66	3.52	2.35		
FH 6	2.80	2.76	1.41	1.22		
Heart	0.75-0.5	0.75-1.0	0.75-1.5	0.75-2.0	0.75-2.5	0.75-3.0
FH 2	7.76	6.38	4.82	3.49	*	*
FH 3	8.42	6.47	5.02	3.22		
FH 4	6.92	5.90	4.67	3.50		
FH 5	8.54	6.09	4.91	2.27	2.01	
FH 6	7.22	5.89	5.32	3.52	2.72	
Heart	1.0-0.5	1.0-1.0	1.0-1.5	1.0-2.0	1.0-2.5	1.0-3.0
FH 2	8.27	8.01	6.09	4.48	*	*
FH 3	9.79	8.04	6.86	5.83		
FH 4	9.38	8.36	7.23	6.03		
FH 5	6.96	6.03	5.54	4.49	3.59	
FH 6	8.74	7.34	6.14	5.74	4.83	

TABLE 3 . (Continued)

	Preload-Afterload (g)					
Heart	1.25-0.5	1.25-1.0	1.25-1.5	1.25-2.0	1.25-2.5	1.25-3.0
FH 2	9.42	8.81	7.79	6.54	4.71	*
FH 3	8.61	8.71	7.34	6.29	3.11	
FH 4	9.83	8.94	8.18	7.09	5.24	
FH 5	6.34	5.99	5.16	4.40	3.77	2.83
FH 6	10.27	9.16	8.45	6.78	5.65	3.32
Heart	1.5-0.5	1.5-1.0	1.5-1.5	1.5-2.0	1.5-2.5	1.5-3.0
FH 2	9.31	9.27	8.01	7.13	5.64	*
FH 3	8.48	8.12	6.96	5.96	5.09	4.31
FH 4	9.23	8.42	7.71	5.86	5.29	
FH 5	5.22	4.82	4.31	3.70	3.11	2.40
FH 6	9.54	8.18	6.22	4.54	2.88	
Heart	2.0-0.5	2.0-1.0	2.0-1.5	2.0-2.0	2.0-2.5	2.0-3.0
FH 2	8.91	8.61	7.74	7.44	6.16	*
FH 3	6.98	6.47	5.72	4.98	3.98	3.20
FH 4	7.87	7.02	6.36	0.00	0.00	0.00
FH 5	4.76	4.44	3.92	3.53	3.10	2.31
FH 6	6.70	6.16	5.32	4.52	2.95	1.56

* Note: Missing values are a result of zero response or a poorly defined curve. Stimulus frequency: 30 per minute.

TABLE 4 . Analysis of variance comparing the function of the right anterior papillary muscle from failing (FH) and non-failing (NFH) hearts*

source	df	s.s.	m.s.	calc. F	tab. F	P
Non-failing hearts vs failing hearts	1	346	346	2.86	5.32	n.s.
Among hearts within groups	8	967	121			
Preload effect	5	350	70	10.9	2.45	<0.005
NFH, FH X preload interaction	5	7	1.4	0.22	2.45	n.s.
Among hearts within groups X preload	40	254	6.4			
Afterload effect	3	418	139	198	2.67	<0.005
NFH, FH X afterload interaction	3	4	1.4	2.00	2.67	n.s.
Residual	144	105	0.7			

$\bar{X}_{NFH}$ - 8.51 $\quad\quad$ $\hat{\sigma}$ - 11.0 $\quad\quad$ $\bar{X}_{FH}$ - 6.11

* Values analyzed were initiated velocities of shortening (mm/sec) over a range of preloads and afterloads.

TABLE 5 . The effect of norepinephrine on the initial velocity (mm/sec) of shortening of the right anterior papillary muscle of non-failing hearts*

	Afterload (g)					
Heart	0.5	1.0	1.5	2.0	2.5	3.0
NFH_c+ 2	12.51	13.71	13.88	12.05	11.34	8.39
NFH_c 3	9.27	12.31	12.86	11.93	9.91	7.82
NFH_c 4	5.74	6.74	5.93	5.77	4.82	4.28
NFH_c 5	9.54	10.55	10.60	10.75	10.27	7.84
NFH_c 6	4.22	5.61	5.43	5.07	4.73	4.01
Heart	0.5	1.0	1.5	2.0	2.5	3.0
NFH_{ne}‡ 2	12.94	14.22	12.05	10.55	8.48	7.90
NFH_{ne} 3	10.13	12.86	10.09	9.38	7.39	5.49
NFH_{ne} 4	5.81	5.49	5.71	5.74	4.78	4.23
NFH_{ne} 5	10.09	9.31	9.96	9.31	9.50	7.09
NFH_{ne} 6	4.66	5.39	5.30	4.69	4.04	3.61

*Note: Stimulus frequency: 30 per minute.

+NFH_c: Non-failing heart muscle without interventions.

‡NFH_{ne}: Non-failing heart muscle treated with norepinephrine.

TABLE 6 . The effect of norepinephrine on the initial velocity (mm/sec) of shortening of the right anterior papillary muscle of failing hearts*

	Afterload (g)					
Heart	0.5	1.0	1.5	2.0	2.5	3.0
FH_c+ 2	8.81	10.75	12.18	10.96	10.22	8.18
FH_c 3	7.22	8.33	7.90	7.02	6.98	5.26
FH_c 4	8.06	10.36	8.81	2.72	0.00	0.00
FH_c 5	6.45	17.62	15.79	12.05	10.85	9.35
FH_c 6	6.04	9.31	8.18	6.16	5.46	3.47
Heart	0.5	1.0	1.5	2.0	2.5	3.0
FH_{ne}‡ 2	9.05	10.55	10.50	9.38	8.04	7.39
FH_{ne} 3	7.90	7.48	6.41	5.96	6.01	6.09
FH_{ne} 4	9.38	8.36	0.00	0.00	0.00	0.00
FH_{ne} 5	9.83	16.47	12.94	10.65	9.31	8.98
FH_{ne} 6	8.27	8.18	7.09	5.71	4.14	2.95

* Note: Stimulus frequency: 30 per minute.

+ NFH_c: Non-failing heart muscle without interventions.

‡ NFH_{ne}: Non-failing heart muscle treated with norepinephrine.

TABLE 7 . Analysis of variance comparing the effect of norepinephrine (ne) on the function of the right anterior papillary muscle from failing (FH) and non-failing (NFH) hearts*

source	df	s.s.	m.s.	calc. F	tab. F	P
Non-failing hearts vs failing hearts	1	20	20	0.23	5.32	n.s.
Among hearts within groups	8	706	88			
With ne vs without ne	1	34	34	20.0	5.32	<0.005
NFH, FH X with ne without ne	1	0.7	0.7	0.41	5.32	n.s.
Among hearts within groups X ne	8	14	1.7			
Afterload effect	3	130	43	35.8	3.01	<0.005
NFH, FH X afterload interaction	3	5	1.7	1.4	3.01	n.s.
Among hearts within groups X afterload	24	28	1.2			
With ne, without ne X afterload interaction	3	7	2.3	2.85	3.01	n.s.

TABLE 7. (Continued)

source	df	s.s.	m.s.	calc. F	tab. F	P
NFH, FH X ne X afterload interaction	3	5	1.7	2.1	3.01	n.s.
Residual	24	19	0.8			
$\bar{X}_{NFH}$ - 7.82		$\hat{\sigma}$ - 9.4			$\bar{X}_{FH}$ - 6.83	

* Values analyzed were initial velocities of shortening (mm/sec) at optimal preload and over a range (1.5-3.0 g) of afterloads.

TABLE 8 . A comparison of the initial velocity (mm/sec) of contraction of the right anterior papillary muscle of failing (FH) and non-failing hearts (NFH) following the indicated interventions (corrected for fatique)*

NFH^{+}	9.13±1.80	NFH_c	11.00±0.93
$FH^{\ddagger}$	7.23±1.54	NFH	9.13±1.80
P:	N.S.	P:	0.10
NFH_c §	11.00±0.93	NFH_{ne}	10.14±1.20
NFH_{ne} A	10.14±1.20	NFH	9.13±1.80
P:	N.S.	P:	N.S.
FH_c	10.65±2.50	NFH_{60}	10.68±3.20
FH_{ne}	9.35±2.32	NFH	9.13±1.80
P:	N.S.	P:	N.S.
NFH_{60} B	10.68±3.21	FH_c	10.65±2.50
FH_{60}	9.76±3.66	FH	7.23±1.54
P:	N.S.	P:	0.05
NFH_c	11.00±0.93	FH_{ne}	9.35±2.32
FH_c	10.65±2.51	FH	7.23±1.54
P:	N.S.	P:	N.S.

TABLE 8. (Continued)

NFH_{ne}	10.14±1.20	FH_{60}	9.76±3.66
FH_{ne}	9.35±2.32	FH	7.23±1.54
P:	N.S.	P:	N.S.

* Values listed are mean velocities ± the standard deviation at optimal preload and over a range (0.5-2.5 g) of afterloads.

+ NFH: Non-failing heart muscle: represents values collected during the pretreatment phase of the experimental procedure.

‡ FH: Failing heart muscle: represents values collected during the pretreatment phase of the experimental procedure.

S
Sc: Controls accompanying interventions.

A
ne: Treated with norepinephrine.

B
60: Stimulus frequency increased from 30 per minute to 60 per minute in order to observe the effects of increased frequency of contraction on contractility.

TABLE 9. Analysis of variance comparing the effect of increased stimulus frequency on the function of the right anterior papillary muscle from failing (FH) and non-failing hearts* (NFH)

source	df	s.s.	m.s.	calc. F	tab. F	P
Non-failing hearts vs failing hearts	1	4.55	4.55	0.12	5.32	n.s.
Among hearts within groups	8	306.54	38.32			
Afterload effect	3	218.05	72.70	71.20	2.96	< 0.005
Residual	27	27.50	1.02			

$\bar{X}_{NFH} - 9.42$ $\quad \hat{\sigma} - 6.20$ $\quad \bar{X}_{FH} - 8.74$

* Values analyzed were initial velocities of shortening (mm/sec) at optimal preload and over a range (0.5-2.0 g) of afterloads.

TABLE 10 . The effect of increased stimulus frequency on the initial velocity (mm/sec) of shortening of the right anterior papillary muscle of non-failing (NFH) and failing hearts (FH)

	Afterload (g)					
Heart	0.5	1.0	1.5	2.0	2.5	3.0
NFH_{60}* 2	15.16	12.51	9.91	7.95	7.61	6.36
NFH_{60} 3	15.90	13.55	10.00	8.54	7.39	5.24
NFH_{60} 4	9.54	8.36	7.11	5.99	4.97	3.54
NFH_{60} 5	13.88	12.05	8.24	7.61	7.27	5.74
NFH_{60} 6	7.58	5.87	4.70	3.82	3.40	3.01
Heart	0.5	1.0	1.5	2.0	2.5	3.0
FH_{60}+ 2	16.36	13.63	11.93	10.96	9.54	9.12
FH_{60} 3	12.44	8.64	7.87	5.44	4.76	3.23
FH_{60} 4	10.90	5.09	2.43	0.00	0.00	0.00
FH_{60} 5	13.55	11.99	9.09	8.77	7.46	6.19
FH_{60} 6	9.54	6.92	4.94	4.33	3.41	2.10

* NFH_{60}: Non-failing heart muscle with stimulus frequency increased from 30 per minute to 60 per minute.

+ FH_{60}: Failing heart muscle with stimulus frequency increased from 30 per minute to 60 per minute.

TABLE 11 . The initial velocity of shortening (mm/sec) of the right anterior papillary muscle from failing (FH) and non-failing (NFH) hearts following the indicated interventions* (corrected for fatigue)

Afterload	NFH_c +	NFH_{ne} ‡	NFH_{60} §	NFH^A	FH_c	FH_{ne}	FH_{60}	FH
0.5	10.08	10.65	15.14	11.38	8.93	10.84	15.32	8.87
1.0	11.93	11.53	12.77	10.37	13.75	12.46	11.28	8.41
1.5	11.88	10.52	9.75	8.90	12.90	9.02	8.84	7.43
2.0	11.11	9.67	8.27	8.21	9.49	7.73	7.20	6.34
2.5	10.02	8.34	7.48	6.80	8.17	6.71	6.14	5.08
3.0	7.89	6.90	5.83	B	6.40	6.20	5.04	B

* Values listed are mean velocities at optimal preload and the indicated afterload.

\+ c: Controls accompanying interventions.

‡ ne: Treated with norepinephrine.

§ 60: Stimulus frequency increased from 30 per minute to 60 per minute in order to observe the effects of increased frequency of contraction on contractility.

A Represents values collected during the pretreatment phase of the experimental procedure.

B Missing values are a result of zero response or a poorly defined curve.

TABLE 12. A comparison of the effects of norepinephrine and increased stimulus frequency on the time intervals of contraction of the right anterior papillary muscle from failing (FH) and non-failing hearts (NFH)*

Comparison	t_1+	t_2‡	T_S§
NFH_c [A]	0.120±0.039	0.415±0.081	0.535±0.077
FH_c [B]	0.117±0.023	0.386±0.011	0.503±0.025
P:	N.S.	N.S.	N.S.
NFH_c	0.120±0.039	0.415±0.081	0.535±0.077
NFH_{ne} [C]	0.067±0.008	0.262±0.035	0.329±0.035
P:	0.05	0.025	0.01
FH_c	0.117±0.023	0.386±0.011	0.503±0.025
FH_{ne} [D]	0.081±0.039	0.217±0.058	0.297±0.038
P:	N.S.	0.005	0.001
NFH_{ne}	0.067±0.008	0.262±0.035	0.329±0.035
FH_{ne}	0.081±0.039	0.217±0.058	0.297±0.038
P:	N.S.	N.S.	N.S.
NFH_{60} [E]	0.065±0.007	0.269±0.053	0.334±0.057
FH_{60} [F]	0.105±0.059	0.212±0.071	0.317±0.033
P:	N.S.	N.S.	N.S.

TABLE 12. (Continued)

Heart	t_1 [+]	t_2 [‡]	T [§]
NFH_c	0.120±0.039	0.415±0.081	0.535±0.007
NFH_{60}	0.065±0.007	0.269±0.053	0.334±0.057
P:	0.05	0.05	0.01
FH_c	0.117±0.023	0.386±0.011	0.503±0.025
FH_{60}	0.105±0.059	0.212±0.071	0.317±0.033
P:	N.S.	0.005	0.001

* Values listed are mean values ± the standard deviation at optimal preload and a randomly selected afterload.

+ t_1: Time (sec) from stimulus to initiation of contraction.

‡ t_2: Time (sec) from initiation of contraction to peak amplitude.

§ T: $t_1 + t_2$.

A NFH_c: Non-failing heart muscle control accompanying interventions.

B FH_c: Failing heart muscle control accompanying interventions.

C NFH_{ne}: Non-failing heart muscle treated with norepinephrine.

D FH_{ne}: Failing heart muscle treated with norepinephrine.

E NFH_{60}: Non-failing heart muscle with stimulus frequency increased from 30 per minute to 60 per minute in order to observe the effects of increased frequency of contraction on contractility.

F FH_{60}: Failing heart muscle with stimulus frequency increased from 30 per minute to 60 per minute in order to observe the effects of increased frequency of contraction on contractility.