PHYSIOLOGY OF THE HEART

Mechanical Aspects of Muscle Contraction.

By

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This communication attempts to summarise current concepts of the mechanical properties of heart muscle. Not considered here are the electrophysiological antecedents of contraction and the nervous control of the heart and circulation.

The Contractile Element

The contractile properties of the myocardium are best understood by experiments which have been conducted on isolated strips of papillary muscle in which the fibres are parallel. The active tension developed by a strip of muscle which is not allowed to shorten (isometric contraction) increases with its length at the time of stimulation to a maximum and declines as the length is increased beyond the physiological range (Fig. 1.).

The ultrastructural basis of this phenomenon, which is a characteristic of the contractile element, is the sarcomere, a segment of a myofibril (Fig. 2). The parallel arrangement of myofibrils consisting of series of sacomeres gives the characteristic striations observed by light microscopy. In both skeletal and cardiac muscle, the length of a sarcomere associated with the development of the maximum active tension is approximately 2.2 μm, the length of which corresponds with the optimum overlap of the actin and myosin filaments enabling the maximum number of cross links between them. Active tension is not developed when the average length of sarcomeres is reduced to 1.5 μm. Unlike skeletal muscle sarcomeres which can be stretched to 3.5 μm at which length there is no overlap of the filaments or development of active tension, cardiac muscle sarcomeres cannot be stretehed beyond about 2.6 μm.

Gross distending pressures applied to intact ventricles have failed to lengthen sacomeres beyond 2.3 μm. Stretch alone does not explain the poor contraction of a failing ventricle.

Elastic Elements

The contraction of muscle liberates heat. The amount of heat is related directly to the degree of shortening of the muscle; thus, if the muscle is stretched while it is stimulated, less heat is released than if the muscle is held at a constant length.

During the early period after stimulation, the pattern of the release of heat is the same whether the muscle develops tension while its

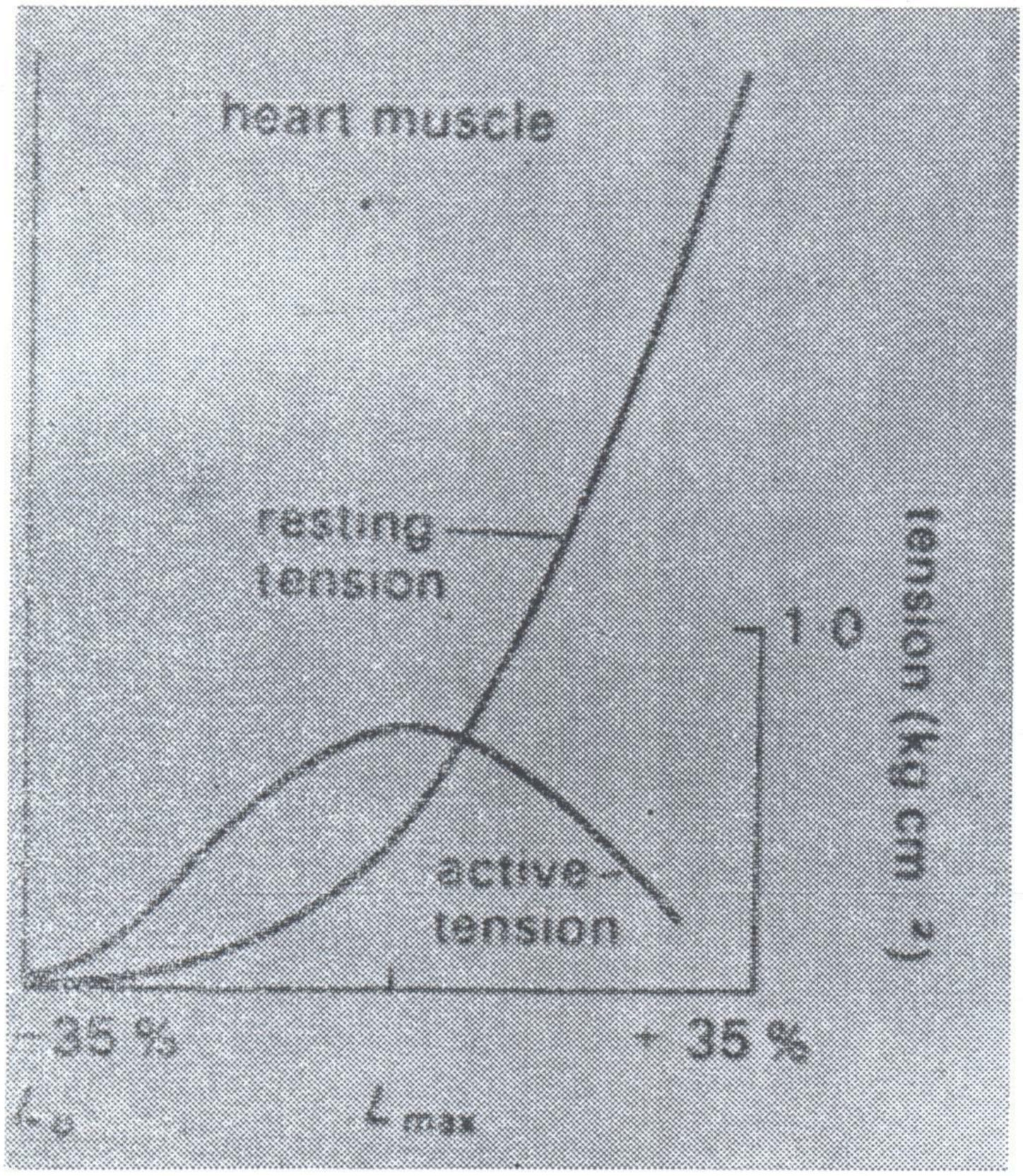


Figure 1 :
Length—tension curves of a strip of cardiac muscle. The length of the muscle at which maximum active tension is developed (Lmax) is associated with sarcomere lengths of 2.2—2.3 μm. Resting tension is that which occurs passively as a function of the length of the muscle. (Spiro and Sonnenblick (1964) Circulation Res. 15, Supplement 2, 14).

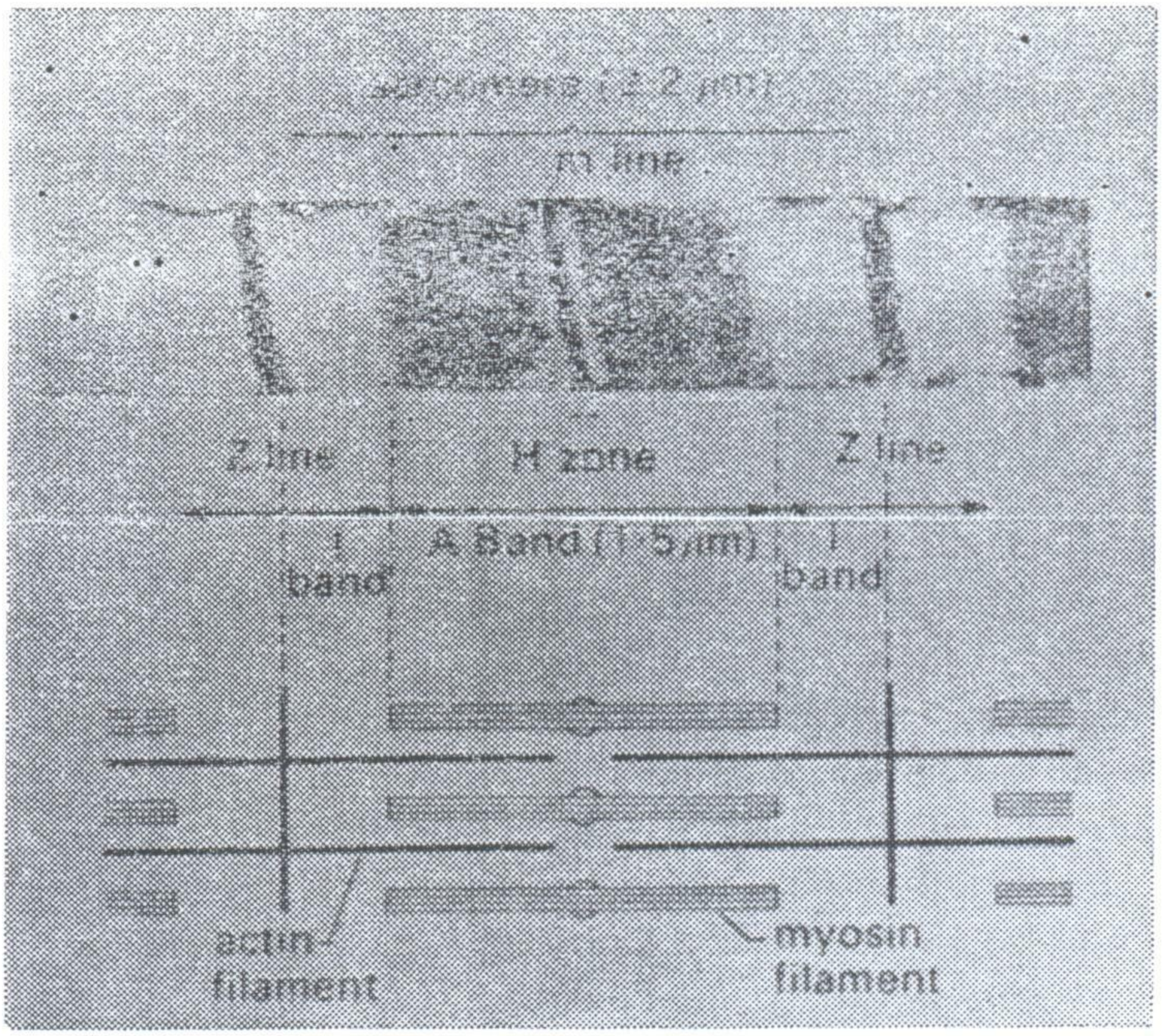


Figure 2 :
Above: Sarcomere structure as seen with an electron microscope. The sarcomere is bounded by a pair of Z bands. Within it is the dark central A band marked at its midpoint by the darker m line, and two paler I bands.

Below: Diagram of the actin and myosin filations which correspond with the structure of the sarcomere. Sonnenblick, Spiro and Spotnitz (1964). Am. Heart J. 68, 336.

length is held constant or while it shortens against a constant load. This indicates that similar mechanical processes ocur in the early phase of contraction irrespective of actual shortening of the muscle. The observation led to the concept of an elastic element which is placed in series with the contractile element so enabling the latter to shorten while the length of the muscle is constant.

The time course of contraction and relaxation of muscle is a modified form of that generated by the contractile element. The term active state refers to the tension developed by the contractile element. under conditions in which it is prevented from shortening. To measure the active state, therefore, the muscle has to be stretched after stimulation in order to maintain a constant length of the contractile element while its tension is measured. Figure 3 shows the time course of the active state of the contractile element and of the final tension development in skeletal muscle. The active state of cardiac muscle reaches a peak about 150 ms after stimulation. In both the maximum of the active state precedes the peak tension of the muscle and wanes while the muscle still shows active tension. The modifications of the active state is a function of the series elastic element.

The resting tension of a strip of cardiac muscle rises markedly, more so than skeletal muscle, as its length increases beyond that associated with the development of maximum active tension (Figure 1). This property is attributed to an elastic element which functions parallel with the contractile element. The structural associates of the series and parallel elastic elements have not been identified.

Properties of the Contractile Element

The relationship of shortening of muscle to the tension it develops is shown in Figure 4. In this study the length of the muscle at the onset of stimulation was constant and the load to be moved was varied. The muscle shortened when the active tension became equal to the load and remained constant while the muscle shortened. The amount and duration as well as the velocity of shortening (dl/dt just after the onset of shortening) decreased as the load increased.

The inverse relationship of the velocity of shortening of the contractile element to load was observed initially in skeletal muscle in which a constant active state was achieved by tetanic stimulation. As cardiac muscle is incapable of tetanic contraction and the active state varies during a twitch response, the velocity of shortening of the muscle is not as true an indicator of the contractile element as in the case of skeletal muscle.

Within the physiological range, the length of a strip of cardiac muscle at the time of stimulation has profound effects upon the properties of the contractile element as shown by the maximum load moved and the relationship of the velocity of shortening to load. Figure 5 shows that increasing the length of the muscle increases both the maximum load and the velocity of shortening for a given load.

Independent of length, contractility of the muscle, i.e. the intensity of the active state, is affected by external influences. For example, catecholamines enhance contractility; figure 6 illustrates that the maximum active tension developed and the velocity of shortening for a

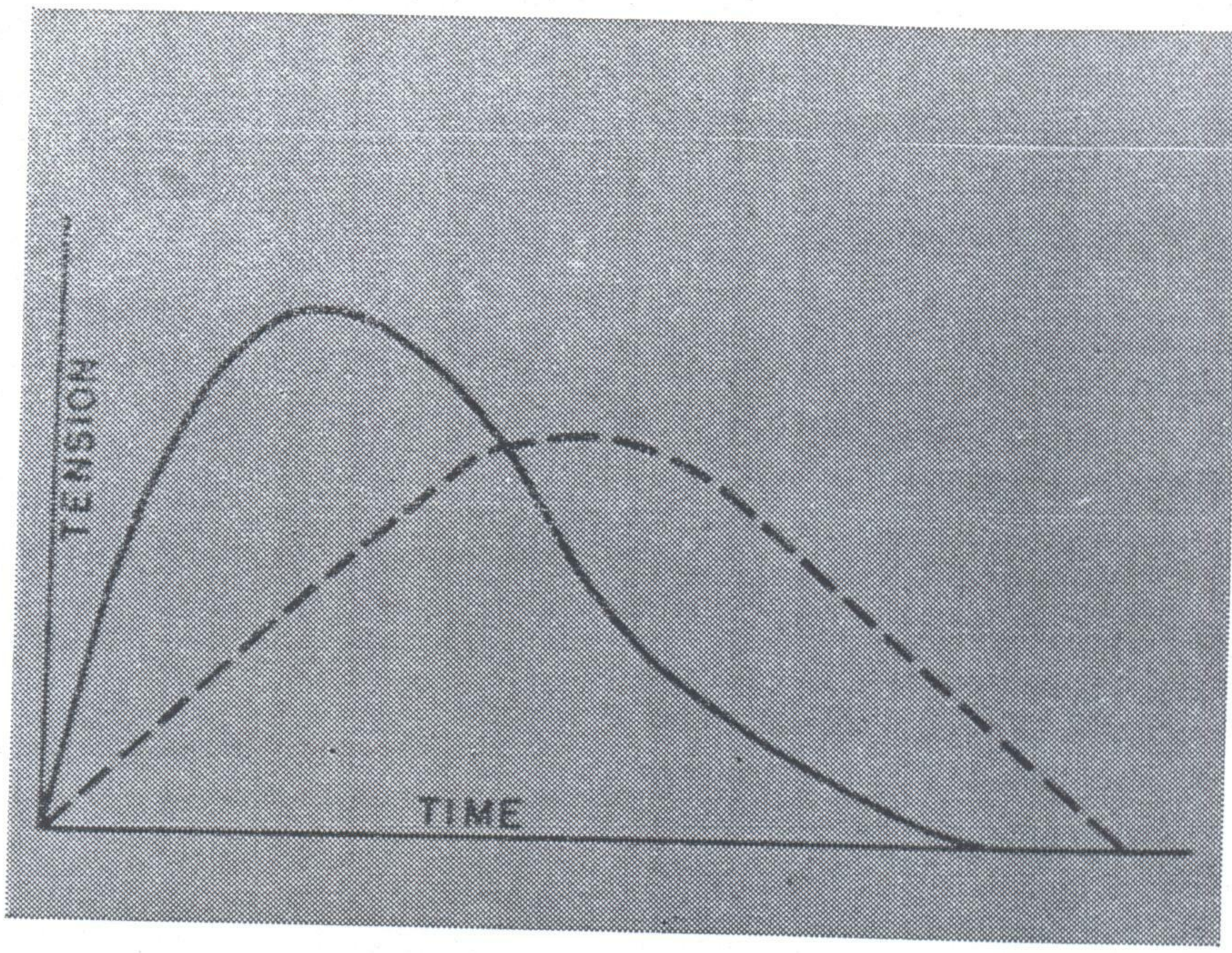
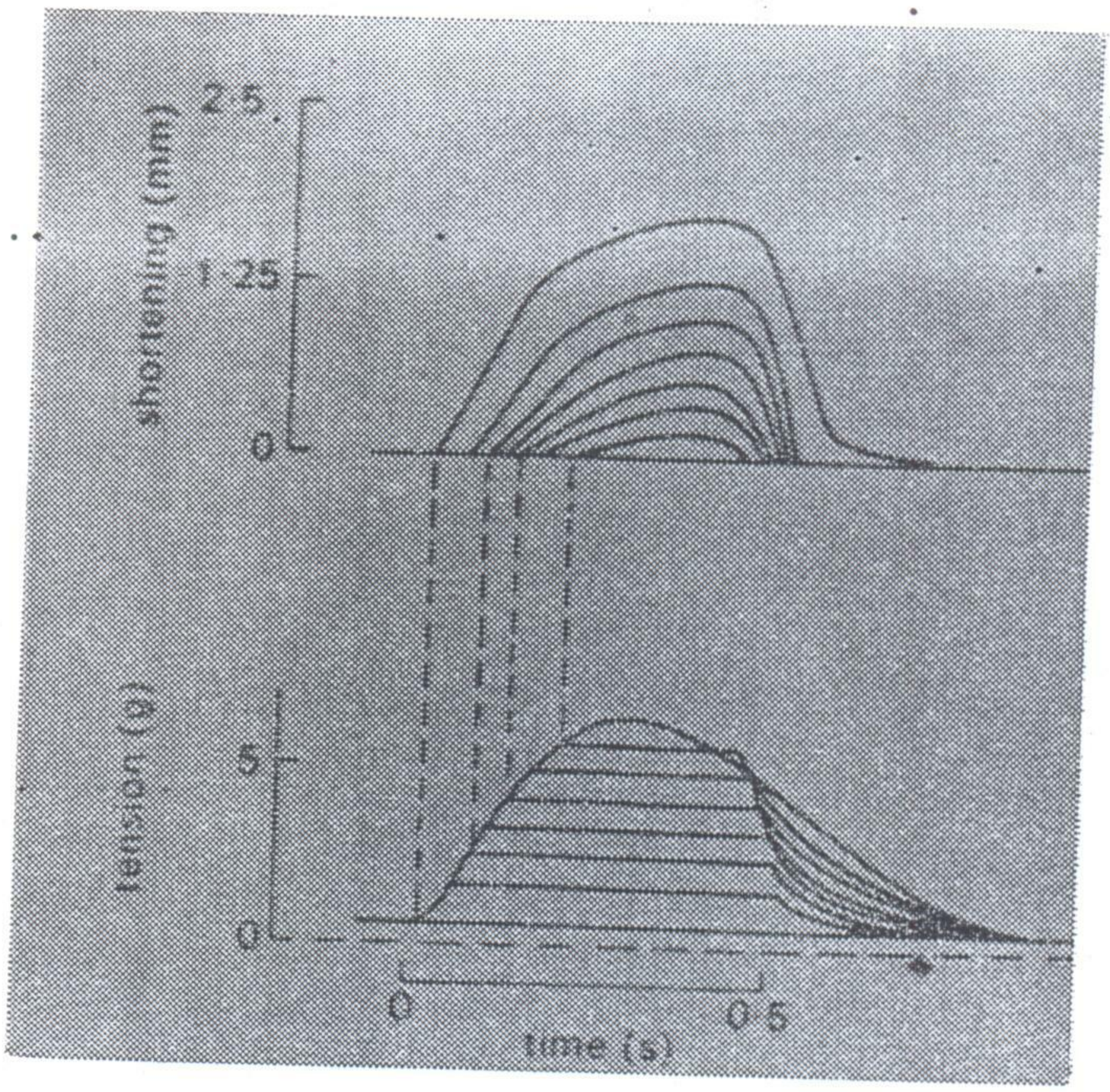


Figure 3 : Diagramatic representation of the development of tension by the contractile element, the active state (solid line), and the muscle as a whole during isometric contraction of skeletal muscle as a function of time. (Gasser and Hill (1924). Proc. Roy. Soc. London. Ser. B-96:398)

Figure 4:

A series of superimposed records showing the length and tension changes that occur in a cat papillary muscle which contracts against a series of different loads. The initial length was held constant; the lower family of curves shows that tension rose to match the load in each case, and then remained constant whilst shortening occured. The amount of shortening at each load is shown in the upper curve. The final tension curve shows the response when the muscle cannot liftthe load; this is the isometric twitch response. (Sonnenblick (1962). Am. J. Physiol. 202, 931).



given load are increased by the presence of nor-adrenalin in the perfusate.

The state of contractility cannot be measured directly but it can be described by the maximum active tension attainable at zero velocity of shortening and the relationship of the velocity of shortening to load moved when the length of muscle at the time of stimulation is constant.

By extrapolation, the observations shown in figure 5 suggest that the velocity of shortening would be constant at zero load (Vmax.), independent of changes in the length of the muscle. On the other hand the enhanced contractility induced by nor-adrenalin is reflected in a higher value of Vmax. (Figure 6). Thus Vmax held promise of a means of measuring the contractility of cardiac muscle. However, the derivation of Vmax takes no account of the resting tension which is dependent on the length of the muscle and is a function of the parallel elastic element. The functional model of the muscle is an essential factor is the interpretation of Vmax. Hence there is no simple means of measuring contractility.

Contractile Properties of Ventricles

Ventricles are endowed with the remarkable property of automatic adjustment of contractile performance to filling and after-load. While correlates of the properties of muscle strips can be recognised, the additional properties of intact ventricles possibly result from the distribution of the muscle fibres.

Muscle fibres arise from and are inserted into the fibrous skeleton which contains the heart valves at the base of the heart. From endocardium to epicardium of the left ventricle there is a progressively changing orientation of fibres. The fibres are distributed initially parallel to the long axis, then oblique to it due to a spiral arrangement, then circumferential in the mid thickness of the wall, then oblique due to a spiral disposition in the opposite direction to the first spiral layer, and finally parallel to the long axis in the sub-epicardium.

Pre-Load and Cardiac Output

Following on observations in frog hearts by Frank in the latter part of the nineteenth century, Starling studied canine heart-lung preparations and confirmed that ventricles respond to increased filling, within limits, by increasing the cardiac output. The mechanism is understood now on the basis of the relationship of load moved to the length of muscle. The end-diastolic volume of a ventricle is one determinant of its end-diastolic pressure, another factor being distensibility. The ventricular end-diastolic pressure (VEDP) is reflected by the mean pressure of the corresponding atrium. Thus the VEDP and mean atrial pressure are conventent indicators of muscle length at the onset of ventricular excitation and are referred to by the term pre-load. The contribution of atrial systole to ventricular filling is greatest in early diastole and least in late diastole. As the diastolic volume increases, a ventricle becomes less distensible thus an impressive rise in pressure due to atrial contraction in late diastole is associated with a small contribution to ventricles filling.

The work done by contraction of a strip of muscle is given by the product of the load against which contraction occurs and the dis-

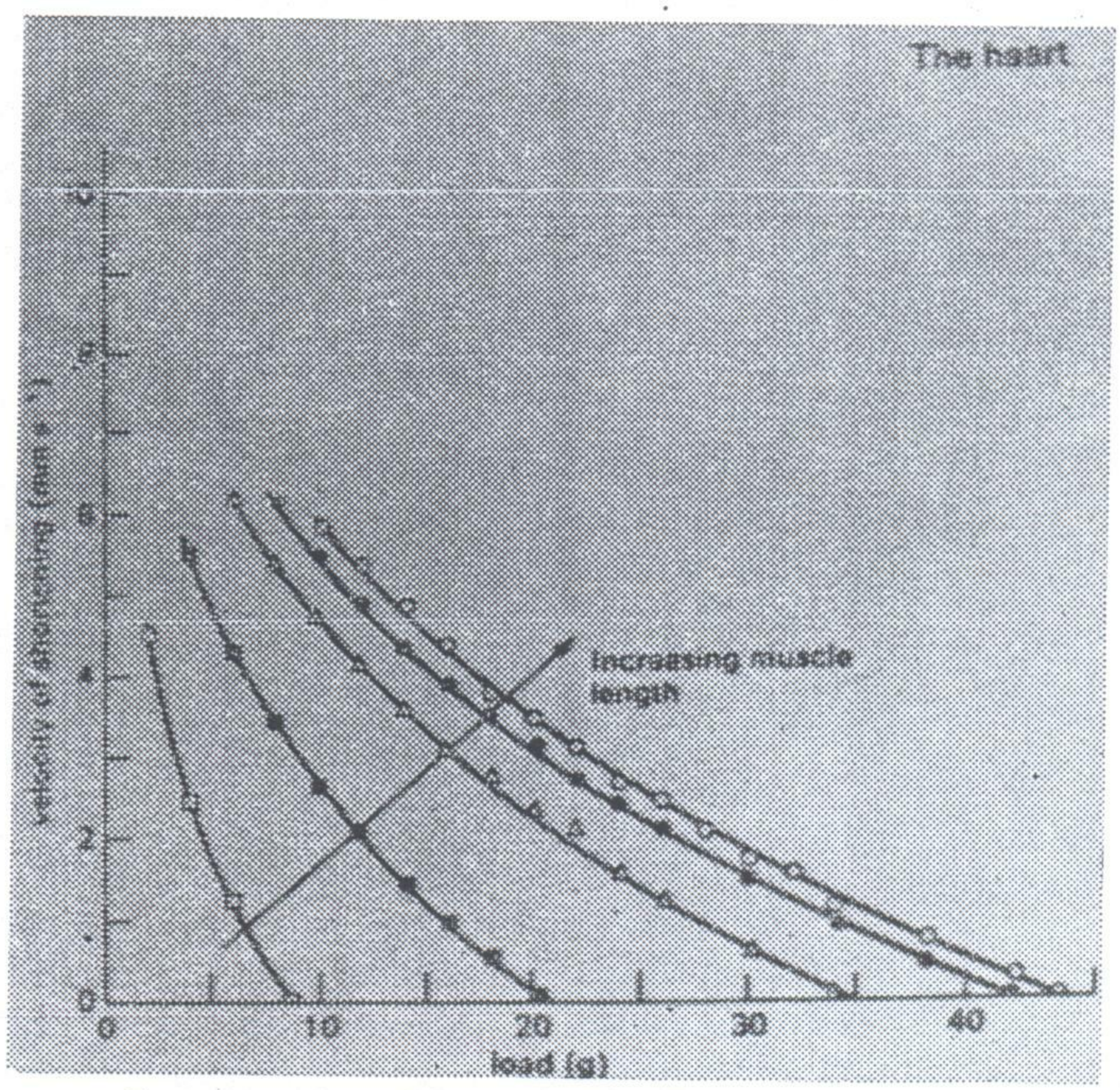


Figure 5*:* The contractile properties of a strip of cardiac muscle, shown by the force-velocity relationship, are altered by the length at the time of stimulation. (Sonnenblick (1962) A,m. J. Physiol. 202, 931).

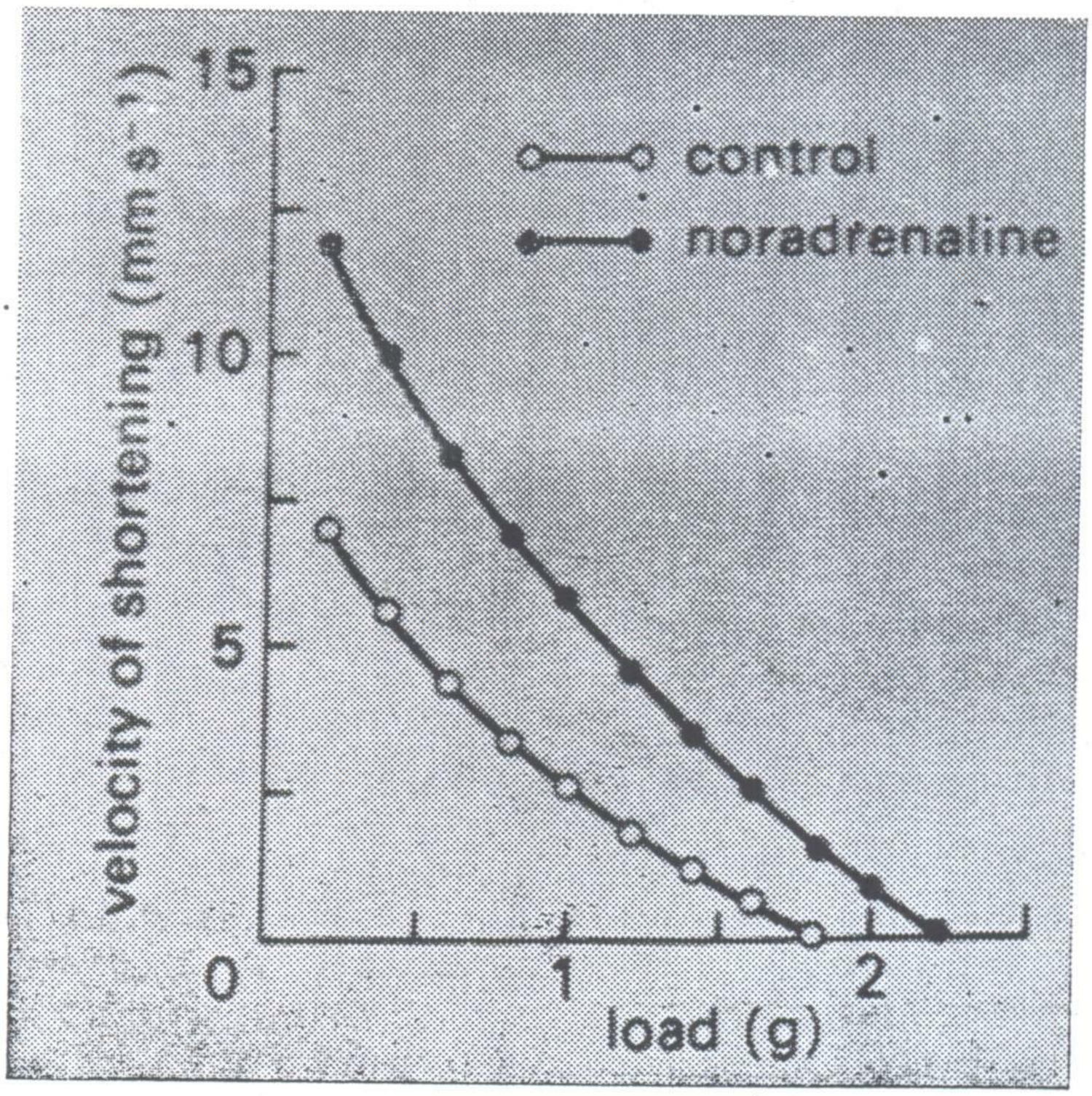


Figure 6*:* Effect of a positive inotropic intervention (the addition of noradrenalin to the perfusing bath) on the force-velocity relationship of isolated heart muscle. Initial muscle length held constant throughout. (Sonnenblick (1962). Am. J. Physiol. 202, 931).

tance it is moved. In the case of an intact ventricle, the product of stroke volume and the mean aortic pressure is a measure of the external work done per stroke. The relationship of stroke work to pre-load (ventricular function curve) defines the contractile state or contractility of the ventricle. A change in the contractile state is reflected by a different relationship of external work to pre-load. Figure 7 shows the effect of the intensity of sympathetic nerve stimulation upon contractility of the canine left ventricle. Each level of stimulation is distinguished by a separate ventricular function curve. Increased stimulation results in the ability to perform more stroke work for a given pre-load.

After-Load and Contractility

The ability of the left ventricle to adapt its contractility to work requirements is shown by the effect of increasing the after-load by raising the resistance to flow in the aorta. Initially the stroke volume is decreased slightly as the aortic pressure rises while the left ventricular end-diastolic pressure (LEVDP) and volume are increased. In subsequent beats the LEVDP and volume and the stroke volume return to the control value indicating that contractility has changed so that greater stroke work is achieved at the original pre-load. Accompanying this effect are a faster rate of change of pressure during isometric contraction and relaxation, a shorter period of ejection and hence a longer diastole. The rate of ejection of a ventricle is the counterpart of the velocity of shortening of a strip of muscle. Similar changes occur when there is a sudden, marked increase in the rate of stimulation. These changes are similar to the positive inotropic influence, i.e. enhanced contractility, induced by stimulation of the sympathetic nervous sytem. Figure 8 shows the effect of increasing the pre-load and after-load upon stroke volume and stroke work. Changes in after-load are more effective than ventricular filling, reflected by the mean left atrial pressure, in causing changes in stroke work. However, the pre-load determines the magnitude of stroke work which can be achieved by increasing after-load.

It appears that myocardial tension, which is dependent upon after-load, is the main determinant of enhanced contractility. In an experiment designed to decrease stroke work by reducing the inflow to a canine left ventricle while increasing the resistance to flow in the aorta, the sustained increase in aortic pressure was associated with a slow decline in LVEDP sometime after the steady state of the reduced stroke work was achieved (Figure 9). The slow reduction of LVEDP indicates an increase in contractility. Furthermore, during this period, myocardial oxygen consumption was increased although external work was decreased. Thus myocardial tension rather than stroke work seems to be the prime determinant of myocardial consumption of oxygen.

Asynchronous Contraction

The contractile properties of an intact ventricle are strongly dependent upon synchronous contraction of the whole ventricle which is assured by the sequence of depolarisation determined by the distribution of the specialised conduction tissue. In the canine heart, changing the site of pacing from atrium to ventricle causes a marked reduction of stroke volume and stroke work and an increase in the ejection time of the ventricle. All these parameters indicate decreased contractility.

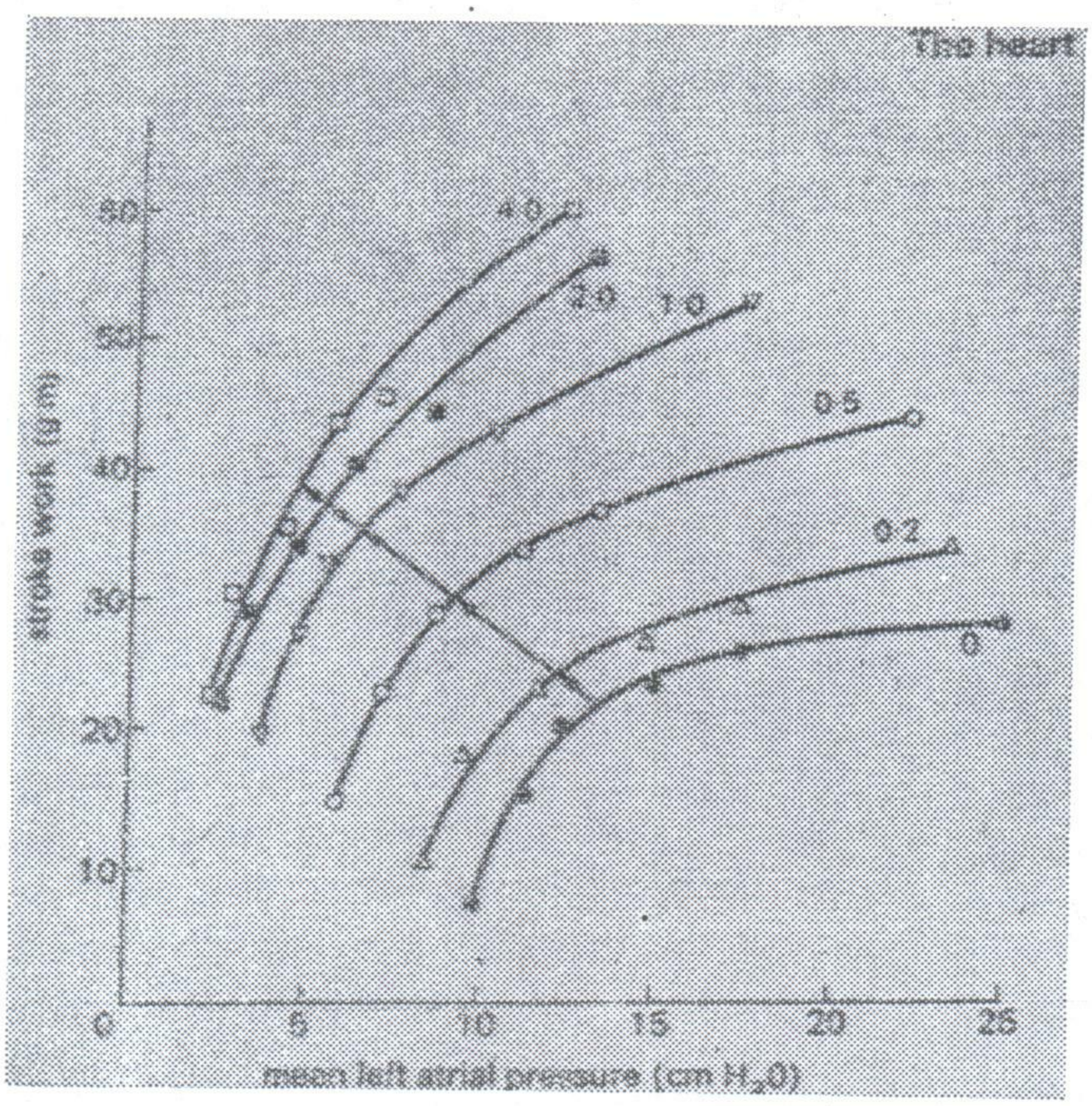
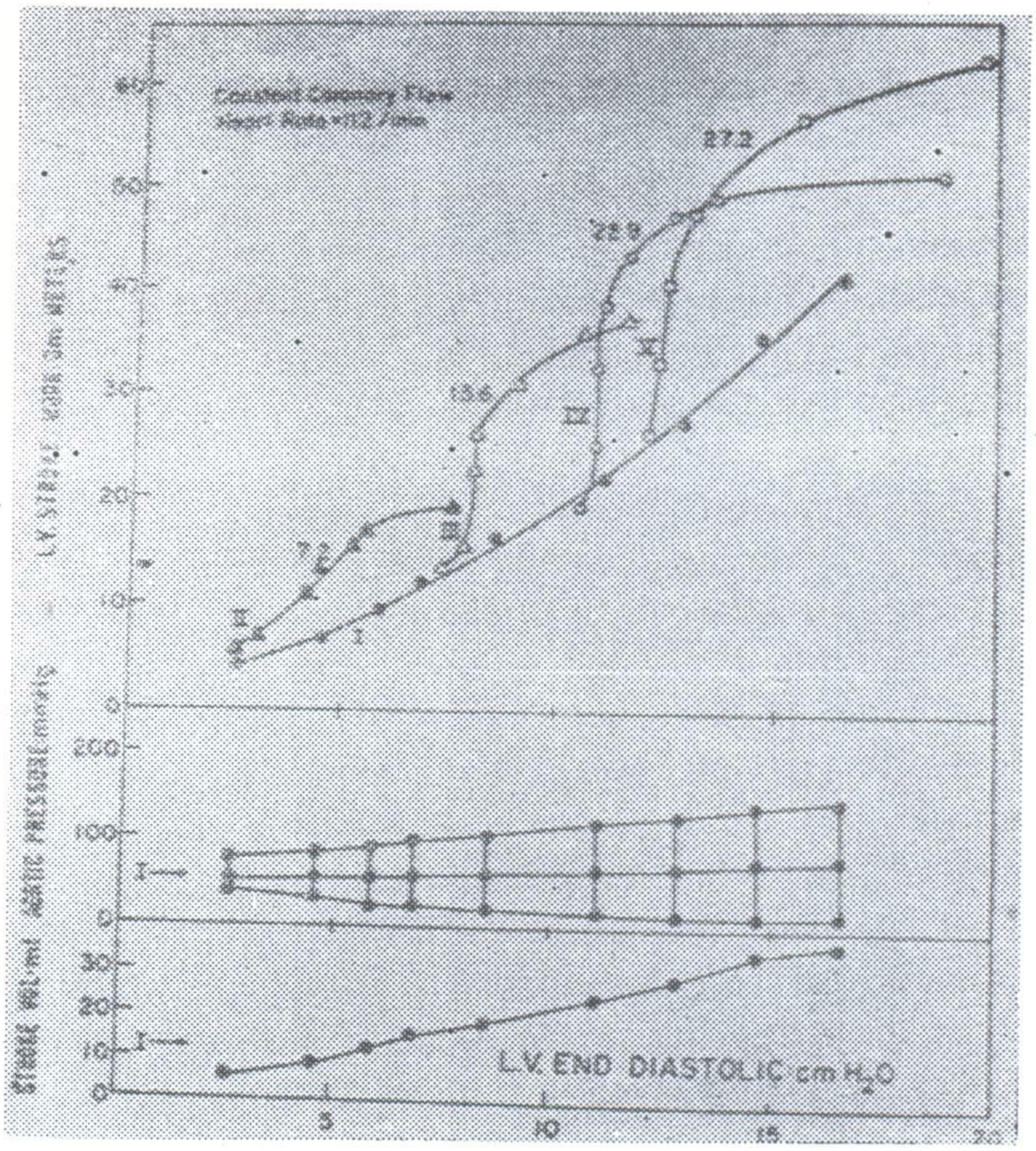


Figure 7:

The effect of sympathetic nerve stimulation, which has a strong positive inotropic effect, on ventricular function in the isolated heart-lung preparation. Each curve shows the relationship between mean left atrial pressure and left ventricular stroke work (the 'ventricular function curve') at successively increasing frequencies of stimulation of the sympathetic nerves to the heart (stimulus frequency in shocks per second, marked on each curve). (Sarnoff and Mitchell (1961). Am. J. Med. 30, 747).

Figure 8.

In an intact canine heart, the effect of increasing ventricular inflow (pre-load, LVEDP), is shown by the curves marked I on the stroke volume (bottom panel), aortic pressure (middle panel) and stroke work (solid dots, upper panel). At selected levels of pre-load, stroke work was increased progressively by increasing the aortic pressure while the stroke volume (the number to the left of the curves) was constant. The curves II-V show the considerable increase in stroke work as the after-load is increased, and the marked influence of pre-load upon the work capacity of the left ventricle. (Sarnoff and Mitchell (1962). In Handbook of Physiology, Section 2: Circulation Volume 1, P.4 89-53 2).



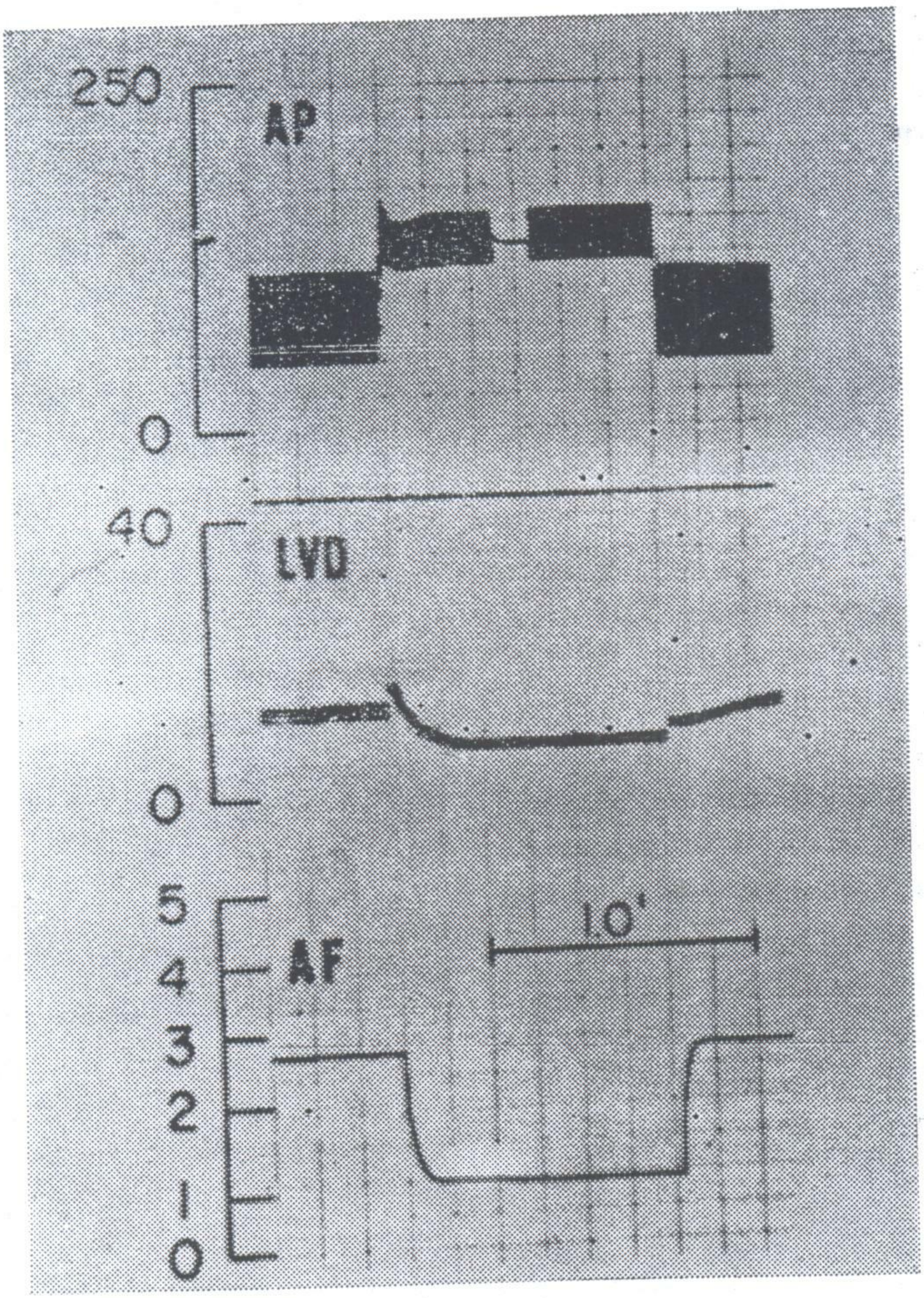


Figure 9: The aortic flow (AF) from a canine left ventricle was reduced by decreasing the inflow. At the same time the resistance to flow in the aorta was increased causing a rise in aortic pressure (AP). Overall, stroke work was reduced. The steady fall in left ventricular diastolic pressure for a brief time after the fall in aortic flow indicates an increase in contractility. When stroke work is restored to its control valve, the pre-load (LVD) is lower than the initial value and rises slowly indicating again that contractility had increased during the time when after-load was increased although the stroke work was reduced. (Sarnoff and Mitchell (1962). In Handbook of Physiology, Section 2: Circulation Volume 1, P. 439-532).

The enhanced contractility demonstrated by stimulation of the sympathetic nervous ystem and by sudden increase in heart rate could be due, at least in part, to the fact that both manoeuvres cause more synchronous depolarisation of the ventricles than the natural state.

Wall Stress and The Coronary Circulation

The force developed by the left ventricle to overcome the after-load, set by the peripheral vascular resistance, is directed outwards by the blood in the ventricle perpendicular to its walls. This outward force is resisted by the stress within the walls of the ventricle. The stress, consisting of forces perpendicular to the outward force, is distributed through the thickness of the walls being greatest in the sub-endocardium and least at the pericardium. Maximal sub-endocardial stress is at least as high as the aortic systolic pressure or even higher so that coronary blood flow to the endocardial myocardium is restricted to diastole. The stress in the ventricular wall varies with the radius of the cavity and increases therefore with the volume of the ventricle. An increase in ventricular volume raises its diastolic pressure which reduces the pressure gradient between coronary arteries and the ventricular cavity and hence myocardial blood flow. These factors render the sub-endocardial myocardium susceptible to ischaemic damage in cardiac failure particularly when it is associated with a low aortic diastolic pressure.

Acknowledgement

Figures 1, 2, 4, 5, 6 and 7 were taken from reference 1, and figures 3, 8 and 9 were taken from reference 2.

The references were used extensively in compiling this communication.

References

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