Meeting June 28 1971
at St Catherine's College, Oxford

Problems in Measurement of Myocardial Contractility

Dr Jere H Mitchell
and Dr Kern Wildenthal
(Pauline and Adolph Weinberger Laboratory for Cardiopulmonary Research, University of Texas Southwestern Medical School, Dallas, Texas 75235, USA)

Analysis of Left Ventricular Function

Two basic approaches may be used to characterize the mechanical function of the left ventricle. One of these is to consider the left ventricle as a pump and base the evaluation on measurements of its volume, pressure, and flow; the other is to consider the left ventricle as a muscle and apply the concepts of instantaneous length, exerted force, and velocity of shortening. The latter approach has been discussed by Jewell and Saunders in papers listed on page 552.

In this paper we shall analyse the changes that occur in cardiac muscle length and in ventricular volume between end-diastole and end-systole and show how these can be used to evaluate left ventricular performance in terms of function curves. It is clear that greater understanding can be achieved if the velocity of contraction is studied as well as simply the total amount of contraction or shortening. For many purposes, however, changes in the function of the left ventricle can be analysed satisfactorily by careful observation of changes in its volume and dimensions at end-diastole and at end-systole.

The three basic determinants of the performance of isolated cardiac muscle are the initial length of the muscle fibre, the load lifted by the muscle, and the contractile or inotropic state. The effect of increasing initial length while load and contractile state are kept constant is an increase in the amount of shortening, with the muscle ultimately contracting almost as far as before (Fig 1A). It is important to note that the contracted length of cardiac muscle is affected relatively little by the initial or resting muscle length (Sonnenblick 1965, Taylor 1970). The effect of increasing the load while the amount of shortening and the contractile state are held constant is shown in Fig 1B. For this to be accomplished, there is an equal increase in initial length and in contracted length. As shown in Fig 1C, when the contractile state of the muscle is increased while load and initial length are held constant, the muscle is able to shorten further; if the amount of shortening is held constant there is a decrease in both initial length and contracted length.

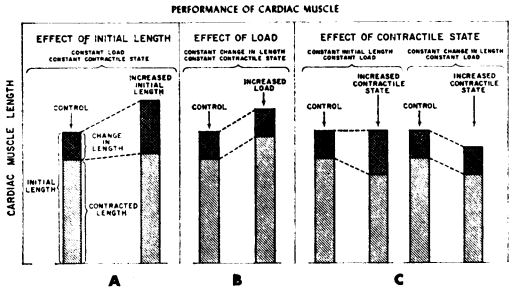

Fig 1 *Determinants of mechanical performance of cardiac muscle*

The importance of the influence of initial fibre length or end-diastolic volume on ventricular performance has been appreciated for many years. Even before Starling (1918) stated his 'law of the heart' in its most general form ('the energy of contraction, however measured, is a function of the length of the muscle fibre'), Frank (1895) had dealt extensively with the influence of filling pressure in controlling tension development in frog ventricles, and Hales (1733) had studied the hæmodynamic effects of blood loss and noted that a distended heart ejected a larger volume of blood per stroke. This concept is now generally referred to as the 'Frank-Starling principle' or, more recently, as 'heterometric autoregulation' (Sarnoff & Mitchell 1962), and it forms the foundation for evaluating the

The determinants of the performance of the intact left ventricle *in vivo* are the same as those for the isolated muscle: (1) initial length of cardiac muscle fibre, or end-diastolic volume of the ventricle; (2) resistance to ejection or aortic pressure, analogous to the load lifted by the isolated cardiac muscle; and (3) integrated contractile state of the left ventricular cardiac muscle, which is influenced by such things as heart rate, level of circulating catecholamines, and neural activity.

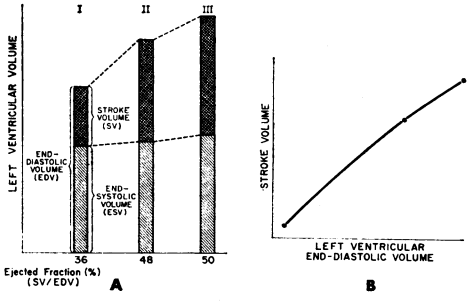

Fig 2 *Effects of increasing ventricular inflow on ventricular end-diastolic volume, end-systolic volume, and stroke volume.* A, *ventricular inflow is progressively increased from* I *through* III *while heart rate, aortic pressure, and contractile state are unchanged.* B, *ventricular function curve relating stroke volume to end-diastolic volume*

mechanical function of the left ventricle in terms of a compression pump.

When left ventricular end-diastolic volume is increased by increasing inflow to the heart, there occurs an increase in stroke volume and ejected fraction (Fig 2A). As with isolated muscle, contraction proceeds until the ventricle has reached almost the same end-systolic size as before the change in diastolic volume (Monroe & French 1961, Mitchell *et al.* 1969, Taylor *et al.* 1969). Fig 2B illustrates the relation between stroke volume and end-diastolic volume when heart rate, aortic pressure, and contractile state are constant. A curve of this sort, relating some index of ventricular action to an index of end-diastolic fibre length, has been termed a ventricular function curve (Sarnoff & Berglund 1954, Mitchell & Mullins 1970), and shifts of the curve

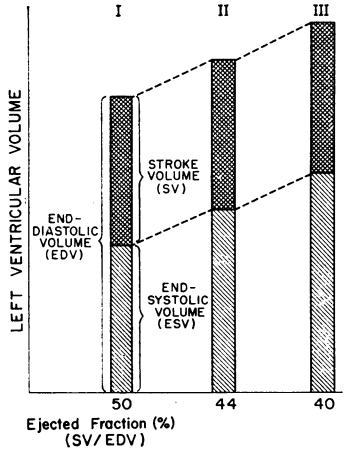

Fig 3 *Effect of increasing aortic resistance on ventricular volumes. Heart rate and venous return are held constant as aortic pressure rises to progressively higher levels from* I *through* III

can, within limits, be used to describe a change in the contractile state of the left ventricle.

The effects of progressive steady-state increases in aortic pressure while stroke volume is maintained constant are shown in Fig 3. End-diastolic and end-systolic volumes increase equally as the resistance to ejection rises. With an increase in end-diastolic volume and a constant stroke volume, there is a progressive decrease in the ejected fraction (Tsakaris *et al.* 1969).

It has also been found that in reaching a steady state at an increased aortic pressure, the left ventricle goes through two stages. Immediately after resistance to ejection is raised, left ventricular volumes increase, but within a few beats an intrinsic change in the contractile state of the left ventricle occurs and both end-diastolic and end-systolic volumes are reduced toward original

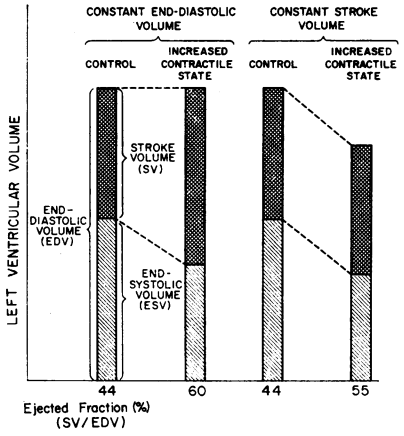

Fig 4 *Effect on ventricular volumes of increasing contractile state while heart rate and aortic pressure are constant*

control values. This delayed improvement in the contractile state was first observed by Anrep (1912) and has been termed the 'Anrep effect' or 'tension-induced homeometric autoregulation' (Sarnoff & Mitchell 1962). Use of the ventricular function curve to describe changes in the contractile state of the left ventricle is complicated by the effects of changes in aortic pressure. For completely accurate results, therefore, it is necessary to keep aortic pressure constant when this method is being used.

The changes in left ventricular volumes that accompany alterations in the contractile state are illustrated in Fig 4. On the left are shown the changes in left ventricular volumes that occur when the contractile state is increased and aortic pressure and end-diastolic volume are held constant. There is an increase in stroke volume and a decrease in end-systolic volume, with an

increase in the ejected fraction. As shown on the right, if stroke volume is held constant while the contractile state is enhanced, there is a fall in both the end-diastolic volume and the end-systolic volume. Changes in the ejected fraction are somewhat less when end-diastolic volume is allowed to change.

The pattern of changes in end-diastolic and end-systolic volumes following inotropic interventions can be distinguished from that accompanying the Frank-Starling mechanism. With varying left ventricular inflows, end-diastolic volume changes significantly while end-systolic volume stays relatively constant. In contrast, with varying contractile states definite alterations in end-systolic volume occur. It is apparent that when both the end-diastolic volume (Frank-Starling mechanism) and the contractile state of the ventricle are altered simultaneously, as occurs during most physiological changes *in vivo*, the ultimate effect on end-systolic and end-diastolic volume relations may be quite complex. Thus, the unmodified use of the ejected fraction or similar measurements as an index of left ventricular inotropic state is inadequate. For full understanding of alterations in left ventricular performance, a complete description of both end-diastolic and end-systolic volume changes is essential.

In the intact animal the contractile state of the left ventricle is under neurogenic and humoral control. Both sympathetic and parasympathetic nerve activity can influence left ventricular function. Dimensional effects of increased cardiac sympathetic nerve stimulation at various rates of venous return are shown in Fig 5A. At any given

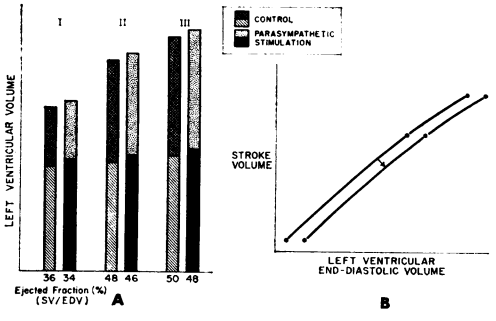

Fig 5 *Effect of stimulating cardiac sympathetic efferent nerves on mechanical activity of left ventricle.* A, *hatched bars = control state; solid bars = sympathetic stimulation; equivalent increases in ventricular inflow occur in both groups* (I *through* III) *while aortic pressure and heart rate are held constant. Volumes are depicted as in previous figures.* B, *the change in the ventricular function curve is indicated by the arrow*

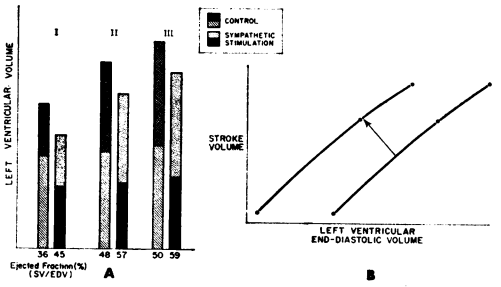

Fig 6 *Effect of stimulating cardiac parasympathetic efferent nerves on mechanical activity of left ventricle.* A, *hatched bars = control; solid bars = vagal stimulation. Conditions are as stated for Fig 5.* B, *the change in the ventricular function curve is indicated by arrow*

rate of ventricular inflow the left ventricle contracts to a smaller end-systolic volume during sympathetic stimulation, and the same stroke volume can be achieved from a smaller end-diastolic volume. Ventricular function curves illustrating the relation between stroke volume and end-diastolic volume are drawn in Fig 5B. With stimulation, the curve is shifted upward and to the left, indicating that an increase in the contractile state of the left ventricle has occurred.

Parasympathetic stimulation has an opposite effect. As illustrated in Fig 6A, stimulation of efferent vagal nerve fibres prevents the left ventricle from being able to contract to as small an end-systolic volume as during control conditions. In order to eject the same stroke volume, the end-diastolic volume must dilate during parasympathetic stimulation. Ventricular function curves during control and parasympathetic stimulation are shown in Fig 6B. It should be noted that although increased vagal activity alters left ventricular contraction, its effects are much less marked than those of sympathetic stimulation (Wildenthal *et al.* 1969). This corresponds well with anatomical descriptions of the autonomic nerve supply to the left ventricle (Jacobowitz *et al.* 1967) which have demonstrated an abundance of sympathetic fibres but a paucity of parasympathetic fibres.

In summary, analysis of left ventricular function by observation of changes in ventricular volumes reveals that the intact heart functions in a manner analogous to isolated muscle strips. End-diastolic volume (fibre length), aortic pressure (load), and neural regulatory mechanisms (contractile state) are all important determinants of ventricular performance. When aortic pressure and heart rate are held constant, the relation of stroke volume to end-diastolic volume is a useful

index of the contractile state of the left ventricle. Observations of alterations in the end-systolic volume may provide a useful key for differentiating changes in the contractile state of the left ventricle from changes induced by the Frank-Starling mechanism.

REFERENCES
Anrep G V (1912) *Journal of Physiology* **45**, 307
Frank O (1895) *Zeitschrift für Biologie* **32**, 370
Hales S (1733) Statical Essays: Containing Hæmastatics. London
Jacobowitz D, Cooper T & Barner H B (1967) *Circulation Research* **20**, 289
Mitchell J H & Mullins C B (1970) In: Pathophysiology of Congenital Heart Disease. Ed. F H Adams, H J C Swan & V E Hall. Los Angeles; p 163
Mitchell J H, Wildenthal K & Mullins C B (1969) *Federation Proceedings* **28**, 1334
Monroe R G & French G N (1961) *Circulation Research* **9**, 362
Sarnoff S J & Berglund E (1954) *Circulation* **9**, 706
Sarnoff S J & Mitchell J H (1962) In: Handbook of Physiology: Circulation, Vol. 1. Ed. W F Hamilton. Washington; p 489
Sonnenblick E H (1965) *Circulation Research* **16**, 441
Starling E H (1918) The Linacre Lecture on the Law of the Heart. London
Taylor R R (1970) *Circulation Research* **26**, 279
Taylor R R, Covell J W & Ross J jr (1969) *American Journal of Physiology* **216**, 1097
Tsakaris A G, Donald D E, Sturm R E & Wood E H (1969) *Federation Proceedings* **28**, 1358
Wildenthal K, Mierzwiak D S, Wyatt H L & Mitchell J H (1969) *American Journal of Physiology* **216**, 577

DISCUSSION

Dr M I M Noble (*Charing Cross Hospital Medical School, Fulham Hospital, London W6*) asked whether Dr Mitchell would agree that the problem was that the very great degree of control of the preparation used in the experimental set-up was impracticable in the intact animal or in patients. In the conscious dog a decrease in end-systolic volume was not obtained by just increasing the contractile state, presumably because the preparation could not be controlled as precisely.

Dr Mitchell agreed that one certainly could not utilize his techniques in man. However, there was a range in which the variation in aortic pressure was not too great to preclude use of the ventricular function curve.

Professor Peter Harris (*Institute of Cardiology, London W1*) said that although aortic pressure was constant, he presumed the pressure in the ventricle must be varying because of the forces involved in different volumes of blood being ejected at different rates. Did Dr Mitchell know to what extent this affected the ventricular function curve?

Dr Mitchell replied that it was very difficult to know because, as Professor Harris had pointed out, the load at which the ventricle was working was constantly changing throughout ejection. In Dr Mitchell's studies the mean pressure against which the heart was contracting was kept constant. It would probably have been better to keep left ventricular or mean aortic ejection pressure constant, but this had not been possible.

A Member said that at constant pressure in the ventricle an increase in heart size entailed an increase in force in the wall of the heart. So presumably the real load on the muscle was increased, even though aortic pressure was kept constant.

Dr Mitchell said that Dr Roger Taylor's group had shown that if wall tension was kept constant, the heart returned even closer to the same end-systolic volume when end-diastolic volume was increased.

Dr Abraham Guz (*Charing Cross Hospital Medical School, London*) asked what had happened to the descending limb of the Starling curve.

Dr Mitchell replied that usually if one continued to increase the inflow in animals, stroke volume increased with end-diastolic volume until there was mitral incompetence.

Dr Lee (President) asked how much contractile state changed as a result of deterioration of the preparation.

Dr Mitchell replied that some deterioration of the preparation had to be accepted to be sure that the circulatory reflexes were blocked. The carotid sinus nerves and vagi were cut, but there could have been an increase in circulating catecholamines, so the studies were repeated using propranolol; the results were the same, but the animal was much more depressed.

Dr G C van den Bos
(*Laboratorium voor Fysiologie, Vrije Universiteit, Amsterdam*)

Indices of Contractility in the Intact Heart

The heart is a pump which generates energy in the form of pressure and flow, so that it should be possible to characterize ventricular function in terms of these variables. If this is true it might be possible to define contractility unequivocally from these variables or by an index derived from them.

The heart's prime function is to deliver sufficient oxygenated blood to meet the metabolic requirements of the tissues (Braunwald 1971). Cardiac output in this regard should be a key test of cardiac function, but it gives only limited information about the functional state of the