Cardiac Work and Contractility

J. HAMER*

It has been customary to regard the heart as a pump maintaining the flow of blood, and to assess the work done by the heart from the pressure and volume of blood leaving the ventricles. While correct in physical terms, measurement of external cardiac work in this way is a poor index of the myocardial oxygen consumption which is related to the work done by the ventricular muscle. Systolic pressure seems to be a more important determinant of ventricular work than stroke volume, and under some conditions myocardial oxygen consumption can be predicted from the systolic pressure, duration of systole, and heart rate (Sarnoff *et al.*, 1958). This relationship does not hold in other situations, as ventricular work depends on the force of the contraction in the ventricular wall rather than on the systolic pressure. The force developed for a given pressure increases as the cavity becomes larger†, so ventricular work is affected by the size of the chamber as well as by the pressure and volume of blood ejected. A better prediction of myocardial oxygen consumption follows if the calculation is based on ventricular wall force instead of pressure, as alterations in ventricular volume are then taken into consideration (Britman and Levine, 1964). Some work is wasted at the early stages of contraction in stretching non-contractile tissue in the ventricular wall, but this factor becomes relatively unimportant once ejection has begun. Accurate measurement of ventricular wall force requires a detailed knowledge of the changes in ventricular volume during systole. The ventricles can be regarded as spherical in shape without producing serious error in these calculations.

The dilatation of the ventricle in heart failure might be expected to lead to an increase in ventricular work, but the effect of greater force in the ventricular wall is offset by the mechanical advantage of a larger chamber. Less shortening of the muscle

fibres is needed to maintain the stroke volume in a larger ventricle, and ventricular work is correspondingly reduced (Gorlin, 1962). Simple calculations suggest that there is, in fact, little change in work as the ventricle dilates (Table). The more forceful contraction produced by increased stretching of the muscle fibres through the Starling mechanism probably gives the dilated ventricle a functional advantage.

Estimates of ventricular work based on force measurements still give an incomplete picture of myocardial behaviour, as a rapid contraction needs more energy than a slow one. The velocity of contraction of the muscle fibres is an important additional determinant of myocardial oxygen consumption (Sonnenblick, 1966). The increase in myocardial contractility due to inotropic agents such as digitalis or noradrenaline is associated with an increase in the velocity as well as the force of contraction, and the converse effect is seen in heart failure where contractility is reduced. Ventricular volume measurements are needed before the velocity of contraction in the ventricular wall can be calculated. However, if the ventricle does not alter in size, changes in the rate of ejection or in the rate of rise of pressure are indications of variations in velocity.

A fundamental consideration in the assessment of ventricular performance is the inverse relation between the force and the velocity of contraction. Velocity becomes less as force increases, suggesting

TABLE
EFFECT OF VENTRICULAR DILATATION ON
VENTRICULAR WORK

End-diastolic volume (ml.)	Mean-systolic force (F) (mm. Hg cm. ²)	Change in radius (Δr) (cm.)	Ventricular work ($W = 4F \cdot \Delta r$)
75	1650	0.81	5350
100	2150	0.59	5050
200	3800	0.33	5000
500	7350	0.17	5000

(Theoretical calculations assuming a mean systolic pressure of 100 mm. Hg and a stroke of 50 ml. in a spherical ventricle.)

* Address: St. Bartholomew's Hospital, London E.C.1

† The force per unit circumference is given by $f = \frac{1}{2}Pr$, and the total force as $F = \frac{1}{2}Pr \times 2\pi r = \pi r^2 P$, where P is the pressure and r the radius of the ventricle.

that there is only a limited amount of energy available which can be used in either way. Similarly, the extent of shortening of the fibres is reduced as the force of contraction increases, and the duration of contraction is reduced as velocity increases. The interdependence of these various aspects of myocardial contraction is evident in heart disease. In aortic stenosis, for instance, ejection is prolonged because of the mechanical obstruction, and the sustained systole is accompanied by a great reduction in the velocity of contraction, with a corresponding economy in myocardial oxygen consumption. The metabolic requirements for the slow prolonged systole of aortic stenosis may not be very different from those needed for the fast but brief contraction of aortic incompetence. Although contractility is impaired in myocardial disease, a reduced velocity of contraction in the intact heart does not indicate that the behaviour of the heart muscle is abnormal if the ventricle is increased in size. The greater force needed to maintain the systolic pressure under these circumstances may in itself lead to a fall in velocity (Gorlin, 1962), offering a further possible advantage of ventricular dilatation in heart failure.

An increase in the activity of the sympathetic nervous system might be expected in heart failure in an attempt to maintain contractility. The finding of an increase in urinary catecholamine excretion appeared to confirm this hypothesis, but direct measurement has shown a reduction in catecholamine concentration in myocardial tissue removed at operation in patients with heart failure, which parallels the impairment of contractility (Braunwald and Chidsey, 1965). It has been suggested that excessive sympathetic stimulation may produce depletion of the myocardial catecholamines and a loss of response to sympathetic stimulation. However, other studies do not support this view. Sympathetic blocking drugs such as propranolol tend to accentuate heart failure, and our own work in patients with severe aortic stenosis (Hamer and Fleming, 1967) has shown that the deleterious effect on myocardial function includes a reduction in the velocity of contraction of the left ventricular muscle. These changes after sympathetic blockade point to a considerable degree of sympathetic activity in patients with left ventricular failure. The inotropic effect of sympathetic stimulation seems to play an important part in maintaining cardiac performance under these conditions, though we cannot rule out exhaustion of the mechanism under more prolonged and severe load.

Interference with the natural inotropic effect of sympathetic stimulation has been shown to have an important clinical application in the treatment of hypertension and ischaemic heart disease. The

reduction in blood pressure produced by propranolol is mediated entirely by a fall in the cardiac output. The finding of a reduced rate of ejection of blood into the aorta under these circumstances suggests that a decrease in the velocity of contraction of the heart muscle is a major factor in the response (Shinebourne, Fleming, and Hamer, 1967). The effect is not dependent on the reduction in heart rate produced by the drug. The suspicion that these changes might be due to a direct depressant action of propranolol on the heart has been eliminated by the finding that a beta-sympathetic blocking drug without local anaesthetic or quinidine-like action (ICI 50, 172) has a similar effect to propranolol. The fall in velocity of contraction produced by sympathetic blockade would be expected to reduce myocardial oxygen consumption and so increase exercise tolerance in patients with angina pectoris.

The consistent fall in cardiac output found after propranolol is difficult to explain on the basis of reduced myocardial contractility alone. A similar fall in output is seen supine and erect, in normal subjects and in heart disease, and is not due to slowing of the heart as the effect persists when the heart rate is maintained by pacing (Bloomfield, Redwood, and Sowton, 1966). There is evidence in normal subjects and in aortic stenosis of an increase in left ventricular size after propranolol. The larger volume will produce a more forceful contraction by the Starling mechanism, and give a mechanical advantage which will help to maintain the stroke volume, but an increase in stroke volume to restore the cardiac output to the previous level in spite of bradycardia does not seem possible. The patients are usually capable of an increase in heart rate and cardiac output on exercise in spite of the action of propranolol, though they seem unable to compensate for the reduction in contractility produced by the drug in the absence of an increase in venous return.

The apparent interrelation between the force, duration, and velocity of myocardial contraction is of interest in view of recent evidence as to the mechanism by which contraction is produced. The sarcoplasmic reticulum, a system of tubules running alongside the muscle fibrils within the myocardial cell, has been shown to take up calcium ions very actively. It is postulated that electrical activation of the myocardial cell is associated with the release of calcium ions from the sarcoplasmic reticulum, and that each calcium ion initiates contraction at one site in the actomyosin complex (Weber, 1966). The long period of depolarization, which is such a striking feature of the active state in heart muscle, may be needed to allow the release of a sufficient number of calcium ions. A rapid contraction may follow when the ions are released quickly, and a more

forceful contraction when the total number released is greater than usual. A rapid systole will necessarily be shorter in duration if the total number of ions released is unchanged. The inverse relations between the force, duration, and velocity of contraction are, therefore, explicable if calcium ions are involved in a quantitative way. The Starling mechanism, which leads to a more forceful contraction when the muscle fibres are increased in length, is probably due to increased separation of the actin and myosin filaments exposing a larger number of active sites to the calcium ions. Relaxation of the muscle is produced by the rapid withdrawal of calcium ions into the sarcoplasmic reticulum by an active metabolic process after the cell membrane has been repolarized. An adequate metabolic background in the form of high-energy phosphate bonds is certainly needed for contraction, and also for the recovery process, but attempts to demonstrate an abnormality of energy supply in heart failure have been disappointing. The availability of calcium ions may be a more direct regulator of myocardial contraction than the metabolic activity of the muscle.

The decrease in contractility in heart failure may be related to loss of activity of the sarcoplasmic reticulum. Studies of isolated sarcoplasmic reticulum from the failing dog heart show a reduced uptake of calcium ions, and it is postulated that, as a consequence, less calcium ions are released when the cell is activated so that contractility is impaired. The reduced activity of the failing sarcoplasmic reticulum is restored by digitalis (Gertz *et al.*, 1967), suggesting that the inotropic effect of the drug is due to an increased release of calcium ions. It is difficult to provide a unifying hypothesis for the action of digitalis at a molecular level, as different effects are found in the surface membrane and in the sarcoplasmic reticulum. At the cell surface the active extrusion of sodium is blocked and the electrical changes that follow are probably responsible for the rhythm disturbances produced by digitalis. In the sarcoplasmic reticulum the active uptake of calcium ions is facilitated. The only common feature is that active transport of cations is involved in each case.

It is possible that other inotropic agents also act by promoting the release of calcium ions from the sarcoplasmic reticulum. There is some evidence that sympathetic stimulation is mediated in this

way. Work in our laboratory has shown that nor-adrenaline and isoprenaline increase the calcium uptake of sarcoplasmic reticulum from dog hearts. The effect is prevented by propranolol, suggesting that it is a specific result of sympathetic stimulation. As in the case of digitalis, it is suggested that increased storage of calcium ions in the sarcoplasmic reticulum may allow a greater release of calcium ions when the myocardial cell is stimulated. These findings indicate a new way in which the sympathetic nervous system may produce its effects on the heart muscle. The similar actions of digitalis and of sympathetic stimulation, the increase in contractility produced when depolarization is prolonged by coupled pacing, and the direct effect of calcium ions on the myocardium suggest that all inotropic effects may be mediated by increasing the concentration of calcium ions near the myofibrils.

REFERENCES

- Bloomfield, D., Redwood, D., and Sowton, E. (1966). Distinction between negative inotropic and chronotropic effects of beta-adrenergic blockade. *Brit. Heart J.*, **28**, 849.
- Braunwald, E., and Chidsey, C. A. (1965). The adrenergic nervous system in the control of the normal and failing heart. *Proc. roy. Soc. Med.*, **58**, 1063.
- Britman, N. A., and Levine, H. J. (1964). Contractile element work; a major determinant of myocardial oxygen consumption. *J. clin. Invest.*, **43**, 1397.
- Gertz, E. W., Hess, M. L., Lain, R. F., and Briggs, F. N. (1967). Activity of the vesicular calcium pump in the spontaneously failing heart-lung preparation. *Circulat. Res.*, **20**, 477.
- Gorlin, R. (1962). Recent conceptual advances in congestive heart failure. *J. Amer. med. Ass.*, **179**, 441.
- Hamer, J., and Fleming, J. (1967). Effect of propranolol on left ventricular work in aortic stenosis. *Brit. Heart J.*, **29**, 871.
- Sarnoff, S. J., Braunwald, E., Welch, G. H., Case, R. B., Stainsby, W. N., and Macruz, R. (1958). Hemodynamic determinants of oxygen consumption of the heart with special reference to the tension-time index. *Amer. J. Physiol.*, **192**, 148.
- Shinebourne, E., Fleming, J., and Hamer, J. (1967). Effects of beta-adrenergic blockade during exercise in hypertensive and ischaemic heart-disease. *Lancet*, **2**, 1217.
- Sonnenblick, E. H. (1966). The mechanics of myocardial contraction. In *The Myocardial Cell*, p. 173. Ed. by S. A. Briller and H. L. Conn. University of Pennsylvania Press, Philadelphia.
- Weber, A. (1966). The role of Ca in the regulation of muscle activity. In *The Myocardial Cell*, p. 131. Ed. by S. A. Briller and H. L. Conn. University of Pennsylvania Press, Philadelphia.