TO DETERMINE cardiac performance, a comparison between the whole heart and isolated (skeletal) muscle often has been made. Otto Frank (1895) designed his beautiful experiments on the frog heart following "the same pattern which Fick and Von Kries used in their studies of skeletal muscle. . . . " A similar comparison between heart and muscle can be found in Starling's formulation of his "law of the heart" (Patterson et al., 1914): "The law of the heart is therefore the same as that of skeletal muscle that the mechanical energy set free on passage from the resting to the contracted state depends . . . on the length of the muscle fibers." Presently, the same line of thinking prevails, since variables derived from studies on isolated muscle are determined for the whole heart to establish its performance (Mason et al., 1970).

The task of the heart is to transport arterial blood to the various organs and venous blood to the lungs. It does this by ejecting a sufficient amount of blood at a given pressure against the resistance of the arterial system. Although this pump function of the heart has been fully recognized since Harvey wrote his "de motu cordis" (1628), it is still not clear how to quantify it. Cardiac output, stroke volume, left ventricular function curves, peak systolic pressure, stroke work, peak wall stress, rate of rise of left ventricular pressure, maximum velocity of shortening, and many other variables all have been put forward as a measure of the function or performance of the heart (Abel, 1976; Ahmed et al., 1977; Baylen et al., 1977; Frank et al., 1965; Kreulen et al., 1975; McDonald et al., 1972; Raphael et al., 1977; Sonnenblick and Downing, 1963). However, a single universal quantitative description of the function of the cardiac pump is still lacking. Has the comparison between isolated muscle and the whole heart not been fruitful in this respect?

Pump Function of the Heart

How should the pump function of the heart be characterized? To answer this question it is useful to turn to fluid pumps, whose pump function is given by a head-capacity curve. Such a graph relates, for a given setting of the pump, the amount of fluid it can handle to the pressure head it has to overcome. This is necessarily an inverse relationship, because for a certain head the pressure opposing flow is so high that output will be zero, whereas at zero pressure, flow is at its maximum.

The pump function graph of a roller pump which does not completely occlude the tubing is presented in Figure 1. Pressure (head) is plotted as a function of pump output (capacity). Three different settings of the pump are studied: (1) control, (2) increased speed of the roller pump, (3) speed of the roller pump same as during control, but pressure exerted by the rollers on the tubing is higher (more occlusive position). All three inverse relationships, obtained by varying the height of the outlet tubing (see inset in Fig. 1), happen in this case to be virtually linear. An increase in the speed of rotation causes a more or less parallel shift of the line. A better occlusion of the tubing results in an increased ability to generate pressure while the output at zero pressure remains constant.

The idea of characterizing pump function of the heart by relating the amount of blood it can handle per unit time to the pressure it has to overcome is not new. Already in the last century, as reported by Frank (1895), investigators had studied the effect of an increased arterial pressure on cardiac output (Blasius, 1872; Dreser, 1887-1888; Marey, 1881). Unfortunately, as Frank correctly pointed out, car-
Cardiac pump function was in their experiments affected by the various arterial loading conditions used, because end-diastolic volume was not kept constant. A similar objection holds for the work of Starling in which he studied the effect of arterial pressure on cardiac output (Patterson et al., 1914). As he himself admitted, he also allowed cardiac enlargement at higher levels of arterial load. When we want to determine the pump function of the heart, it is an essential requirement to keep the "setting" of the heart constant; i.e., changes in end-diastolic volume or inotropic state are not permitted.

A number of investigators (Von Anrep, 1912; Muller, 1939; Sarnoff and Mitchell, 1962; Monroe et al., 1974) have stated that a change in arterial pressure, which is needed to obtain the graph describing cardiac pump function, is in itself an inotropic intervention (the Von Anrep effect). If this is so, the setting of the cardiac pump would change during the measurement of its function, rendering the description invalid. Elzinga et al. (1977) tested this possible error in experiments on isolated ejecting cat hearts and in intact dogs with denervated hearts. They found the inotropic effect of an increase in arterial pressure to be negligible.

Sagawa (1967) was probably the first to relate systematically left ventricular output to the pressure the left heart has to overcome. He used a preparation in which mean left atrial pressure was kept constant, and used mean aortic pressure as a measure of ventricular load. Later, Herndon and Sagawa (1968) studied pump function of the whole heart (left and right in series) in the same way by keeping right atrial pressure constant. However, the use of mean aortic pressure as a measure of the pressure head the heart has to overcome has some drawbacks, as will be explained below.

The use of left ventricular pressure instead of aortic pressure to plot against left ventricular output for the determination of cardiac pump function was advocated by Elzinga and Westerhof (1973). They used mean values to obtain this relationship. Buoncristiani et al. (1973) averaged the left ventricular pressure over the ejection period only and plotted that value against mean flow, whereas Weber et al. (1974) and McGregor et al. (1974) made graphs of peak ventricular pressure against stroke volume. Although different in a number of experimental and theoretical details, all these studies had the same objective: the description of the pump function of the heart by relating the amount of blood it ejects to the pressure it has to overcome.

Mean aortic pressure ought not to be used in the pump function graph, because force generated by the myocardial fibers, the basic elements responsible for cardiac pump function, is related to the pressure in the lumen of the ventricle. Experimental results sustain this point of view. Figure 2 shows data taken from an experiment in which the effects of nine different arterial loads on an isolated ejecting cat heart were studied (Elzinga and Westerhof, 1973). These nine different loads were obtained by combining three values of the arterial compliance with three values of the peripheral resistance. The three symbols used in the two plots indicate the three compliance values. In Figure A, mean aortic pressure is plotted against mean left ventricular output, and three relationships are found (solid lines). The slopes of the three dotted lines are equal to the three values of the peripheral resistance. This sensitivity to the differences in input impedance of the arterial load in the nine situations is lost when...
mean left ventricular pressure is used (Fig. 2B). That graph therefore appears to be determined only by the pump function of the left heart.

To obtain the left ventricular pump function graph, we choose to analyze both aspects of cardiac pump function (i.e., flow and pressure generation) in a similar manner. Mean left ventricular output is found by averaging stroke volume over the complete cycle. Therefore, we prefer averaging left ventricular pressure over the full period to taking (1) pressure averaged over systole, (2) pressure averaged over the ejection period, or (3) peak left ventricular pressure. When values averaged over the whole cardiac cycle (mean values) are used, changes in heart rate affect the pump function curve in the appropriate manner; i.e., an increase in heart rate decreases the averaging period proportionally and vice versa. This is in contrast to relationships obtained by using values averaged over systole, values averaged over the ejection period, or peak values.

It has been shown that the behavior of the heart can be approximated by a time-varying compliance (Suga, 1971; Suga et al., 1973; Suga and Sagawa, 1974). We could demonstrate, for a model mimicking this behavior, that a very close relationship exists between the compliance changes and the pump function graph constructed from mean values (Westerhof and Elzinga, 1978). The three relationships in this paper are measured over a larger range than the one shown in Figure 2B, due to differences in experimental technique. When ventricular filling is increased, the pump function graph shifts in a parallel fashion. An enhancement in contractility results in a rotation of the curve such that the intercept on both axes and the slope of the line could be expressed in terms of compliance changes. Another argument in favor of mean ventricular pressure consists of its close relationship to myocardial wall force. It has been shown in papillary muscle and intact heart that the integral of the systolic force is linearly related to the energetic costs of contraction (Gibbs and Gibson, 1970; Weber and Janicki, 1977).

What are the changes in cardiac pump function produced by changes in initial muscle fiber length and contractility (for definitions see Noble, 1972)? The effects of these interventions on the pump function graph of an isolated ejecting cat heart are shown in Figure 3 (data taken from Elzinga and Westerhof, 1978). The three relationships in this figure are measured over a larger range than the one shown in Figure 2B, due to differences in experimental technique. When ventricular filling is increased, the pump function graph shifts in a parallel fashion. An enhancement in contractility results in a rotation of the curve such that the intercept on the mean output axis does not change. Two multiplication factors, one for the mean pressure and one for the mean output values, are needed to describe the shift due to a certain increase in ventricular filling. Only one multiplication factor (for the mean pressure values) can characterize the change in pump function resulting from a given enhancement in contractility (Elzinga and Westerhof, 1978). The similarity between the results obtained from the intact heart and the relationships found for the roller pump is striking (compare Figs. 1 and 3).

**Pump Function and Contractility**

There has been an extensive search for indices of contractility of the heart. These measures have to be, by definition, independent of the initial length of the muscle fibers and should not be influenced by changes of arterial load. A great many of the attempts to find such an index were based on theory derived from studies on isolated muscle. The force-velocity relationship attracted particular interest, because it has been suggested that velocity of shortening of the contractile element at zero force ($V_{max}$) is independent of initial muscle length in isolated muscle (Noble, 1973).

However, measurement of (parts of) the force-velocity relationship in the intact heart is complex. The complications arise from a number of uncertainties, such as the unknown changes in active state during the isovolumic contraction period, what extrapolation procedure to use to obtain $V_{max}$, assumptions in the calculations, the model to be used, etc. (Noble, 1972; Pollack, 1970; Sonnenblick et al., 1969; Van den Bos et al., 1973). Apart from the more theoretical problems, these indices appear in experimental practice not to fulfill the criteria of independence of initial muscle length and arterial load (Moreno et al., 1976; Parmley et al., 1975; Quinones et al., 1976; Van den Bos, 1973).

What is the value of these indices in quantifying cardiac pump function? The majority of indices of contractility are determined during the isovolumic contraction period. During this time, dimensions of the heart are approximately constant, and pressure and force are linearly related. It is therefore the period of choice to obtain information on the be-
behavior of the (average) muscle fiber in the ventricular wall. It is obvious that such indices cannot give information about the amount of blood ejected at a given pressure level. There is also no theoretical reason to think that these indices are in any way quantitatively related to the amount of blood the heart can pump against various pressures. Nevertheless, we cannot yet exclude the existence of such a relationship. Therefore we have compared the change of the left ventricular pump function graph due to a change in contractility (see Fig. 3), which can be quantified by a single multiplication factor, with the corresponding change in $V_{max}$, $[(dP/dt)/P]_{max}$, and $dP/dt_{max}$. We used for this comparison six experiments in which contractility of the heart was altered by well-defined postextrasystolic potentiation, keeping left ventricular end-diastolic pressure constant (for details see Elzinga and Westerhof, 1978). The results of this comparison (Fig. 4) show that the change in pump function is not reflected in a similar change in the contractility indices. The points are not on the line of identity and the relationships are nonlinear. Moreover $dP/dt_{max}$ seems to give an overestimation if used as a measure of pumping ability, whereas $V_{max}$ and $[(dP/dt)/P]_{max}$ are underestimating the effect of this intervention. Therefore we conclude that changes in pump function, due to augmented contractility, are not reflected by changes in indices of contractility which have been derived from studies on isolated muscle.

Pump Function and Initial Muscle Length

In the comparison between heart and muscle, the length-tension relationship of skeletal muscle was first taken into consideration. Frank (1895) stated that "length and tension changes in skeletal muscle correspond to changes in volume and pressure (in the heart)." Even if one ignores such problems as the existence of an activation sequence in the heart, the distribution of sarcomere lengths in the wall, fiber orientation, and the irregularities in geometry, the transformation of the (isometric) length-tension curve into the (isovolumic) volume-pressure relationship is complex. This can be demonstrated by the very simple model shown in the inset of Figure 5 (Gabe, 1974). The muscle fibers in this cylindrical thin-walled pump all run circumferentially. When we assume a length-tension relationship for the sarcomeres in the wall (solid line), we can calculate the relationship between volume and pressure (dotted line). Because of Laplace's law, the shapes of the two relationships differ in such a way that the maximum for the volume-pressure curve is found at shorter sarcomere lengths. A similar result can be seen in an article by Monroe et al. (1970) in which the measured volume-pressure relationship is compared with the volume-calculated stress relationship based on a thick-walled sphere as a ventricular model.

Starling plotted cardiac output as a function of venous pressure on the right side of the heart (Patterson and Starling, 1914) and related this result to the length-tension curve obtained from isometric twitches in isolated muscle (Starling, 1918). This comparison formed the basis for the formulation of

**FIGURE 4** The relation between the change in "contractility" and the change in pump function resulting from well-defined potentiated beats. Three different indices of contractility are analyzed.

**FIGURE 5** For a cylindrical thin-walled pump (inset), the isovolumic pressure-volume relationship (dotted line) is calculated from an assumed length-tension relationship (solid line).
his “law of the heart” as quoted above. Two remarks can be made against the use of these so-called ventricular function curves as a quantitative description of cardiac pump function, regardless of whether stroke work or cardiac output is plotted on the ordinate. First of all, ventricular end-diastolic volume, or a closely related variable, is used as the independent variable in these relationships. This implies that the setting of the contractile machinery of the heart at the start of the contraction is different along the horizontal axis because of the changes in initial muscle fiber length in the wall of the heart. According to our point of view, as presented above, pump function of the heart should be determined with end-diastolic volume and inotropic state of the heart kept constant. The second objection against the ventricular function curve as a description of cardiac pump function is that the former relationship is not determined by the heart alone. It is also affected by the arterial load. Different function curves are found when peripheral resistance of the arterial system is kept constant and when mean aortic pressure is held at a given level (Elzinga and Westerhof, 1976). Thus, since a description of cardiac pump function should reflect the performance of the heart only, the ventricular function curve is rendered unacceptable.

The question remains whether the similarity between the left ventricular function curve and the length-tension relationship is indeed as great as Starling thought it to be. He did his experiments using a “Starling resistor.” This device keeps aortic pressure at almost a fixed level irrespective of the amount of blood ejected by the heart. Recently it has been reported (Mahler et al., 1975) that, in conscious dogs, end-systolic diameter is hardly dependent on the resting fiber length and hence on the amount of prior shortening, when systolic pressure is constant. Even in more isolated heart preparations, end-systolic volume at a given pressure level seems to vary little with different degrees of filling (Suga and Yamakoshi, 1977). These results allow us to draw the schematic diagrams of Figure 6. In the top panel of Figure 6, the isovolumic pressure-volume relation is shown, and diagrammatically drawn are a number of pressure-volume loops taken at different degrees of ventricular filling, but against the same ejection pressure. From this figure a ventricular function curve can be constructed (bottom panel). The horizontal axes are the same in the two diagrams but, in the function curves, stroke volume instead of pressure is plotted on the vertical axis. Instead of stroke volume, cardiac output or stroke work can be plotted equally well, because heart rate and aortic pressure should be constant. In Figure 6, stroke volumes can be found from the horizontal parts of the pressure-volume loops. If end-systolic volume is the same at all levels of ventricular filling, as is assumed in the diagram, the function curve will be a straight line, as is sometimes found (Kissling and Gallitelli, 1977), even up to the extreme situation in which all valves are open all the time. Since end-systolic volume is, if anything, somewhat larger for bigger stroke volumes (Suga and Yamakoshi, 1977), a curvature will occur as is often reported in the literature (Sarnoff and Mitchell, 1962; Guyton et al., 1973). These arguments suggest that the shape of the left ventricular function curve is not related to the shape of the length-tension graph found in isolated muscle.

Conclusions

We show in this paper how pump function of the heart can be quantified. Subsequently, a number of quantities, determined in the intact heart but derived from the length-tension and force-velocity relationships found in isolated muscle, are evaluated as descriptive of cardiac pump function. The interest in these quantities results from the relevant comparison between the function of heart and isolated muscle. Since so much basic information is available on the behavior of isolated muscle, this knowledge usually is taken as a basis for such a comparison. However, we demonstrate for a number of variables derived in that way, that they cannot give a quantitative description of the heart as a pump.

It seems to us that the efforts to understand cardiac pump function by applying muscle data and theory to the whole heart have entered a phase of diminishing returns. Another more fruitful possibility for bringing heart and muscle together seems to

![Figure 6](http://circres.ahajournals.org/)

**Figure 6** Schematic representation of the relationship between the pressure-volume graph of the left heart (upper panel) and the left ventricular function curve (lower panel). Two different contractile states are shown (a and b).
orient research in the opposite direction, i.e., to study isolated heart muscle as if it were part of the ventricular wall.

References

Elzinga G, Noble MIM, Stubba J: The effect of an increase in aortic pressure upon the inotropic state of cat and dog left ventricles. J Physiol (Lond) 273: 597-615, 1977
Noble MIM: Problems concerning the application of concepts of muscle mechanics to the determination of the contractile state of the heart. Circulation 45: 252-255, 1972
Noble MIM: Problems in the definition of contractility in terms of myocardial mechanics. Eur J Cardiol 1: 209-216, 1973
Patterson SW, Starling EH: On the mechanical factors which determine the output of the ventricles. J Physiol (Lond) 48: 357-378, 1914
Sonnenblick EH, Paremyr WW, Ureschl CW: The contractile state of the heart as expressed by force-velocity relations. Am J Cardiol 23: 488-503, 1969
van Meer G: On the part played by the supraregulars in the normal vascular reactions of the body. J Physiol (Lond) 45: 604-610, 1973
How to quantify pump function of the heart. The value of variables derived from measurements on isolated muscle.
G Elzinga and N Westerhof

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