Problems Concerning the Application of Concepts of Muscle Mechanics to the Determination of the Contractile State of the Heart

There has been much recent interest by clinical cardiologists in the question of myocardial "contractility" or "contractile state." To the clinician, the quest for a measure of "contractility" or "contractile state" becomes the quest for an early indication of myocardial disease that may be of prognostic value and open up the possibility of preventative measures to forestall serious myocardial disease and failure. Braunwald has pointed out that there is a dissociation between the heart's output and its contractile state. In the normal intact dog, an increase in end-diastolic volume (i.e., initial fiber length) increases stroke volume and cardiac output whereas an increase in contractility does not. How then can we characterize contractility in the intact heart? The first step is to define it.

By contractility or contractile state I mean the following: If one keeps a strip of isolated heart muscle at a constant length, depolarization is either followed by no response (e.g., in a Ca++ free medium), i.e., there is no contractility, or by the development of force, i.e., there is contractility. Can one quantify the degree of contractility? The amount of force developed increases progressively as the length at which the muscle is held is increased (Frank-Starling mechanism). This phenomenon is here defined as the "length effect." By a change of contractility, I mean an altered response which is independent of muscle-fiber length. If this length effect is excluded by holding the muscle at a constant length (isometric) one can now quantify contractility by the amount of isometric force or stress (force/cross-sectional area of muscle) developed. The distinction between changes in cardiac performance due to the Frank-Starling mechanism and those due to changes in contractility are crucial to any study of the subject of contractile state in both isolated heart muscle and intact heart.

When heart muscle shortens, one has to consider not only its ability to develop force but also its ability to shorten. These two functions can be expressed by the inverse relation between force and velocity (F-V relation). In skeletal muscle this relationship is a hyperbolic one, the intercept on the velocity axis (velocity at zero force) being called \( V_{max} \) and the intercept on the force axis (force at zero velocity), i.e., during isometric contraction, being called \( P_n \). The force-velocity curve is length-dependent following the relationship between active force development and muscle length. However, it has been claimed that in cardiac muscle only \( P_n \) is length-dependent and that \( V_{max} \) is independent of length. This result has not been found consistently and the original conclusion has been disputed on theoretical grounds. The resolution of this dispute is of great importance because, if \( V_{max} \) is length-dependent, it does not distinguish between change due to the Frank-Starling mechanism and change due to altered contractility.

The application of these concepts to intact heart depends on the assumption that heart muscle has a contractile element (CE) which has the properties outlined above and which shortens during isometric contraction of the muscle. When a muscle contracts, it behaves as if there were contractile properties in series.

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with elastic properties, the so-called contractile (CE) and series elastic (SE) elements. During isometric contraction the CE is said to shorten and stretch the springlike SE, developing force. It is important to emphasize that these are the elements of a model which characterizes the way the muscle behaves. They may not actually exist in the muscle itself, and recent work by Huxley and Simmons suggests that the model is not correct for skeletal muscle. Much further work is needed to investigate the validity of the model for heart muscle. The important features of a contractile element (CE) and elastic element (SE) in series are that under isometric conditions the force on the two elements is the same and that the CE shortens at the velocity at which it stretches the SE $(V_{CE} = -V_{SE})$. The workers who have tried to apply the principles of muscle mechanics to the intact heart have usually had as their chief objective the calculation of the velocity of contractile-element shortening $(V_{CE})$. This is done during isovolumic contraction, with the assumption that the isovolumic contraction is isometric, and $V_{SE}$ is calculated by dividing the rate of rise of wall force $(dF/dt)$ by the slope of the relationship between force and stretch of the SE $(dF/dl)$. (The "stretch" or "extension" is the extra length above the unstretched length, which is the length at zero force [unknown in the case of the SE]). The relationship between force and stretch in isolated papillary muscle has been determined experimentally and shown to be not linear but exponential (i.e. $dF/dl$ is not constant). To calculate $V_{CE}$ in the intact heart, something needs to be known about the force-stretch relationship of the SE in the intact heart. Nothing is known about it. Even when attempts are made to measure it, the assumption is made that the force-stretch relationship is exponential as in papillary muscle and that $dF/dl$ is linearly related to force with an intercept $(c)$ which is small and can therefore be ignored.

It is unjustified to make such an assumption about the unknown relationship one is trying to elucidate. If $c$ is ignored, equations describing the SE are obtained which are physically impossible.

This assumption concerning the SE is very unfortunate because it is a necessary preliminary to the calculation of $V_{CE}$ during isometric contraction by dividing the rate of the rise of the isovolumic left ventricular pressure $(dP/dt)$ by the pressure $(P)$ and a constant $K$ (i.e. $dF/dt/KP$). In order to avoid this error, some workers have divided $dF/dt$ by $KP + c$ but the values $K$ and $c$ are assumed ones taken from papillary muscle. This practice has never been justified; $K$ and $c$ have not been measured in intact heart and it is likely that they vary from heart to heart. There is thus an unknown error in $V_{CE}$ obtained this way, making comparison between different hearts impossible. It also makes it impossible to study changes in $V_{CE}$ in one heart because if there is an intervention which changes $dF/dt$ and $P$, each pair of values for $K$ and $c$ will cause a different change in calculated $V_{CE}$.

The calculation of $V_{CE}$ in isolated papillary muscle is not enough to determine contractile state because $V_{CE}$ is length-dependent at any finite force. However, one can calculate the relationship between $V_{CE}$ and wall force and extrapolate the relationship to zero force to obtain $V_{max}$ which may be independent of length. Unfortunately wall force cannot be measured in humans; the optimists resort to calculations from pressure based on assumptions of heart size and shape varying in fantasy from a thin-walled sphere to a thick-walled ellipsoid.

The difficulties of defining contractility become immense when the muscle is allowed to shorten. The force-velocity relationship is changing throughout the contraction because (1) like isometric force, it is a function of time, and (2) like isometric force, it is a function of length. The muscle is continuously

\[ dF/dl = KF + c \] where $K$ and $c$ are constants and $F = (c/K)e^{kt} - (c/K)$. If $c$ is ignored (i.e., $c$ is set equal to zero), $F = 0$ for all values of $t$ (the stretch). If $dF/dl = KF$, $F = Ae^{kt}$ and $F$ is finite $(=A)$ when $1 = 0$. Both solutions defy the definition of a spring; they are absurd.

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changing length and therefore moving from one force-velocity curve to another according to the length effect. These problems are ignored when the F-V relation is calculated during ejection. Moreover, in the intact heart, mural force, which is a function of the pressure within and the size and shape of the ventricle, is changing considerably during a normal heart beat; there is nothing analogous to an "afterload" (constant muscle load during shortening) in the intact heart.

The wall of the heart develops force as it is stretched in diastole. Is this achieved by the contractile element at a low level of activity or is diastolic stiffness a purely passive property? The latter is commonly assumed, and diastolic force is subtracted from total force during isometric papillary-muscle contractions to give developed (i.e. CE) force. Developed force ("active tension") reaches a maximum at a sarcomere length of 2.2 μ (the length at which there is a maximum overlap of actin and myosin active sites according to the sliding-filament theory), whereas total systolic force continues to increase beyond this optimum sarcomere length. This supports the idea that diastolic force is passive and should be subtracted, i.e. it is attributed to a so-called parallel-elastic element (PE).* However, when Vce during ejection is calculated, the shortening of the PE is completely ignored. It is impossible to have one's cake and eat it. The presence of a PE also has implications for the isovolumic indices dp/dt/KP and dp/dt/(KP + c) because some of the total pressure in the denominator, perhaps as much as enddiastolic pressure (EDP) according to which model one adopts, is distributed to the PE and should be subtracted. Subtraction of EDP from total pressure makes an enormous difference to the quotient.

In view of all these problems, it is surprising that concepts of muscle mechanics are applied to the determination of the contractile state of the heart with such apparent confidence. One may list a number of other problems that require thought. (1) The heart changes in shape during both isovolumic contraction and ejection. (2) The wall of the heart changes in thickness during the cardiac cycle. (3) The orientation of muscle fibers within the heart is extremely complex. The fibers are not parallel as in papillary muscle. (4) Wall force in different parts of the heart will differ depending on the radii of curvature of the wall. (5) The muscle fibers in the heart do not all contract synchronously. (6) There is a considerable variance of sarcomere length at any given heart size. (7) There is buckling of muscle fibers within the wall of the heart. These factors are not taken into account when concepts of muscle mechanics are used to estimate contractility in the intact heart.

My conclusion is that, in the present state of knowledge of the mechanics of isolated heart muscle, there does not appear to be a variable which is a well-validated index of myocardial contractility. At the moment, any answer to this problem must necessarily be somewhat arbitrary and strongly dependent upon the point of view and objectives of the individual worker. In view of the difficulties with basic isolated-muscle mechanisms, the application of concepts of muscle mechanics to the determination of the contractile state of the intact heart would appear to be premature. This view is reinforced when one considers the complexities of the intact heart compared with isolated muscle strips. If this type of analysis in the intact heart is based on unsound principles, the submission of patients to complex cardiac catheterization procedures in order to determine contractile state seems to me to be of doubtful ethics; this applies particularly to "normal controls." I think that much more animal work is required before

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*A minimum of three elements is thought to be necessary to model heart muscle (CE, SE, and PE).* More complicated models have also been proposed to account for viscous effects, etc., but the greater the complexity of the model the less useful it is and the less susceptible to mathematical solution. A two-element model in which the CE rather than the PE supports diastolic force implies that diastolic force cannot be subtracted from total systolic isometric force in the usual way.

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concepts of muscle mechanics can reasonably
be applied to clinical cardiology.

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