SPECIAL ARTICLE

Effect of Afterload Reduction on Myocardial Energetics

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SUMMARY Consideration of muscle energetics suggests that the ventricle has a very definite optimum range of operating wall tensions, and that clinical advantage can be gained by maintaining the tension within this range. Circ Res 46: 161-166, 1980

UNLIKE skeletal muscle, which may consume energy to maintain posture without doing external work, the sole function of cardiac muscle is to perform work, transmitting the energy of contraction into the flow of blood. In the healthy ventricle, myocardial efficiency, defined as the ratio of external work to total energy consumed, is probably near its optimum. Furthermore, there appears to be sufficient energy reserve to accommodate substantial increases in work with little fall, or possibly a slight increase, of efficiency. In contrast, the increased wall stress in the failing ventricle results in a decreased efficiency. Afterload reduction in the failing ventricle can cause an increase in myocardial efficiency by decreasing wall stress. It also can diminish total energy expenditure by decreasing muscle length. In addition, the reduced afterload allows more of the energy to be expended in ejecting blood, rather than in developing pressure. The reasons for these changes can be found both in the physiology of the isolated muscle and in the geometrical characteristics of the ventricle.

Isolated Muscle

Instantaneous Efficiency of Isolated Muscle

The contractile capability of muscle can be determined from its force-velocity characteristics. The velocity of shortening is related inversely to the force of contraction, as shown in Figure 1A. At the shorter length, both force and velocity are diminished. The exact shapes of these curves, particularly the points of maximum velocity, have been the subject of some controversy (for a brief review, see Ford and Forman, 1974). For the present discussion, maximum velocity is of little consequence, because, as shown in the lowest (dotted) curves of Figure 1B, the muscular work rate (power = force \times velocity) is zero at maximum velocity, when force is zero. Work rate is also zero at isometric force, when velocity is zero, and the curve reaches a maximum at intermediate values of force. The area of interest is the region of the curves between isometric force and maximum velocity, where work rate is finite. Unlike the question of maximum velocity, there is no argument that work rate is diminished at short lengths. The work rate curves in Figure 1B illustrate that it is possible to increase muscle work by decreasing force when the muscle is operating to the right of the peak, where the slope of work rate vs. force is negative. Decreasing one component of work, the force, will nonetheless increase work; but since the work requires energy expenditure, the beneficial effect of reducing force can be determined only when the total energy cost of contraction is known.

Energy other than external work is ultimately realized as heat, so that total energy is equal to the heat plus the work, as shown in the uppermost (solid) curves of Figure 1B. The most reliable data on heat are from skeletal muscle, which can be studied under conditions of constant activation. The data from cardiac muscle are more ambiguous because activation (and therefore the rate of energy
FIGURE 1  Instantaneous energy relationships in muscle and ventricle. The lower curves in each figure represent a 7% shorter length, corresponding to a 20% reduction in volume. Velocity in A is determined as the slope of the length record after release to an isotonic load, as shown in the inset. Work rate, dotted line in B, is force × velocity (force-velocity data from Forman et al., 1972). Total power (solid line) in B is work rate plus heat rate (dashed line), and efficiency in C is work rate divided by total power. The pressure (Pr.) and ejection rates (E.R.) in D, E, and F are derived from the values for linear muscle, using the equation in the inset of D.
liberation) is affected by several factors that are difficult to control. When allowances for these factors are made, the data from heart muscle are similar to those of skeletal muscle, but by no means as accurate (for a review, see Gibbs, 1978). Because of this inaccuracy, the parameters for determining the heat of shortening in the middle (dashed) curves of Figure 1B are from skeletal muscle (Hill, 1964), corrected for the length dependence of isometric heat in cardiac muscle (Gibbs and Gibson, 1970). As the figure shows, there is a high energy cost in maintaining a contraction, even when there is no work done, such that the maximum muscle efficiency (Fig. 1C) is of the order of 20–25%.

Figure 1, B and C, also shows that when the muscle is operating near maximum efficiency, the total energy cost of maintaining a contraction at different lengths varies in almost direct proportion to the work. Thus, the maximum efficiency is affected only slightly by work rate changes resulting from length changes. Reducing muscle length can reduce energy consumption without much decrease in efficiency, provided that the muscle is functioning near its most efficient tension. In addition, the curves of Figure 1B show that the relative changes in work rate that result from variations in force are substantially as the load is lowered from the iso-ventricle.

The equations in the inset of Figure ID show that, at a constant circumference, ventricular ejection rate (E.R.) is proportional to muscle shortening velocity (Vel.) and intraventricular pressure (Pr) is proportional to muscle tension (F). Consequently, for each muscle length, corresponding to a given volume, the pressure-ejection rate curves can be scaled to match exactly the force-velocity curves. The curves change their relationship to each other, however, when volume and muscle length change.*

Because pressure is inversely related to ventricular radius, pressure changes resulting from volume changes are not as great as the tension changes resulting from corresponding muscle length changes. The opposite is true for velocity and ejection rate. Because ejection rate is directly related to radius, changes in ejection rate resulting from volume changes are greater than the corresponding velocity changes.

Ventricular work rate (pressure × ejection rate) must equal muscle work rate (force × velocity) and muscle heat rate must equal ventricular heat rate, so that the ordinate axis of Figure 1B applies exactly to the ordinate axis of Figure 1E. Since the efficiency is derived from the energy rate values, the scale in Figure 1C also applies to Figure 1F, as shown. The net effect of these changes is to move energy rate and efficiency curves closer to each other along the pressure axis; i.e., wall tension changes are larger than the corresponding pressure changes that result from variations of ventricular volume.

Beneficial Effects of Afterload Reduction

There are three ways that afterload reduction can improve the energy balance in the failing myocardium. These three mechanisms are illustrated by movement along the curves of Figure 1, D, E, and F. (1) A reduction in ventricular volume will decrease the total energy expenditure (movement from upper to lower curves in Figure 1E). In spite of the decreased work, this reduction in energy consumption may be clinically beneficial in the presence of coronary artery disease; the decreased energy expenditure can bring the myocardium into more optimum balance with its blood supply. (2) A pressure decrease will result in an increased ejection rate (Fig. 1D). Cardiac output therefore will be increased, frequently, but not always, with a decrease in total myocardial energy expenditure resulting from the shorter muscle length. Furthermore, the greater the failure, the larger the relative increase in ejection rate for a given change in pressure. For example, if the maximum (isovolumic) pressure for the upper curve in Figure 1D is 150 mm Hg, a reduction from 120 to 110 mm Hg will be associated with a 40% increase in ejection rate, which will rise from 5 to 7% of its maximum value.

Intact Ventricle

Geometrical Factors

The equations in the inset of Figure 1D assume that each layer of ventricular muscle changes equally in all three dimensions, as for a sphere (Ford, 1976). The relationship between ejection rate and velocity for such a ventricle can be derived by writing the equation for the volume of a sphere (Vol = 4/3πr³) and differentiating it once with respect to time, to obtain d Vol/dt = 4πr² dr/dt. The term d Vol/dt is ejection rate, and term dr/dt is proportional to circumferential muscle shortening. The relationship between volume and pressure can be derived from the Laplace relationship (pressure = -2 tension/radius) and from the consideration that the same number of muscle cells must spread out to cover a larger area when the ventricle expands. Since the number of cells covering a unit length of circumference is inversely proportional to the radius, the force exerted by these cells also diminishes in proportion to the radius. Hence the r² term in the denominator of the second equation in the inset. It is intuitively obvious that the proportionalities derived for a sphere will apply to other three-dimensional configurations, provided that they change proportionately in all dimensions, retaining the same shape. The proportionality constants will vary, however, depending on the shape assumed. Thus, the equations in the inset are written with undefined proportionality constants. To the extent that some dimensions change less than others [e.g., the apex-to-base dimensions change less than the transverse radius (Rushmer and Thal, 1951)], the radius term in the figure will be raised to a power less than 2. The figure therefore illustrates the maximum effect that can be caused by geometrical factors. Finally, ventricular work rate (Pr × E.R.) must equal muscle work rate (F × Vel), irrespective of muscle length, which can be shown to hold when the two equations in the inset are multiplied together and the r² terms cancel. The term K × K is then a proportionality constant which relates the way in which linear muscle work is converted to volume work. This equality suggests that the equations are not substantially in error, since the two forms of work must be equal.
If the maximum pressure is 300 mm Hg, the same pressure reduction will increase ejection rate from 24 to 26% of maximum, but this will now represent only an 8% increase. This is simply a matter of relativity, but shows that it is not necessary to invoke a concept of dynamic impedance to explain why small changes in pressure can produce variable changes in cardiac output. This example also illustrates the value of assessing hemodynamic function before lowering afterload; the relative increase in ejection rate will be worth the risk only in those patients with significant failure. (3) The efficiency of the failing myocardium can be greatly improved by pressure reduction. When pressure is much greater than the optimum, i.e., well to the right of the peak of the efficiency curve in Figure 1F, a pressure reduction will increase the work rate to a much greater extent than total energy expenditure, such that the efficiency will increase substantially. In contrast, when the muscle is operating near its peak efficiency, large changes in performance cause only small changes in efficiency. For example, movement from the peak of the lower curve to the peak of the upper curve in Figure 1F will result in less than a 20% increase in efficiency. Within this efficiency range, 2-fold changes of pressure and ejection rate can be accommodated.

Finally, the curves of Figure 1 show why “pressure work” is more energy costly than “flow work” as originally suggested by Sarnoff et al. (1958).

**Total Systolic Efficiency**

It is reasonable to ask what happens when ventricular afterload is reduced below the level at which the muscle functions optimally, to the left of the peak of the efficiency curve. In answer, it is important to emphasize that the curves in Figure 1 represent instantaneous values in maximally activated muscle. To determine total systolic energy it would be necessary to integrate the energy rates throughout systole. This integration would be quite complex because, as the muscle shortens, it moves to progressively lower curves, appropriate to the shorter lengths. In addition, muscle activation is changing continuously during systole, rising relatively slowly (Brady, 1966; Sonnenblick, 1967; Edman and Nilsson, 1968), and then declining. The time course of activation is influenced further by the history of the contraction. Active shortening tends to deactivate the muscle partially for the remainder of the contraction (Brady, 1966), and the amount of deactivation depends both on the speed of shortening and on the distance shortened (Briden and Alpert, 1972). A complete representation of muscle function, such as is shown in Figure 1, would contain several families of curves, each representing different levels of activation and a different contractile history for each muscle length. Such complete data are not available, but some estimate of total systolic energy can be gained from measure-
mments made during afterloaded contractions. Figure 2 shows the total energy expenditure during entire twitch contractions in papillary muscles allowed to shorten isotonically under different afterloads, beginning each contraction from the same length. The curves are similar to the curves of Figure 1, except for one important difference: the total energy expended is least at the lowest loads, whereas the opposite is true of the instantaneous energy rate curves. This difference arises because muscle shortening at low loads decreases the duration of activation, as shown by the tension record in the inset of Figure 2A. The deactivating effect of shortening suggests a mechanism whereby the muscle is protected from expending much energy at inefficiently low loads. Although the muscle will operate inefficiently when the load is reduced sufficiently, the rapid shortening at these very low loads causes deactivation, which greatly limits energy expenditure. Extreme afterload reduction, as might occur during intra-aortic balloon counterpulsation, therefore provides benefit by resting the myocardium.

Other Benefits of Afterload Reduction

The increased efficiency of muscular contraction is only one of several reasons why afterload reduction may be clinically beneficial. Other benefits result from the interaction of the ventricle with the remainder of the circulation. As Forrester et al. (1976) have suggested, there is an optimal balance between increased filling pressure and increased ventricular performance. Because muscle performance is dependent on length, and because the passive stiffness of the muscle increases progressively at longer lengths, large increases in diastolic pressure are required in a dilated heart to produce small increases in length, with concomitantly small increases in ventricular performance. As filling pressure increases, there is a progressively smaller increase in performance, until a point is reached where the deleterious effect of increased pulmonary venous pressure outweighs the beneficial effect of increased muscle performance. Reducing the afterload to keep end-diastolic pressures below this point avoids pulmonary edema without seriously compromising ventricular function. Another benefit of decreased diastolic filling pressure is an increased coronary perfusion (Kirk et al., 1978) particularly of the subendocardial layers of the heart (Munch and Downey, 1979). Since there is probably some recruitment of muscle in these subendocardial layers in the dilated heart (Ford and Forman, 1974), the subendocardial layers may require more optimal energy expenditure. Finally, the agents used to reduce afterload may increase blood flow to the kidney (Guiha et al., 1974), thereby improving the overall clinical state.

**Chronic Afterload Reduction**

A recent review (Ford, 1976) has shown that, over a 2000-fold range of heart size and a wide variety of hemodynamic conditions, the normal mammalian left ventricle grows to maintain a constant tension on the individual contractile elements. Heart failure can be viewed as the reverse of the growth process, with some of the contractile elements losing their ability to develop physiological forces. The dilation that accompanies failure stretches the remaining viable muscle to longer lengths, where it can do more work. Afterload reduction reduces the work done by the active muscle, both by a direct reduction in pressure and by a reduction in ventricular radius. Whether this afterload reduction will have any long-term benefit depends upon the initial causes of heart failure. In those instances in which the cause of failure is due to the loss of some cells, with the remaining cells retaining their normal capability, it might be expected that the viable cells would grow to match the increased demands. Afterload reduction in this instance provides a means of avoiding overt failure until the heart can re-grow its normal function. In other cases, progression of the disease may be sufficiently slow to allow a prolonged beneficial effect from this therapy. In many instances, however, the type of severe congestive failure that requires vigorous afterload reduction results from progressive death of cells. The remaining cells are not able to grow to meet these new demands, and afterload reduction only transiently matches the load to the heart's reduced capability. In the end, the underlying disease progresses to the point where the heart cannot meet its new demands and congestive failure recurs. Although it is not possible yet to determine which patients will benefit from long-term afterload reduction, it is likely that further experience with this treatment will reveal finer distinctions in types of congestive failure, and that these distinctions will be based on the ability of the myocardium to recover during periods of prolonged assistance.

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