Triple control of relaxation: implications in cardiac disease

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EARLY DETECTION of impaired relaxation has been emphasized recently for the evaluation of global and regional ventricular function in patients with heart disease. Although early relaxation abnormalities have been found in various cardiac diseases, the underlying mechanisms are not as yet fully understood. Given the recent progress in our understanding of relaxation of the heart, these mechanisms can now be discerned more easily. We will first summarize our present knowledge of relaxation of cardiac muscle or, more specifically, how relaxation is controlled by the three following interacting determinants: (1) load, (2) (in)activation, and (3) nonuniform distribution of load and (in)activation in space and in time. Then, the concept of triple control will be extended to that of the intact heart in situ as a pump. We will also review how multiple factors, acting either alone or in concert depending on the nature of the disease, underlie early relaxation abnormalities in patients with heart disease. Finally, measurements of ventricular relaxation will be critically discussed in view of these newer concepts.

Mechanical aspects of relaxation of isolated cardiac muscle

Performance of the heart during the contraction phase, both as a muscle and as a muscle-pump system, is regulated through two distinct but interrelated functions, namely heterometric autoregulation or control by changes in load (volume and/or pressure) and homeometric autoregulation or control by changes in contractility. Although regulation of performance by changes in load is conceptually related to heterometric autoregulation and regulation of performance by changes in contractility to homeometric autoregulation, these concepts are not quite identical. By the same token, although changes in contractility are usually believed to be the mechanical expression of changes in activation, the concepts of contractility and activation should not be used interchangeably. Given the complexity of the intact heart, one should also take into account some degree of nonuniform distribution of the former two mechanisms as a third important physiologic determinant of performance.

We have recently learned that a similar triple control mechanism also operates during the relaxation phase. Relaxation of the heart, both as a muscle and muscle-pump system, is governed by the continuous interplay of the sensitivity of the contractile system to the prevailing load and the dissipating activation (inactivation). For a given set of loading conditions, relaxation can be modulated by subtle alterations of the load dependence due to changes in the underlying dissipation of activation. Alternatively, for a given load dependence, and hence unchanged dissipation of activation, relaxation will be influenced by alterations of the prevailing load. As in the contraction phase, this control of relaxation is continuously modulated by the regional and temporal nonuniform distribution of load and inactivation. Within a given range, nonuniformity is a third physiologic determinant of relaxation. Hence, a triple instead of a dual control regulates relaxation in physiologic conditions. This concept of triple control of relaxation constitutes a logical extension of that of the triple control of the contraction phase.

Control by load. The concept of load dependence of relaxation was derived from experiments (figure 1, II) in which load or changes in load during relaxation (relaxation load, RL) acted upon the relaxation phase itself. Once peak shortening is reached in the isotonic twitches (figure 1, IIA), lengthening occurs at an increasingly faster rate, followed — in the isometric phase of the afterloaded isotonic twitch — by an abrupt fall in force below the force level of the isometric twitch, thereby separating both isometric relaxation phases in time. Some force potential is therefore lost during the lengthening phase and before the isometric relaxation phase. Load dependence is even more ap-
During the contraction phase, the twitch isometric twitch occurs early in the cycle. During the afterload phase, the twitch is late in the cycle. The effects of small load clamps at various times in the systolic phase of the cardiac cycle on relaxation. The transition zone plays a major role in the control of systolic performance in the intact heart.

**Control by inactivation.** Sensitivity to load of mammalian cardiac muscle relaxation diminishes under conditions in which the reuptake of the myoplasmic activating Ca\(^{++}\) has been suppressed.\(^1,2\) Here relaxation seems to be governed solely by the process of inactivation, i.e., the totality of processes leading to the disappearance of force-generating sites (detachment of cross-bridges). Accordingly, load dependence of relaxation in mammalian cardiac muscle requires the presence of Ca\(^{++}\)-sequestering membranes, and load predominates over inactivation at sufficiently lowered levels of myoplasmic [Ca\(^{++}\)]. Inactivation modulates relaxation in a subtle interplay with the load, which is continuously faced by the force generated by the muscle at any time during contraction or relaxation. Relaxation of ventricular cardiac muscle thus normally depends on the interaction of load and inactivation.

**Control by nonuniformity.** In most studies of myocardial and ventricular function, mechanical nonuniformity has been tacitly assumed. We have recently studied this problem in our laboratory. In normal single cells sarcomere distribution and behavior is uniform throughout contraction and relaxation. In multicellular preparations, an increasing degree of nonuniformity has been found both in space and in time; this physiologic nonuniformity was most marked during relaxation and at higher loads. Accordingly, a given degree of nonuniform distribution of load and inactivation in space and time constitutes a third important physiologic control mechanism of relaxation. It will contribute further to load dependence, since during relaxation shortening fibers in some areas of the muscle would add to the external load to more easily disrupt already relaxing fibers in other areas.

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**FIGURE 1.** Effects of load on relaxation during contraction, relaxation, and transition zone. In all panels, several twitches obtained in isolated cat papillary muscle have been superimposed with the shortening traces above and the corresponding force traces below. I and II. The numbers 1 and 2 refer to comparable afterloads. Twitch 3 in A and B is the isometric control twitch (omitted in panel C and in III). Twitch 4 in IIa is a reloaded isotonic contraction at length \(l_{max}\). A. Effects of afterload. B. Effects of abrupt load alterations (load clamps) early (I) and late (II) during the cardiac cycle. C. Effects of changes in preload (from 1 to 2) either before the twitch (I) or at the end of a physiologically sequenced (isometric-isotonic) relaxation (II, during the isotonic lengthening phase). III. The effects of small load clamps at various times in the systolic phase of the cardiac cycle on relaxation. CL = twitches 1 to 3; RL = twitches 7 to 9; the load clamps in twitches 4 to 6 occurred during the transition phase from contraction into relaxation. Muscle characteristics (12/min and 29C): length at \(l_{max}\) = 7.5 mm; mean cross-sectional area, 0.84 mm\(^2\); ratio of resting to total tension at \(l_{max}\), 8%. Changes in load established during relaxation, or more specifically, after the first two-thirds of contraction and throughout relaxation. Accordingly, at a higher afterload (figure 1, IA) or after a clamp to a higher load early during the contraction phase (figure 1, IB) or at higher preload (figure 1, IC), the onset of relaxation is delayed and the net separation of the isometric relaxation phase of this twitch at the higher load from the isometric control twitch becomes smaller. The resulting delay in relaxation for higher contraction loads has been described previously.\(^2\)

The transition from the effects on relaxation induced by CL to the opposite effects on relaxation induced by RL occurs over a rather short period of time after approximately the first two-thirds of the contraction phase (figure 1, IIB). As will be outlined below, this transition zone plays a major role in the control of systolic performance in the intact heart.
Mechanical aspects of relaxation of the intact heart

Although relaxation in the intact heart is more complex than in isolated muscle, it is also regulated by loading conditions and inactivation. In addition, complexity of the ventricular wall and time and space distribution of the electrical depolarization and repolarization make nonuniformity an obligatory additional determinant of relaxation. Yet, this triple control of relaxation is not directly evident from observation of isovolumetric relaxation and filling phases of the intact heart.

Control by load. We previously discussed some of the major loadings that must be taken into account in the intact heart during the RL phase. Deformation during contraction, impedance alterations late in ejection, filling of the coronary reservoir during isovolumetric relaxation, and the Laplace relationship after mitral valve opening constitute the four major loading conditions in the intact heart during relaxation and, together, explain the almost explosive character of the rapid-filling phase. In this sense, the familiar phenomenon of diastolic suction during rapid filling is a mere consequence of load dependence. Diastolic suction is absent when relaxation is load independent.

It must be remembered that an increase in preload and/or afterload, once established during the first two-thirds of the CL phase, will delay the onset of relaxation. From the readjustment of force in the muscle fibers to a new load early in the contraction cycle, one can predict the prolongation in isovolumetric pressure decline (τ) — indicating slower relaxation — with increased volume or pressure loading, both these latter interventions are analogous to increased preload and/or afterload in the isolated muscle. This dependence of relaxation on early systolic pressure or volume loading (CL) does not reflect, however, sensitivity of relaxation to load with regard to the concept of “load dependence of relaxation” as described above.

Given the continuous interaction between the ventricle and the arterial impedance during ejection, the existence of a transition zone during ejection, in which the effects of CL change into those of RL, is of major importance for the control of mechanical performance of the ventricle during subsequent relaxation. Shifts in pressure and volume load from late to early ejection will tend to delay relaxation, while shifts from early to late ejection will induce premature relaxation. These shifts in load can be induced by neurohumoral or pharmacologic adjustments of arterial impedance that then affect timing and amplitude of reflected waves in late ejection (figure 5 in Brutsaert et al.), by alterations in contractility, and by changes in nonuniformity of the distribution of load and (in)activation during ejection, etc. This point can be illustrated by observation of the right ventricle, in which progressive unloading during the second half of ejection helps the complete emptying of the ventricle by delaying relaxation through the mechanism of load dependence.

The transition of CL to RL must be taken into account when the greatly varying effects on relaxation of pressure and volume loading during ejection reported in the recent literature are interpreted. A faster isovolumetric pressure decline with increases in peak or mean systolic pressure or with increases in stroke volume at constant peak or end-ejection pressure probably reflects predominance of factors related to RL. By contrast, a slower isovolumetric pressure decline with increases in end-ejection volume or with increases in left ventricular pressure could indicate that CL conditions have predominated over RL conditions during ejection. Unaltered relaxation velocity with increases in pressure or volume loading during ejection could result from equal effects on CL and RL conditions simultaneously. When comparing short- and long-term load alterations, differences in neurohumoral adjustment must also be considered when interpreting the conflicting data from literature. Moreover, shortening deactivation also partly explains some of the effects of extent of shortening or stroke volume on relaxation.

Control by inactivation. As in isolated muscle, dissipation of activation will modulate relaxation of the intact heart in a subtle interplay with the surrounding loading conditions. Accordingly, relaxation in the intact heart may be controlled by changes in the prevailing loading conditions in the presence of an unchanged inactivation process (or unchanged load dependence), or by changes in the inactivation process (or changes in load dependence) under a constant set of loading conditions, or by both. Factors that influence inactivation in the intact heart include metabolic control by the coronary circulation, neurohumoral control, and use of drugs. When interpreting the effects of these factors on relaxation, it is important to realize that they may have multiple sites of action. Since these actions may often induce opposite effects on relaxation, they should be considered separately. For example, the effect of a drug on relaxation could be traced to its action on the dissipation of activation, to the changes in CL or RL it produces, or to the changes in nonuniformity it generates. The overall effect may be an acceleration of relaxation, a delay, or no change at all. This point is illustrated by the many conflicting results in literature.

Control by nonuniformity. Given the complexity of the intact heart, nonuniform distribution of load and inac-
tivation in space and time constitutes a third control mechanism of the relaxing ventricular wall. Nonuniformity of relaxation in the intact heart results from regional variations in onset and rate of inactivation and in the distribution and decay of developed force, which in turn result when different regions of the ventricle are subjected to different stresses and strains depending on geometry, dimensions, cardiac fiber orientation, regional variations in the filling profile of the coronary reservoir, etc. As in the isolated muscle, this physiologic nonuniformity, which maintains ventricular performance within a narrow but optimal range of mechanical efficiency throughout the cardiac cycle, is important in modulating relaxation of the normal ventricle. As already mentioned, it would be expected to contribute further to the manifestation of load-dependent relaxation. However, as will be discussed below, in the diseased heart an inappropriate increase in nonuniformity will result in impaired or incoordinate relaxation, thus prolonging its overall duration, delaying mitral valve opening, and reducing the rapid filling phase.

Relaxation abnormalities in patients with heart disease

With these concepts in mind, the complex pathophysiology of ventricular relaxation can be understood more easily. Impaired relaxation can reflect either a diminished load dependence induced by impaired inactivation, or diminished loading conditions in the presence of unaltered load dependence or an inappropriate increase in spatial and temporal nonuniformity of load and (in)activation. We will focus mainly on the mechanism underlying early relaxation abnormalities in the ischemic and hypertrophied heart, since it is currently believed that these conditions constitute the major cause of cardiac failure.

Relaxation abnormalities in ischemic heart disease may be transient, but all occur early during the ischemic process and thereby often precede dysfunction of the contraction phase. Figure 2 illustrates the various mechanisms that either separately or in combination may help to explain these abnormalities. Load dependence of relaxation of cardiac muscle is suppressed during hypoxia. This finding is observed even before systolic force falls and it has been ascribed to inhibition of the reuptake of Ca++ by the sarcoplasmic reticulum and/or to an impaired detachment of force-generating sites between actin and myosin. The resulting delayed inactivation, as manifested by the diminished load dependence, would suffice to explain the early relaxation abnormalities in ischemic heart disease. In a more advanced stage of the disease, diminished loading during relaxation may also contribute. Depression of systolic performance, which results in less deformation at end-ejection, is a well-recognized feature of advanced ischemic cardiomyopathy. In addition, depending on the extent of obstruction and of increased impedance in the coronary vasculature, intramural compressive forces resulting from coronary engorgement may also markedly decrease. Given the regional or segmental nature of ischemic heart disease, inappropriately increased nonuniformity may induce or further enhance already existing early relaxation abnormalities or incoordinate relaxation. Experimental proof of nonuniformity was provided by Kumada et al., who showed transient changes in peak (-)dp/dt induced by nonuniform interaction between normal and ischemic zones of the ventricle after coronary ligation. The resulting imbalance of forces will diminish mechanical efficiency both during contraction and relaxation, and will undoubtedly accelerate the development of cardiac failure.

Relaxation abnormalities in hypertrophy are somewhat more difficult to understand. These relaxation abnormalities tend to occur at an earlier stage of hypertrophy than does impairment of contractility. Disturbed left ventricular function in hypertrophy might therefore be a problem of filling rather than of contractile dysfunction or outflow tract obstruction. Although the pathophysiologic of impaired relaxation in hypertrophy is complex, the concept of triple control of relaxation allows us to more easily discern the major mechanisms (figure 2). Loading plays an important role. If loading during relaxation is diminished in the presence of an unchanged load dependence of the cardiac muscle fibers, the time course of relaxation will be prolonged. In hypertrophy, various relaxation loadings may have been altered. When left ventricular function is well preserved in aortic stenosis, peak and mean left ventricular systolic stress are normalized by the development of concentric hypertrophy. The depressed contractile performance in decompensated aortic stenosis is thought to be related to inadequate hypertrophy and high wall stress rather than to a depressed contractile state of the hypertrophied myocardium. Only in the latter case could altered systolic wall stress account for slowing of ventricular relaxation in hypertrophy. The second type of loading to be considered in hypertrophy is stress after mitral valve opening. In the presence of a thickened wall, stress will be smaller for any given filling pressure and radius. Hence, the impact of the loading induced by the Laplace relationship during the rapid filling phase will be
decreased. The third type of loading to be considered in hypertrophy is coronary filling during isovolumetric relaxation. The development of myocardial hypertrophy reduces maximal coronary vasodilator capacity and attenuates the coronary response to acute periods of myocardial ischemia. Medial thickening and reduced total cross-sectional area of the coronary arteries and elevated intracavitary pressures all reduce the impact of coronary filling on relaxation of the hypertrophied ventricle. Impaired inactivation could theoretically delay relaxation in cardiac hypertrophy. For a given set of loadings relaxation will be delayed if inactivation is prolonged. It was recently shown, however, that load dependence of isolated cardiac muscle from hypertrophic hearts is not altered. However, reduction in coronary vasodilator capacity in the hypertrophied ventricle may produce cardiac muscle hypoxia, which could decrease load dependence and partly explain delayed relaxation. Inappropriate spatial and temporal nonuniformity of loading and inactivation may help to explain delayed relaxation in hypertrophy. Changed geometry, regional variations in wall thickness, interstitial fibrosis, and loss of myocardial contractile elements and of normal intercellular connections will undoubtedly further increase nonuniform distribution of load and inactivation in the hypertrophied ventricular wall.

Accordingly, although early relaxation abnormali-
ties are characteristic for various clinical conditions, the mechanisms underlying these abnormalities are not identical. A number of early manifestations of myocardial dysfunction during relaxation in cardiac failure may reflect inappropriately increased nonuniformity rather than a single disturbance in load or in inactivation. Moreover, when considering the effects of cardioactive drugs, one should not only examine their action on loading and (in)activation, but also on nonuniformity. For example, by acting mainly on still-viable tissue in patients with a large extent of nonviable tissue, positive inotropic drugs may further enhance nonuniformity and thereby induce further deterioration instead of improvement in overall ventricular performance.

Measurements of systolic performance

For the evaluation of ventricular function in the cardiac patient, several measurements or derived indexes have been proposed to characterize contraction and/or relaxation properties of systolic performance. In line with the concept of a triple control during relaxation, the familiar subdivision of the cardiac cycle into periods of systole and diastole* (figure 3) ought to be redefined. In Wiggers’ classic physiologic subdivisions of the cardiac cycle, systole ends with the opening of the mitral valve, when the heart is refilling, and then diastole (interpreted as dilatation or expansion) begins. In the slightly modified subdivision in clinical use, the Wiggers’ interpretation of these words was abandoned and it was proposed that systole ended with the second heart sound at the closure of the aortic valve. In view of the concept of load dependence, which is a fundamental manifestation of the relaxing cardiac muscle as reflected during the second half of the ejection period and isovolumic relaxation phase and throughout the rapid filling phase, we believe that the words systole and diastole ought to be reinterpreted in a conceptual rather than a phenomenologic sense, i.e., with respect to an integrated muscle-pump system rather than to a mere pump system. We therefore propose that rapid filling phase should be considered an integral part of systole since it is an integral part of cardiac muscle relaxation. A further logical subdivision of systole into contraction and relaxation phases follows from the existence of the already described transition from CL into RL. According to this latter subdivision, contraction encompasses isovolumic contraction and the first part of ejection, and relaxation a large portion of the second half of ejection, isovolumetric relaxation, and rapid filling phase. These new definitions would solve the confusion about the conflicting use of terms such as end-systole vs end-ejection in recent literature.

*According to Dorland’s Illustrated Medical Dictionary11 Systole, from the Greek word στοίχειον (“a drawing together or contraction”), has come to mean in the English medical literature “the contraction or the period of contraction of the heart, especially that of the ventricles, sometimes divided into components, as preejection and ejection periods, or isovolumic, ejection and relaxation periods.” Diastole, from the Greek word διαστολή (“a drawing asunder, expansion”), has come to mean in the English medical literature “the dilatation or period of dilatation of the heart, especially the ventricles, coinciding with the interval between the 2nd and 1st heart sounds.”

This medical interpretation is only one of several possible interpretations of the two Greek words. Another etymologically justified interpretation of the word diastole could be a division, notch, or separation between two contraction-relaxation cycles. This latter interpretation would be conceptually more appropriate for an integrated muscle-pump system. In this sense, the term relaxation period in Dorland’s interpretation of systole would also include the rapid filling phase and diastole would merely mean separation of active cardiac cycles.
In order for an index of performance to be conceptually useful, it should be interpreted in the context of the phase in which it has been measured. Indexes that are meant to characterize the contraction phase of systolic performance should be restricted to measurements made during the isovolumetric contraction and the first half of ejection. Indexes measured in the second half of ejection or later, including during the rapid filling phase, would then characterize the relaxation phase of systolic performance. The presence near peak pressure of a transition zone between contraction and relaxation and the fact that this transition zone may be displaced in some conditions and that its exact timing has as yet not been delineated in the intact heart limit the usefulness of measurements in the zone. Accordingly, ejection measurements made after this transition zone, such as ejection fraction, end- (or peak, or mean) systolic pressure–volume relationships, or derived indexes do not characterize the contraction phase of systolic performance, since they are measured in the initial part of relaxation in which load dependence is already a prominent feature. These measurements might be useful to characterize overall pump performance, but one should be aware that they do not allow us to distinguish effects of an intervention on contraction from those on relaxation. These measurements may appear to be independent of volume and pressure loading only when the effects of CL on late ejection are canceled by those of RL. Many controversies regarding these measurements should be critically reexamined in view of these newly developed concepts.

Conflicting results obtained with pressure-derived indexes of relaxation are not surprising, since they constitute a mere mathematic approximation of the pressure decay, which is a complex function (monoeponential, biexponential, or asymptote?) of time, sometimes influenced in the opposite way even by minor alterations of many factors. The variety of techniques used for measuring interval-derived indexes of relaxation makes it rather difficult to compare these indexes, most of which are related to valve movements that are mere consequences of pressure crossovers. Volume-derived indexes provide a better characterization of relaxation than pressure- and interval-derived ones. The rapid filling phase, in which most of the volume-derived indexes are measured, is the phase of systole in which the load-dependence concept of relaxation constitutes the most prominent feature. Accordingly, analysis of the rapid filling phase might be most appropriate to reveal alterations in intrinsic myocardial relaxation, as manifested by changes in load dependence. To what extent rapid filling phase is also affected by contraction loading, venous return, right ventricular dynamics, and the pericardium has as yet to be explored.

Accordingly, although none of the as yet described indexes provides a unique description of the relaxation process, dimension-derived indexes appear to be the most promising, but need further evaluation before they can be used meaningfully in clinical practice.

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