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Concepts Related to the Study of Diastolic Function: A Personal Commentary

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Introduction

After more than 30 years of involvement in research dedicated to studying the physiology of diastolic function, as a principal investigator, collaborator, and reviewer, I am pleased to have this opportunity to comment on concepts related to this most important aspect of cardiac physiology. It is particularly fitting to publish this commentary in the *Journal of Cardiology*, because so many significant contributions were made by my collaborators from Japan working with me in my laboratory[1–13], and then, upon their return home, continuing to study diastolic function in human studies[14–27] and in animal experiments[28–39]. For that reason, and because this is a "personal commentary", I will approach the material from the perspective of the body of knowledge that has been the outgrowth of that collaboration.

Why have the last 2 decades seen such a tremendous growth in the study of diastolic function? The development of ultrasophisticated echocardiographic techniques, particularly of pulsed Doppler flowmetry, pioneered in large measure by Japanese scientists[40,41], now makes it possible to non-invasively determine chamber dimensions, valve motion, and transmitral blood velocity. Thus, the functional behavior of the normal and pathologic cardiac chamber can be assessed non-invasively. Because we have now learned that heart failure can occur in the absence of systolic dysfunction we have increasingly turned to diastolic dysfunction as the primary or secondary cause, and it becomes particularly important to understand the basic physiology of diastolic function. It is my hope that this presentation will clarify these issues, or at least encourage an ongoing discussion of them. My purpose is not to provide a comprehensive review of all modalities available for the study of diastole, but to focus on those aspects that will help the reader understand the physiological basis for many of the indices used to describe normal and abnormal diastolic function.

For purposes of this review, I adopt an operational approach and define the period of diastole to begin at the onset of isovolumic relaxation and to end at the onset of ventricular contraction. This approach is reasonable because events during this portion of the cardiac cycle have the most direct effect on ventricular filling, and because the forces that drive blood into the ventricle are the result of the active and passive, *i.e.*, early and late, chamber properties that change with time during this period. The ability to noninvasively measure transmitral flow patterns, when coupled to our knowledge of the relationship between pressure and flow, and when further coupled to our growing understanding of the relationship between pressure and chamber properties, has made the parameters of transmitral flow a prime evaluator of diastolic function. Unfortunately, the separation of diastolic function into early and late events, has led many investigators to unreasonably separate chamber properties into active and passive with little or no interaction between them. Abnormalities of early filling have been ascribed only to ventricular relaxation, and abnormalities of late filling have been related only

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to ventricular compliance. In particular, the important but often misunderstood, concept of diastolic suction has frequently been erroneously coupled to ventricular relaxation, when, in fact, it is a property of chamber compliance. Furthermore, ventricular relaxation is generally analyzed from the measured isovolumic decline of left ventricular (LV) pressure, when, in fact, the measured LV pressure is influenced by factors other than deactivation, *e.g.*, restoring forces due to chamber and myocardial deformation (see below).

This commentary will start by discussing the physiology of the transmitral pressure-flow relations. I will then discuss the sources of the pressure gradients that drive transmitral flow, namely, the active and passive properties of the left ventricle. This will require a discussion of ventricular relaxation, which is the active, time-varying myocardial property, and a discussion of the passive properties that are volume dependent. Among the concepts and properties to be included in the discussion are: equilibrium volume; diastolic suction and elastic recoil; torsion and deformation; and ventricular remodeling.

Transmitral Pressure-Flow Relations

Animal experiments, human studies, and model studies[4] applying the laws of physics, have led to the general acceptance of the following equation of motion governing flow across the mitral valve.

$$\Delta P = (L)\,dQ/dt + (R)\,Q^2 \qquad [1]$$

Where: ΔP is the atrioventricular (AV) pressure difference; Q is the volume flow rate (ml/sec); and L and R are inertial and resistive coefficients, respectively. L varies inversely with the area of the flow stream and R varies inversely with the square of the flow area. Thus, $(L)\,dQ/dt$ represents the pressure difference required to accelerate and decelerate flow, and $(R)\,Q^2$ represents the pressure difference due to energy losses, ultimately, due to turbulence. It is helpful to note that inertial forces are conservative, so that the energy required to accelerate flow is recovered during deceleration. Dissipative forces, on the other hand, lead to a loss of energy in the form of heat and, in the normal valve where R is small, they result in only an insignificant drop in pressure. In mitral stenosis, however, $(R)\,Q^2$ becomes very large, and, as is well known, the AV pressure gradient can be substantial. Thus, the resistive term has only a minor effect on the shape of the flow pattern across the normal valve (more on this below). The presentation of this equation at this point serves 2 useful purposes: it offers the greatest opportunity to understand the physical factors that determine the diastolic parameters measured by pulsed Doppler echocardiography; and it is the basis of the computational model that will be used to illustrate many of the concepts discussed in this paper.

It is clear from equation [1] that the transmitral flow pattern is uniquely related to the time varying AV pressure gradient and the impedance across the mitral valve. Thus, I cannot stress too strongly, that *any physiological property that influences the mitral flow pattern, does so via its influence on the time variation and amplitude of the pressure gradient.* It is useful to distinguish between properties and loading conditions that act directly on ΔP and those that act indirectly. Properties that directly determine the ventricular contribution to ΔP are: the rate and extent of ventricular relaxation, the compliance of the ventricle, and the impedance of the mitral apparatus. Examples of factors that exert their effects indirectly, *i.e.*, by modifying the AV pressure gradient, are: heart rate, contractility, afterload, preload, chamber shape, calcium handling, age, exercise, remodeling, and left atrial properties. To cite some obvious examples, a change in heart rate due to exercise will have a different effect than a change due to pacing; and remodeling due to hypertension will have a different effect than remodeling due to mitral regurgitation. Determinants of impedance are the mitral valve area and shape, *i.e.*, factors that determine the effective flow area, and thus the velocity (kinetic energy) that results in the subsequent energy losses.

The validity and the predictive power of equation [1] is illustrated in **Fig. 1**. The data are recorded from a conscious, chronically instrumented, dog in my laboratory. Similar results have been obtained by others[42]. Mitral flow starts the moment the left atrial (LA) pressure falls below the LV pressure and, as the pressure gradient develops, flow rapidly accelerates to reach its peak value, the E point. Very soon after the E point (c. 10 msec) the AV pressure gradient becomes zero and flow starts to decelerate under the action of a negative gradient. When the gradient reverses again, even by a very small amount, there is a small rebound in flow, the L wave. For other examples of the often neglected L wave see also[42,43]. Finally, flow is again acceler-

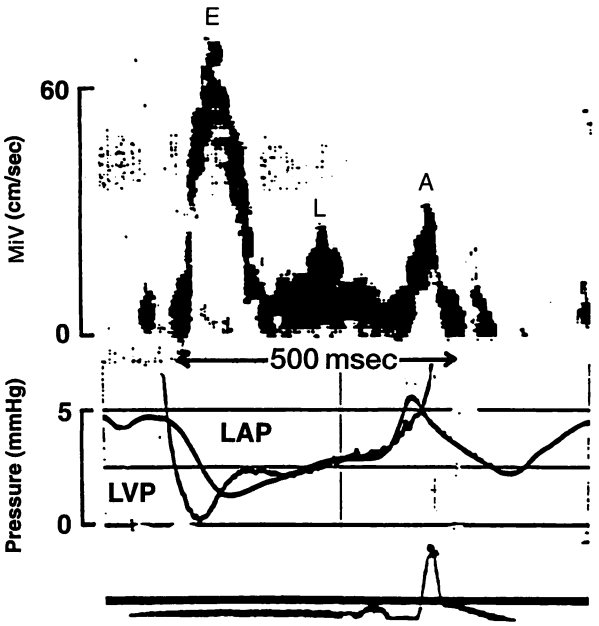

Fig. 1 Oscillographic record of pulsed Doppler mitral flow synchronized with high gain left atrial and left ventricular pressures from a conscious dog
Time from the onset of mitral flow to E point, t_{acc} = 90 msec; time from E point to end of E wave, t_{dec} = 120 msec.
LAP = left atrial pressure; LVP = left ventricular pressure; MiV = mitral flow velocity.
[Redrawn from reference 53 with permission]

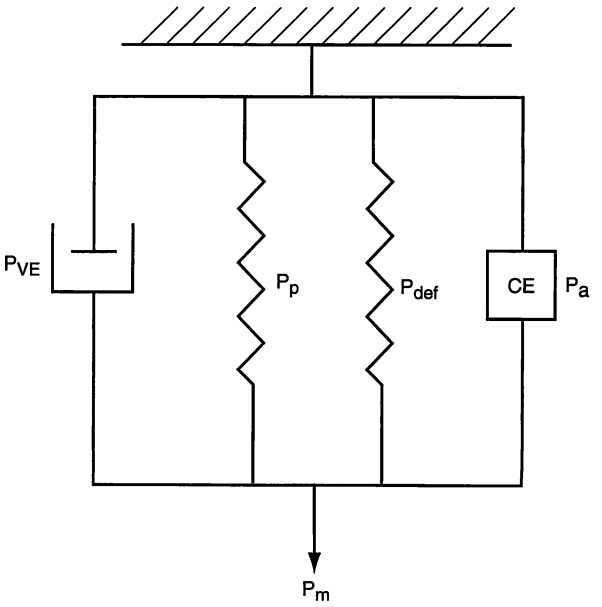

Fig. 2 Model of the myocardial and chamber properties of the left ventricle illustrating the 4 components that determine the measured pressure
P_m = measured pressure; P_{VE} (P_P, P_{def}, P_a) = pressure due to viscoelasticity (passive elasticity, deformation and active state); CE = contractile element.

ated and decelerated by the atrial contraction and relaxation, the A wave. Indices of the transmitral flow pattern that have been found to be useful in the study of diastolic function include: E wave acceleration and deceleration time, t_{acc}, t_{dec}; and E/A ratio. Because the peak of the E wave occurs close to the first reversal of ΔP and after the peak pressure gradient, and because the E wave reaches its minimum when the L wave forms, at the second reversal of ΔP, we conclude that the L/R ratio in equation [1] is very large, *i.e.*, the flow is dominated by inertia. The dominance of inertia is also seen in the observation in **Fig. 1** that mitral flow continues for c. 35 msec after the final reversal of the AV gradient after the atrial contraction[44]. (The clearest example of a small L/R ratio is mitral stenosis where resistance of the mitral apparatus dominates: The E point is then close to the point of maximum ΔP, there are no pressure gradient oscillations and flow follows the decay of ΔP.) Finally, notice that across the normal valve very small values of ΔP produce large accelerations of flow, and that the phasic nature of the flow is determined by the frequency and amplitude of the oscillations in the pressure gradient. It thus becomes particularly important to recognize that the AV pressures are created by the changing stresses (passive and active) in these cardiac chambers, and to thereby understand how they, in turn, determine the pressure oscillations.

Ventricular Contribution to the Pressure Gradient

To examine the active and passive ventricular properties that are the primary determinants of the flow patterns, we begin by assuming that the myocardium behaves like a structure with an active (*i.e.*, contractile) element in parallel with at least 3 types of passive elements (**Fig. 2**). Thus, at any instant of time, the pressure within the ventricular chamber is determined by the sum of forces due to these 4 (possibly more) components. The active component is, of course, due to actin-myosin cross-bridge interaction. The 3 passive components represent forces due to: 1) changes in volume relative to the equilibrium volume, the "classical" force that determines the passive end-diastolic pressure-volume relation; 2) chamber deformation, such as torsion, that exert their effects independently of their

relation to the equilibrium volume; and 3) viscoelasticity, *i.e.*, forces that depend on strain rate and also lead to dissipation of energy. With this model we can conceptualize the cardiohemic system as behaving like a damped harmonic oscillator. The frequency of oscillation of ΔP depends on the stiffness of the deformable components, and the amplitude depends on the amount of initial deformation [proportional to the end-systolic volume (ESV)] and the degree of damping (L/R ratio). It may be conceptually reasonable to postulate this structural model of the ventricular chamber, but what do we know about the individual nature and combined effects of these elements?

We know that myocytes relengthen because of compressive elastic forces due both to the longitudinal deformation of the protein titin[45], and to other structural proteins that store energy during myocyte radial deformation[46]. We know that myocytes within the myocardium are tethered by an extracellular matrix that stores strain energy as a function of ventricular volume[47]. We know that viscoelasticity, *i.e.*, the dependency of force on rate of deformation, has been demonstrated in the intact heart in late diastole and is probably a function of volume[13,48,49], although its effects and its nature have not been quantified; and we know that energy losses, such as in mitral stenosis, damp the rate of fall of LV pressure and thereby eliminate oscillations in ΔP and in transmitral flow. Unfortunately, we know very little about the effects of other forms of chamber deformation, *e.g.*, ellipticalization or torsion. We do know that the first elastic component cited above arises from deformation that is solely volume dependent and exists throughout the cardiac cycle. Torsion, on the other hand, may also be volume dependent, but it exists only during systole and the isovolumic relaxation period and is apparently insignificant after the onset of ventricular filling[50-52]. Thus, when it comes to assessing its impact on the measured pressure, we may assume it is only a function of time. At the same time, we must recognize that when it comes to assessing the effect of the "classical" elastic force on the measured pressure, it is also a function of time because during filling, the volume changes with time. The measured ventricular pressure can now be characterized as follows:

$$P_m(V,t) = P_a(t) + P_p(V,t) + P_{def}(V,t) + P_{ve}(V) \quad [2]$$

Where, the subscripts m, a, p, def, and ve, refer to measured, active, passive, deformation, and viscoelastic, respectively. Because we have defined diastole as starting with isovolumic relaxation, we begin our analysis by first examining the pressure contribution due to decay of the active state.

Isovolumic Left Ventricular Relaxation Rate

For clarity, I will use *relaxation* or *deactivation* to refer to the fall in LV pressure due to the **active** state, and *LV pressure decline* for the fall in **measured** pressure (thus, LV pressure decline includes effects of both relaxation and deformation). It is common practice to characterize the decay of the active state during isovolumic relaxation by assuming that the resultant pressure declines exponentially to a zero asymptote during the diastolic period. Under abnormal conditions it is not unreasonable to assume that the active state may not decay to zero, that is, there may be incomplete relaxation. (As used here, incomplete relaxation is equivalent to diastolic tone, *i.e.*, crossbridge cycling during diastole. It is not to be confused with a relaxation rate so slow that activation, although declining, persists during the diastolic filling period.) It is, therefore, not unreasonable to include an unspecified function in the equation describing relaxation and to then discuss the consequences.

$$P_a(t) = [P_o - P_i(V,t)]e^{-t/\tau} + P_i(V,t) \quad [3]$$

Where, P_o is the pressure at time zero, *i.e.*, at the onset of isovolumic relaxation; P_i is the pressure offset due to incomplete relaxation, and approaches an asymptotic value at large time; and τ is the time constant of relaxation, *i.e.*, the rate of pressure decay due to inactivation.

Several comments are appropriate in discussing this formulation. The inclusion of a pressure offset allows us to include the possibility of incomplete relaxation or residual activation. What do we know about the nature of P_i? It is reasonable to assume that because there is no evidence that crossbridge cycling, *i.e.*, the active state, exerts a negative force, P_i must be equal to or greater than zero. On the other hand, although there is experimental evidence that relaxation is influenced by relengthening[12], there has as yet been no attempt to determine if P_i is a constant, a function of time, independent of τ, or a function of loading. For example, is it non-linear and does it become operative only after filling starts? Although it is unlikely that definitive answers will soon be found to these

questions, it is important to consider them if we are to understand and interpret the concept of ventricular relaxation and its relation to diastolic function.

Regardless of the answers to these questions, the time constant of relaxation remains an important index of diastolic function, and we must discuss how it should be determined. Because the only pressure available from which to calculate τ is the measured pressure, and that is also the pressure that directly influences filling, we therefore continue with the analysis of the components of equation [2], and we now examine the contribution from the passive component of the measured pressure, and we will return to the calculation of τ below.

The Passive Pressure-Volume Relation of the Ventricle

In my opinion, the mathematical formulation that best describes the passive pressure-volume relation of the left ventricle is the logarithmic approach to be described below. Unfortunately it has not yet received general acceptance, therefore I will first introduce and critique the exponential relation because it is used most frequently.

$$P_p = P_\infty [e^{\alpha (V - V_o)} - 1] \qquad [4]$$

and the stiffness of the ventricle is then given by:

$$dP/dV = \alpha (P + P_\infty) \qquad [5]$$

Where, V_o is the equilibrium volume, *i.e.*, the volume in the completely relaxed ventricle at zero transmural pressure, α is a material property, the modulus of elasticity that has the most influence on stiffness, and P_∞ is the pressure asymptote, *i.e.*, pressure at volumes very much less than the equilibrium volume. P_∞ is also a material property since it influences dP/dV, but its nature is unclear. On the other hand, the nature of α is quite clear, and, when normalized by V_o, it should be the same for all sizes of normal hearts. This formulation has proven quite useful, particularly for describing the end-diastolic pressure-volume relation, when $V > V_o$, but it fails to accurately describe the storage of elastic energy when the ESV is less than the equilibrium volume. This is particularly important because this is the volume of the ventricle during isovolumic relaxation and the forces in the myocardium at that time determine the early filling behavior. Nikolic *et al.*[7] raised this very important issue while also pointing out that the exponential relationship of equation [4] was also non-physiologic in that it allowed the end-diastolic volume to increase without limit, whereas it is well known that any elastic structure cannot stretch limitlessly without changing its properties and/or rupturing. The mathematical relationship that resolves these problems are the following logarithmic formulations; one for positive values of pressure, *i.e.*, $V > V_o$, and one for negative values of pressure when $V < V_o$[7].

$$P_p = -S_p \ln[(V_m - V)/(V_m - V_o)] \quad P > 0 \qquad [6]$$

and

$$dP_p/dV = S_p/(V_m - V) \qquad [7]$$

$$P_n = S_n \ln[(V - V_d)/(V_o - V_d)] \quad P < 0 \qquad [8]$$

and

$$dP_n/dV = S_n/(V - V_d) \qquad [9]$$

Where, the subscripts p and n refer to the positive and negative portions of the *P-V* relation, respectfully; S is a material property that determines stiffness; V_m is the maximum volume, reached at very large positive pressures; V_d is the minimum volume reached at very large negative pressures (V_d is, in a sense, a dead volume since it may be the minimum volume that can be reached by an unloaded ventricle at maximum contractility); and V_o is, as above, the equilibrium volume. S_p, V_m, V_o, S_n, and V_d are all material properties of the ventricular chamber and all have physiologic meaning. Note in particular, that because S has the units of stress, and it is equal to the local stiffness, dP/dV, normalized by the ventricular operating volume, $(V_m - V)$ or $(V - V_d)$, then it represents a myocardial elasticity and is constant for all normal ventricles regardless of size. The validity and the usefulness of the logarithmic model was demonstrated in a series of imaginative studies by Nikolic *et al.*[7,12,13] that also determined the magnitudes of the parameters in equations [6–9] for the normal dog ventricle. More recently, Solomon *et al.*[53] demonstrated the usefullness of the log approach for the understanding of ventricular remodeling in the dog with congestive heart failure due to rapid ventricular pacing.

The Concept of Diastolic Suction

It is clear from equations [6] and [8] that at any time in the cardiac cycle there is a component of the measured pressure due to the elastic properties of the ventricular chamber. In particular, during isovolumic relaxation when volume is constant, the

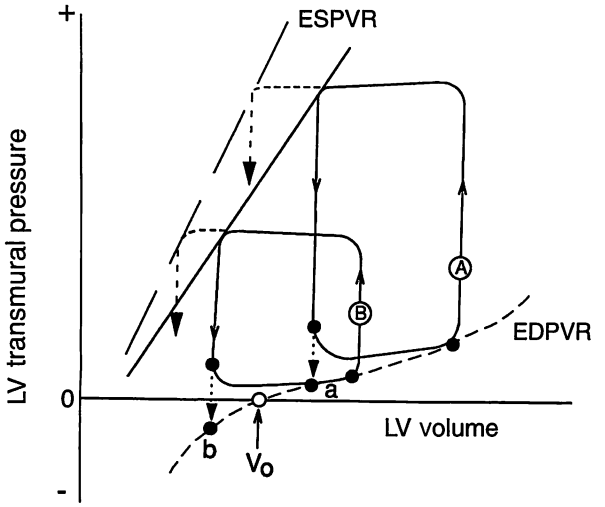

Fig. 3 Schematic illustration of the relations among the equilibrium volume (V_o), the logarithmic end-diastolic pressure-volume relation (EDPVR, equations [6, 8]), the end-systolic pressure-volume relation (ESPVR), and the concept of diastolic suction

A and B are 2 *P-V* loops before and after an increase in contractility leading to a decrease in end-systolic volume (broken lines followed by filled arrows). Dotted lines followed by filled arrows at points a and b indicate the pressure that would be reached in the fully relaxed ventricle in the absence of filling. The negative pressure at point b represents the stored potential energy available for elastic recoil during early diastole. Abbreviation as in Fig. 1.

passive component will be positive when $V > V_o$, and negative when $V < V_o$. Therein lies the origin and the essence of the concept of diastolic suction. When the ESV is below the equilibrium volume, elastic energy is stored in the myocardium and is manifested as a negative component of the measured pressure. Of course, the negative component will not be observed when it is small relative to the other components of the measured pressure and/or after filling starts when the volume increases and the elastic energy is recovered. Nevertheless, when $ESV < V_o$, the stress due to compression of elastic elements is negative, relative to the other internal stresses, and may be defined as diastolic suction. Note also that because $(V_o - V_d)$ in equation [8] is small, small decreases in ESV result in large increases in the negative pressure contribution to the measured LV pressure. The physiological manifestation of diastolic suction is thus seen in the form of a lower left atrial filling pressure because the AV gradient remains normal.

Fig. 3 illustrates these ideas and helps explain the concept of diastolic suction. *P-V* loop A has an $ESV > V_o$ so that during isovolumic relaxation the elastic contribution to the measured pressure is positive, point a. An increase in contractility, represented by the shift to the left of the end-systolic pressure-volume relation, could lead to an $ESV < V_o$ and a small negative contribution. *P-V* loop B, with a lower afterload and the same contractility, has a lower filling pressure and a larger elastic recoil, point b. Because of the non-linearity of the negative portion of the logarithmic end-systolic pressure-volume relation, the same increase in contractility as loop A would lead to a very much larger increase in elastic recoil and a decrease in LA filling pressure. This is the physiological manifestation of diastolic suction.

It should be noted that during isovolumic relaxation, P_p is constant, and that there is no experimental evidence, or theoretical construct, to support an assumption that elastic recoil influences the rate of relaxation. Factors that decrease ESV, such as increased contractility or decreased afterload, may also change both relaxation rate and elastic recoil, but, to repeat, there is as yet no basis for assuming that elastic recoil, per se, affects relaxation rate. We now turn our attention to the third component of the measured pressure, stress due to chamber deformation independent of V_o.

Chamber Deformation *Not* Relative to the Equilibrium Volume

Although there are many studies, both theoretical[50] and experimental[51,52], that demonstrate the existence of chamber deformation due to twist as well as to other shape changes, there are no data indicating the magnitude of their contribution to the measured pressure. The following discussion, then, must of necessity be speculative, but hopefully will serve to clarify our thinking about diastolic function.

Fortunately, we are constrained by the fact that all the experimental evidence indicates that ventricular untwisting occurs almost entirely during the isovolumic relaxation period and is effectively complete by the onset of filling[51,52]. We may therefore limit our discussion to the isovolumic relaxation period and start by asking: if twist or other changes in shape influence the measured pressure what are the mechanisms and what are the consequences?

During isovolumic relaxation when wall stress is

decreasing due to inactivation, untwisting or any other shape change is due to a combination of heterogeneity in sarcomere activity and a decrease in tension of previously distorted extracellular structures. An increase in wall stress due to systolic deformation leads to an increase in pressure, and conversely, during isovolumic relaxation the surface area to volume ratio of the ventricular chamber decreases with untwisting and/or release of deforming forces, leading to a decrease in pressure. Thus, there will be a fall in measured pressure that is some unknown function of time. The magnitude at the onset of isovolumic relaxation is probably a function of ESV, and it must decrease from this value to zero, but in an unknown way. Even if we could assume the fall is linear, we do not know its magnitude at time zero. And, as with the passive pressure component, we do not know if forces due to deformation influence the rate of deactivation.

Myocardial Viscoelasticity

Given the complexity of myocardial tissue and the numerous studies that have demonstrated tissue viscosity in isolated muscle[54], it is not unreasonable to assume that the ventricular chamber possesses the property of viscoelasticity described by:

$$P_{ve} = f(V)\,dV/dt = f(V)\,Q \quad [10]$$

This formulation states that the pressure required to fill the ventricle is proportional to the rate at which it is filled. Although a viscoelastic effect on the diastolic pressure-volume relation has been demonstrated[48,49], its general role remains unresolved. Because there is some evidence that viscoelasticity is insignificant at small volumes[13], we assume herein that the proportionality factor is an unknown function of the chamber volume, but, unfortunately, we can go no further with the analysis.

Analysis of Isovolumic Left Ventricular Pressure Decline

We have established that the measured pressure is a complex sum of many components (equation [2]) and that the active pressure may also be complex (equation [3]), so that neither one is a simple exponential. Because the measured LV pressure is the one that ultimately influences transmitral flow, we recommend that τ, the time constant of fall in measured LV pressure, be calculated from the isovolumic period using a simple exponential with zero asymptote:

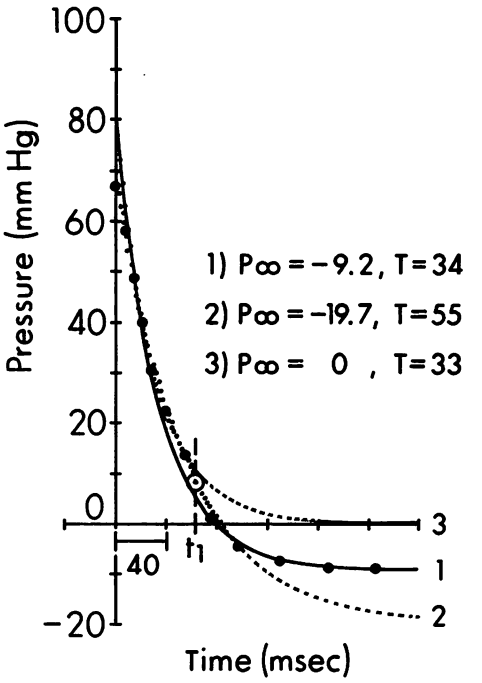

Fig. 4 Exponential analysis of left ventricular pressure decline using the mitral valve occlusion technique[2,5]

Curve 1 is the exponential fit through the data points (filled circles) from the ventricle in the absence of filling when it relaxes to its pressure asymptote (P_∞). Curve 2 is the exponential fit using equation [3] through only the points that were isovolumic during normal filling (fit ends at t_1, open circle). Curve 3 also uses only the isovolumic points but imposes a zero pressure asymptote.

$P_\infty = P_i$ from equation [3]; T = time constant.

[Reproduced from reference 5 with permission]

$$P_m = P_o e^{-t/\tau} \quad [11]$$

This approach was validated in animal experiments where the ventricle was permitted to relax completely isovolumically using the technique of mitral valve occlusion[2,5]. **Fig. 4** demonstrates that the same value for τ was obtained from the data for complete isovolumic relaxation and known asymptote, and from the data for the isovolumic period with filling and zero asymptote[5]. To avoid confusion we therefore urge the reader to conceptually separate deactivation from decline of LV pressure.

Verification of These Concepts in Animal Experiments and Model Studies

The following sections will use examples of dog experiments and model studies to illustrate the relations between the AV pressure gradient, transmitral

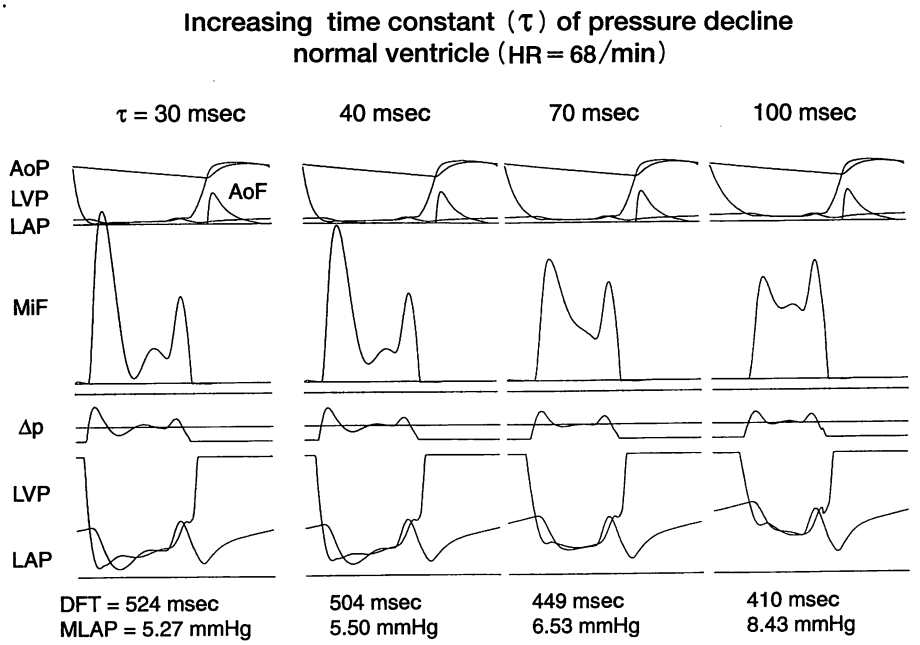

Fig. 5 Analysis of the effect of increasing the time constant of relaxation, τ, on the transmitral pressure-flow relations using the Meisner model[4,55,56]
In particular, note that a 40 msec increase in τ (from 30–70 msec, a large increase but within the pathophysiologic range of possibility) requires only a 1.26 mmHg increase in mean left atrial pressure (MLAP) to maintain a constant filling volume, despite a 75 msec decrease in diastolic filling time (DFT).
HR = heart rate; AoP = aortic pressure; AoF = aortic flow; MiF = mitral flow. Other abbreviations as in Fig. 1.

flow, and diastolic function. The *in vivo* studies have the obvious advantage of being more physiologic; but the model studies have the advantage of control: the effect of a single parameter can be determined while all others are controlled. Because the Meisner model[4,55,56], and others like it[57], have been shown to provide significant physiologic insight, we think the model-based results below will also be of value to the reader.

Influence of Isovolumic Relaxation Rate on Diastolic Function

To study the relation between the rate of relaxation during the isovolumic decline of LV pressure, and diastolic function, we used the Meisner model[55] and asked the following questions. As the rate of relaxation decreases, how would the diastolic indices change, and how much would the mean LA filling pressure have to increase in order to maintain the normal filling volume? The latter question is an attempt to physiologically quantify the role of isovolumic relaxation. Thus, in the model, we kept all the properties and initial conditions of the normal ventricle constant except for the time constant of relaxation, and generated the oscillographic records shown in **Fig. 5**. As expected, the E/A ratio decreased due to both a decrease in E and an increase in A; filling started later and at a higher value of LA pressure; and diastolic filling time decreased. t_{acc} did not change although the rate of acceleration of the E wave decreased and t_{dec} increased. Perhaps unexpectedly, the filling volume could be maintained by only a small increase in mean LA filling pressure (5. 27–8. 43 mmHg) with no change in LV end-diastolic pressure, despite a very large decrease in relaxation rate (τ from 30–100 msec).

These results can be explained by the dynamic effects of the changes in the AV pressure gradient. The slowed rate of fall of LV pressure led to a slowed rate of change of ΔP, particularly important at the time of AV pressure crossover when filling starts, and consequently to a decreased diastolic filling time. The subsequent slower rate of filling led to a slower rate of fall of LA pressure as the atrium emptied more slowly and the magnitude of flow acceleration and deceleration decreased. At higher values of τ, ventricular deactivation was prolonged, so that the ventricle appeared stiffer and a higher LA pressure was required for filling; but by the time of the next LV contraction, even at

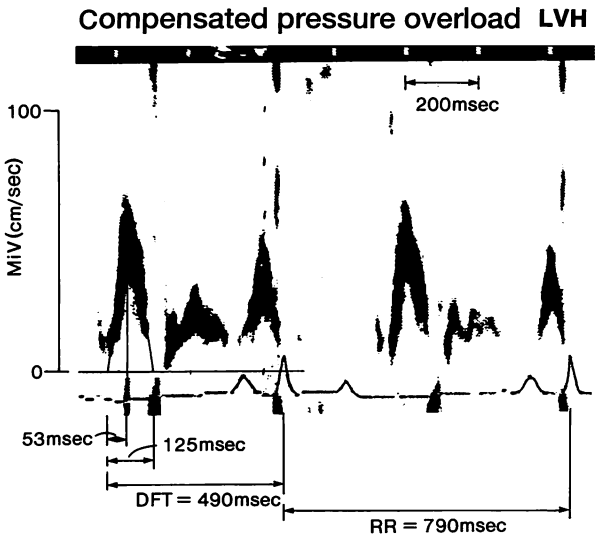

Fig. 6 Pulsed Doppler record of transmitral flow in a dog with compensated pressure overload concentric hypertrophy
Note particularly: $t_{acc} = 53$ msec and $t_{dec} = 72$ msec; compare with Fig. 1.
LVH = left ventricular hypertrophy. Other abbreviations as in Figs. 1, 5.
[Reproduced from reference 56 with permission]

$\tau = 100$ msec, deactivation was far enough along so that LV end-diastolic pressure did not change. This analysis explains the effects of relaxation rate on diastolic indices, and most importantly, it suggests that the rate of relaxation, in and of itself, is not a major determinant of impaired function. Heart failure, for example, cannot be explained solely on the basis of slowed deactivation, there must be other mitigating factors, such as depressed contractility and/or increased myocardial stiffness.

Left Ventricular Hypertrophy and Diastolic Function

Fig. 6 illustrates the effects of increased chamber stiffness in the early stages of pressure overload hypertrophy due to supravalvular aortic stenosis in a dog. The E/A ratio is normal, and although the AV pressures are not included in the figure, we may conclude that the decreased acceleration and deceleration times in early filling are due to the increased ventricular chamber stiffness. When relaxation is normal, at the onset of filling the ventricular pressure falls to its minimum and then rises rapidly because of its stiffness, even when the ESV is small. The rapid change in ΔP leads to a rapid deceleration of flow followed by an L wave. The shortened E wave duration could lead to a decreased filling volume, but compensatory mechanisms maintain an atrial pressure high enough at the onset of filling to provide an adequate amount of early filling. The high LA pressure also serves to increase the magnitude and rate of change of the pressure gradient. The result is analogous to increasing the stiffness of a mass spring oscillating system. The increased stiffness leads to an increased frequency of oscillation and increased acceleration/deceleration rates with shortened acceleration/deceleration times. As the pathology worsens and the ventricle becomes stiffer both intrinsically and due to higher operating volumes, the so-called "restrictive" pattern develops: further increased E wave, shortened t_{dec}, and reduced A wave because of very large LV end-diastolic pressure. A model study illustrating the effect of reduced stiffness is shown in the next section.

Effect of Increasing Compliance on Diastolic Indices

Fig. 7 is a model study that complements **Fig. 6** by describing the changes in the pressure-flow relation subsequent to a decrease in stiffness, *i.e.*, to an increase in myocardial compliance. Left panel shows that, under conditions where the only change in model parameters is a decrease in chamber stiffness (S_p in equation [6]), the *P-V* loops differ only in the value of LV end-diastolic pressure. The effects on the pressure-flow relations are shown in the right panel. As expected, along with the decreased LV end-diastolic pressure there is a decrease in mean LA filling pressure. The lower LA pressure at the onset of filling results in a decreased value of LV$dp/dt$ at that moment and hence a lower rate of change of the AV gradient. The result is a decrease in the magnitude of the E wave as well as of the E/A ratio. t_{acc} remains the same although the rate of rise of the E wave decreases, and t_{dec} increases. Thus, the shape of the transmitral flow wave is determined by the frequency of oscillation of the AV pressure gradient. It is important to note that the increase in deceleration time of the E wave is NOT due to either a slowed ventricular relaxation, *i.e.*, it does not reflect impaired relaxation, or to an increased dissipation of energy, but rather to an increased chamber compliance, and carries with it the benefit of a lower filling pressure.

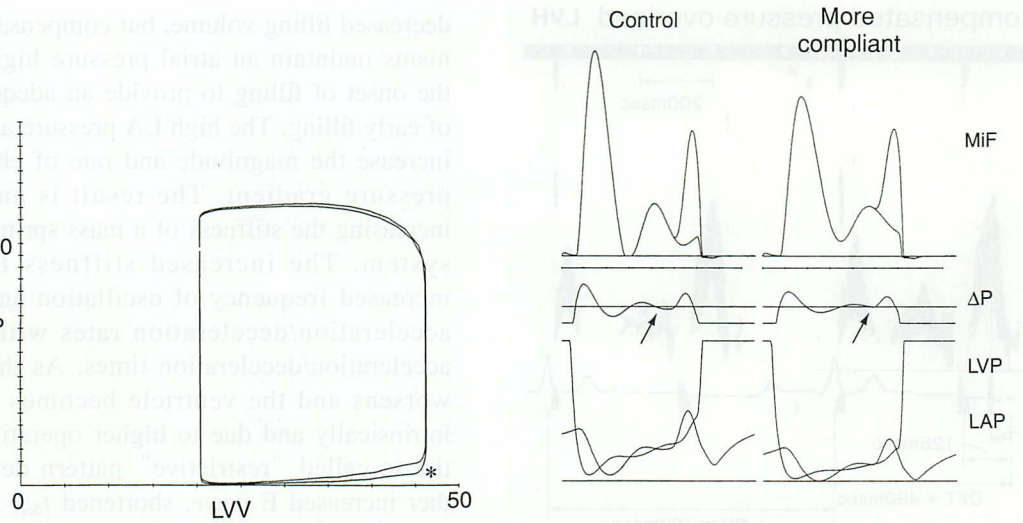

Fig. 7 Model study illustrating the effect of increasing ventricular compliance on the frequency of oscillation of the pressure gradient

Left: Pressure-volume loops of 2 ventricles of the same size and stroke volume but different passive diastolic pressure-volume relations. The more compliant ventricle is identified by the lower end-diastolic pressure (*).

Right: Pressure-flow relations for the 2 ventricles. Note particularly: The frequency of oscillation decreases and the deceleration time increases in the more compliant ventricle, denoted by the time for ΔP to reach the arrow: 377 msec in control vs 433 msec in more compliant.

LVV = left ventricular volume. Other abbreviations as in Figs. 1, 5.

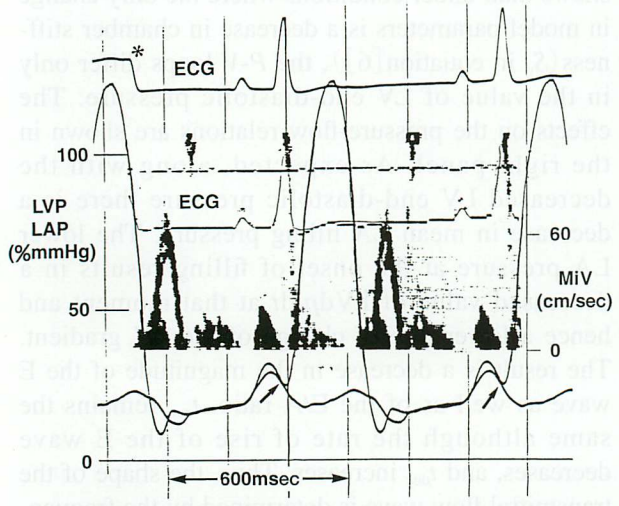

Fig. 8 Oscillographic record of left atrial and ventricular pressures and transmitral flow synchronized by the electrocardiogram (ECG; *) in a dog with congestive heart failure following 3 weeks of rapid ventricular pacing

Note the high LVP_{min} and end-diastolic pressure. t_{acc} = 70 msec, t_{dec} = 70 msec; compare with Fig. 1. The arrows indicate a fall in pressure following the atrial contraction due either to a viscoelastic effect or an atrioventricular interaction at the contracting mitral annulus.

Abbreviations as in Figs. 1, 5.

[Redrawn from reference 53 with permission]

Diastolic Function in a Dog Model of Pacing-Induced Congestive Heart Failure: Remodeling of the Left Ventricle

The pressure-flow relations in a dog following 3 weeks of rapid ventricular pacing are shown in **Fig. 8**. Congestive heart failure is due to the very high LV end-diastolic pressure and mean LA filling pressure. The ventricle has also remodeled to the dilated state with large V_o and V_m. The shape of the LV pressure indicates a very stiff ventricle with the pulsed Doppler flow pattern being restrictive, *i.e.*, small E wave duration and very large E/A ratio. The E wave effects are due to the high frequency oscillation of the AV pressure gradient; and the diminished A wave is due to the very large afterload faced by the atrium when it contracts. It is of interest to examine the large fall in LV pressure preceding its contraction (arrows in **Fig. 8**) because this is not an unusual finding, particularly when the PR interval is long enough to allow time for the pressure to fall. There are 3 possible explanations.

Mitral regurgitation: The atrial pressure is expected to fall because the atrium is emptying as well as relaxing, but the ventricular pressure would fall only if there were mitral regurgitation. But we

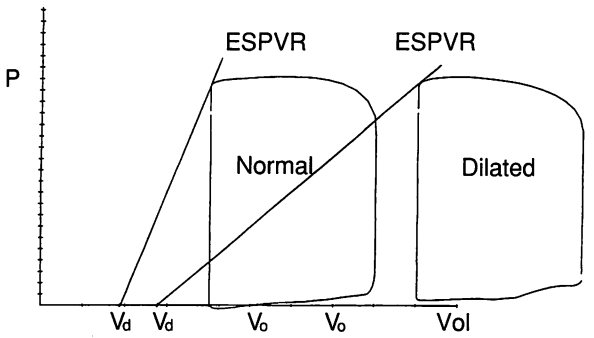

Fig. 9 Model study illustrating the changes in ventricular properties and function in the dogs with congestive heart failure presented in Fig. 8
In this study the ventricle has remodeled to increase the dead volume (V_d), and the equilibrium volume (V_o). Note also the large decrease in contractility (decreased slope of ESPVR) in the failing ventricle, leading to increased operating volumes, end-diastolic volume and end-systolic volume.
P = pressure; Vol = volume. Other abbreviations as in Fig. 3.

reject this hypothesis because the A wave of mitral flow is positive during the period when LV pressure is falling.

Viscoelasticity: At large ventricular volumes a viscoelastic property could be manifest so that ventricular pressure falls as filling rate decreases. This explanation is possible but not yet proven.

Mitral annulus compliance: The contraction and relaxation of the mitral annulus increases and decreases the apparent stiffness of both the atrium and the ventricle. This too is possible but not proven.

It is now necessary to ask: Has ventricular stiffness increased because the myocardium has become less compliant, or because the ventricle is operating on a stiffer portion of its diastolic pressure-volume relation? When the data are analyzed using the exponential approach, equation [4], the ventricular chamber is apparently stiffer because α increases. But we have found that when the data are analyzed using the logarithmic approach, equation [6], myocardial compliance is unchanged because S_p remains constant[53]. Thus, after 4 weeks of rapid ventricular pacing the ventricle has remodeled to an increased equilibrium volume (V_o: 40 to 105 m*l*), an increased maximum volume (V_m: 87 to 175 m*l*), and, contrary to expectations, no change in chamber compliance (S_p: 12.5 and 11.3 mmHg). The physiologic consequences of this remodeling becomes evident, however, when we calculate the local stiffness at the operating end-diastolic pressure (dP/dV_{EDP}: 0.49 to 1.3 mmHg/m*l*). Thus, when the Frank-Starling mechanism is utilized to increase output, the normal ventricle can increase its stroke volume by 5 m*l*, for example, with an increase in end-diastolic pressure of only 2.5 mmHg; whereas the failing ventricle requires a 6.5 mmHg increase in end-diastolic pressure to increase its stroke volume the same amount. Of course, this is also the reason that a failing ventricle benefits from volume reduction: a small decrease in end-diastolic volume leads to a large decrease in LV end-diastolic pressure.

Fig. 9 uses the Meisner model to show the *P-V* loops that describe the remodeling in this model of heart failure and the physiologic reasons for the changes in ventricular properties. Chronic ventricular pacing leads to a depression of contractility, a decreased slope of the end-systolic pressure-volume relation, and the need to maintain stroke volume by chronic use of the Frank-Starling mechanism, *i.e.*, by continually increasing the end-diastolic volume. Myocytes increase in length and the ventricular chamber dilates with sarcomeres added in series. This geometric change leads to changes in all 3 volume derived properties, V_d, V_o and V_m. The reader should note that our conclusion regarding the increase in compliance in this study should not necessarily be applied to all other conditions. The data of this section are presented to illustrate the pressure-flow relations in another example of changes in properties, and to demonstrate the value of the logarithmic approach toward describing the diastolic properties of the ventricular chamber.

Summary

The phasic character of the transmitral flow wave is determined by the AV pressure difference and the impedance of the mitral valve complex. The measured LV pressure is determined by the complex contributions from 4 sources: rate and extent of deactivation, passive myocardial properties, deformation due to shape change, and viscoelasticity. An understanding of the functional value of diastolic indices is helped by an understanding of the basic physiology. Many questions remain unanswered at both the macro level, which has been the focus of this commentary, and the micro level where the ultimate source of function arises. New modalities for the study of diastolic function at the macro level are constantly under development[58], and progress

is being made at the micro level[45,59,60]. It is unfortunate that the role of left atrial properties has not received the attention required, considering that it is more than 10 years since Ishida *et al.*[6] demonstrated the importance of LA pressure in creating the early filling wave.

I trust that the reader understands that this paper is not meant to be a comprehensive review, but rather a discussion of basic principles from the very personal, albeit limited, point of view of my years of collaboration with colleagues from Japan. I dedicate this paper to all my former Fellows included among the authors in References 1−14, whose contributions to the study of diastolic function deserve the highest praise.

References

1) Yellin EL, Peskin C, Yoran C, Koenigsberg M, Matsumoto M, Laniado S, McQueen D, Shore D, Frater RWM: Mechanisms of mitral valve motion during diastole. Am J Physiol 1981; **241**: H389−H400
2) Hori M, Yellin EL, Sonnenblick EH: Left ventricular diastolic suction as a mechanism of ventricular filling. Jpn Circ J 1982; **46**: 124−129
3) Yellin EL, Tsujioka K, Yoran C, Gallo JI, Keren G, Sonnenblick EH, Frater RWM: Inotropic regulation of left ventricular filling: Analysis of phasic mitral flow in the conscious dog. Fed Proc 1983; **42**: 1005(abstr)
4) Meisner JS, McQueen DM, Ishida Y, Vetter HO, Bortolotti U, Strom JA, Frater RWM, Peskin CS, Yellin EL: Effects of timing of atrial systole on LV filling and mitral valve closure: Computer and dog studies. Am J Physiol 1985; **249**: H604−H619
5) Yellin EL, Hori M, Yoran C, Sonnenblick EH, Gabbay S, Frater RWM: Left ventricular relaxation in the filling and nonfilling intact canine heart. Am J Physiol 1986; **250**: H620−H629
6) Ishida Y, Meisner JS, Tsujioka K, Gallo JI, Yoran C, Frater RWM, Yellin EL: Left ventricular filling dynamics: Influence of left ventricular relaxation and left atrial pressure. Circulation 1986; **74**: 187−196
7) Nikolic S, Yellin EL, Tamura K, Vetter H, Tamura T, Meisner JS, Frater RWM: Passive properties of canine left ventricle: Diastolic stiffness and restoring forces. Circ Res 1988; **62**: 1210−1222
8) Oka Y, Hong YW, Tamura T, Kitahata H, Orihashi K, Yellin EL, Goldiner PL: Quantitative analysis of transmitral flow and a preliminary study of pulmonary vein flow. Int J Card Imaging 1989; **4**: 19−22
9) Tanoue T, Pajaro OE, Biasucci LM, Oka Y, Yellin EL: Effects of a bradycardic agent(UL-FS 49)on diastolic function during isoflurane anesthesia in the dog. Anesthesiology 1989; **71**: A492(abstr)
10) Biasucci LM, Tanoue T, Pajaro OE, Nanna M, Nikolic S, Yellin EL: Doppler diastolic flow in compensated and failing canine hearts with pressure-overload hypertrophy. J Am Coll Cardiol 1990; **15**: 157A(abstr)
11) Biasucci LM, Pajaro OE, Tanoue T, Nikolic SD, Frater RWM, Oka Y, Nanna M, Yellin EL: Mid-diastolic mitral flow rebound: Mechanisms, importance and relation to Doppler indexes of diastolic function. Circulation 1990; **82**: III-127(abstr)
12) Nikolic S, Yellin EL, Tamura K, Tamura T, Frater RWM: Effect of early diastolic loading on myocardial relaxation in the intact canine left ventricle. Circ Res 1990; **66**: 1217−1226
13) Nikolic SD, Tamura K, Tamura T, Dahm M, Frater RWM, Yellin EL: Diastolic viscous properties of the intact canine left ventricle. Circ Res 1990; **67**: 352−359
14) Tanouchi J, Kitabatake A, Asao M, Morita T, Masuyama T, Hori M, Inoue M, Abe H: Role of left ventricular relaxation on transmitral flow dynamics during early diastole: Pulsed Doppler flowmetry. J Cardiogr 1983; **13**: 301−307 (in Jpn with Eng abstr)
15) Ishida Y, Matsubara N, Tani A, Ozaki H, Matsuyama T, Sato H, Hori M, Kitabatake A, Kamada T, Kozuka T: Regional left ventricular diastolic function in hypertrophic cardiomyopathy: Application of "sector analysis" to ECG forward and reverse gated radionuclide ventriculography. J Cardiol 1989; **19**: 473−485(in Jpn with Eng abstr)
16) Kitabatake A, Tanouchi J, Masuyama T, Fujii K, Ishihara K, Uematsu M, Ito H, Yoshida Y, Hori M, Inoue M, Kamada T: Limited atrial compensation to reduced early diastolic filling in hypertensive patients with advanced left ventricular hypertrophy: A Doppler echocardiographic study. Heart Vessels 1989; **5**: 33−40
17) Tanouchi J, Kitabatake A, Hori M, Kamada T: Alterations in left ventricular filling in hypertensive patients with left ventricular hypertrophy as assessed by Doppler echocardiography. Front Med Biol Eng 1990; **2**: 211−215
18) Masuyama T, Lee JM, Yamamoto K, Tanouchi J, Hori M, Kamada T: Analysis of pulmonary venous flow velocity patterns in hypertensive hearts: Its complementary value in the interpretation of mitral flow velocity patterns. Am Heart J 1992; **124**: 983−994
19) Lee JM, Masuyama T, Nagano R, Yamamoto K, Nariyama K, Tanouchi J, Hori M, Kamada T: Effects of vasodilators on pulmonary venous and mitral flow velocity patterns in patients with congestive heart failure. Jpn Circ J 1993; **57**: 935−946
20) Sato H, Hori M, Ozaki H, Yokoyama H, Imai K, Morikawa M, Takeda H, Inoue M, Kamada T: Exercise-induced upward shift of diastolic left ventricular pressure-volume relation in patients with dilated cardiomyopathy: Effects of beta-adrenoceptor blockade. Circulation 1993; **88**: 2215−2223
21) Nagano R, Masuyama T, Lee JM, Yamamoto K, Naito J, Mano T, Kondo H, Hori M, Kamada T: Transthoracic Doppler assessment of pattern of left ventricular dysfunction in hypertensive heart disease: Combined analysis of mitral and pulmonary venous flow velocity patterns. J Am Soc Echocardiogr 1994; **7**: 493−505
22) Kondo H, Masuyama T, Ishihara K, Mano T, Yamamoto K, Naito J, Nagano R, Kishimoto S, Tanouchi J, Hori M, Takeda H, Inoue M, Kamada T: Digital subtraction high-

frame-rate echocardiography in detecting delayed onset of regional left ventricular relaxation in ischemic heart disease. Circulation 1995; **91**: 304–312
23) Watada H, Ito H, Masuyama T, Hori M, Aburaya M, Higashino Y, Fujii K, Minamino T: Alterations in the mitral flow velocity pattern induced by acute myocardial infarction: Doppler findings before and after infarction. Jpn Circ J 1995; **59**: 274–283
24) Masuyama T, Nagano R, Nariyama K, Lee JM, Yamamoto K, Naito J, Mano T, Kondo H, Hori M, Kamada T: Transthoracic Doppler echocardiographic measurements of pulmonary venous flow velocity patterns: Comparison with transesophageal measurements. J Am Soc Echocardiogr 1995; **8**: 61–69
25) Yamamoto K, Masuyama T, Doi Y, Kondo H, Naito J, Mano T, Nagano R, Hori M, Kamada T: Progressive intraventricular drop of early diastolic flow velocity reflects impaired active ventricular diastolic function in hypertensive heart disease: Comparative study between early diastolic and atrial contraction phases. J Am Soc Echocardiogr 1995; **8**: 654–658
26) Yamamoto K, Masuyama T, Tanouchi J, Naito J, Mano T, Kondo H, Nagano R, Hori M, Kamada T: Intraventricular dispersion of early diastolic filling: A new marker of left ventricular diastolic dysfunction. Am Heart J 1995; **129**: 291–299
27) Nagano R, Masuyama T, Naka M, Hori M, Kamada T: Contribution of atrial reservoir function to ventricular filling in hypertensive patients: Effects of nifedipine administration. Hypertension 1995; **26**: 815–819
28) Hori M, Inoue M, Kitakaze M, Tsujioka K, Ishida Y, Fukunami M, Nakajima S, Kitabatake A, Abe H: Ejection timing as a major determinant of left ventricular relaxation rate in isolated perfused canine heart. Circ Res 1984; **55**: 31–38
29) Hori M, Inoue M, Fukunami M, Kitakaze M, Ishida Y, Tsujioka K, Nakajima S, Kitabatake A, Abe H: An increase in afterload augments ventricular relaxation rate in isolated perfused canine hearts. Cardiovasc Res 1985; **19**: 649–654
30) Hori M, Inoue M, Kitakaze M, Tsujioka K, Ishida Y, Fukunami M, Nakajima S, Kitabatake A, Abe H: Loading sequence is a major determinant of afterload-dependent relaxation in intact canine heart. Am J Physiol 1985; **249**: H747–H754
31) Hori M, Inoue M, Kitakaze M, Kitabatake A, Abe H: Altered loading sequence as an underlying mechanism of afterload dependency of ventricular relaxation in hearts in situ. Jpn Circ J 1985; **49**: 245–254
32) Hori M, Kitakaze M, Ishida Y, Inoue M: Impaired ventricular relaxation during myocardial ischemia and after reperfusion in isolated perfused canine hearts. Jpn Circ J 1987; **51**: 107–113
33) Hori M, Kitakaze M, Ishida Y, Fukunami M, Kitabatake A, Inoue M, Kamada T, Yue DT: Delayed end ejection increases isovolumic ventricular relaxation rate in isolated perfused canine hearts. Circ Res 1991; **68**: 300–308
34) Yamamoto K, Masuyama T, Tanouchi J, Uematsu M, Doi Y, Naito J, Hori M, Tada M, Kamada T: Decreased and abnormal left ventricular filling in acute heart failure: Role of pericardial constraint and its mechanism. J Am Soc Echocardiogr 1992; **5**: 504–514
35) Yamamoto K, Masuyama T, Tanouchi J, Uematsu M, Doi Y, Mano T, Hori M, Tada M, Kamada T: Peak early diastolic filling velocity may decrease with preload augmentation: Effect of concomitant increase in the rate of left atrial pressure drop in early diastole. J Am Soc Echocardiogr 1993; **6**: 245–254
36) Yamamoto K, Masuyama T, Tanouchi J, Uematsu M, Doi Y, Naito J, Hori M, Tada M, Kamada T: Importance of left ventricular minimal pressure as a determinant of transmitral flow velocity pattern in the presence of left ventricular systolic dysfunction. J Am Coll Cardiol 1993; **21**: 662–672
37) Yamamoto K, Masuyama T, Tanouchi J, Doi Y, Kondo H, Hori M, Kitabatake A, Kamada T: Effects of heart rate on left ventricular filling dynamics: Assessment from simultaneous recordings of pulsed Doppler transmitral flow velocity pattern and hemodynamic variables. Cardiovasc Res 1993; **27**: 935–941
38) Yamamoto K, Masuyama T, Tanouchi J, Kitabatake A, Hori M, Kamada T: Contribution of chamber compliance and left ventricular minimum pressure to abnormal left ventricular filling dynamics. Jpn Circ J 1994; **58**: 57–68
39) Yamamoto K, Masuyama T, Doi Y, Naito J, Mano T, Kondo H, Nagano R, Tanouchi J, Hori M, Kamada T: Noninvasive assessment of left ventricular relaxation using continuous-wave Doppler aortic regurgitant velocity curve: Its comparative value to the mitral regurgitation method. Circulation 1995; **91**: 192–200
40) Nimura Y, Matsuo H, Mochizuki S, Aoki K, Wada O, Abe H: Analysis of a cardiac cycle of the left side of the heart in cases of left ventricular overloading or damage with the ultrasonic Doppler method. Am Heart J 1968; **75**: 49–65
41) Kitabatake A, Inoue M, Asao M, Tanouchi J, Masuyama T, Abe H, Morita H, Senda S, Matsuo H: Transmitral blood flow reflecting diastolic behavior of the left ventricle in health and disease: A study by pulsed Doppler technique. Jpn Circ J 1982; **46**: 92–102
42) Courtois M, Kovacs SJ Jr, Ludbrook PA: Transmitral pressure-flow velocity relation: Importance of regional pressure gradients in the left ventricle during diastole. Circulation 1988; **78**: 661–671
43) Nishimura RA, Abel MD, Hatle LK, Tajik AJ: Relation of pulmonary vein to mitral flow velocities by transesophageal Doppler echocardiography: Effect of different loading conditions. Circulation 1990; **81**: 1488–1497
44) Laniado S, Yellin, EL, Miller H, Frater RWM: Temporal relation of the first heart sound to closure of the mitral valve. Circulation 1973; **47**: 1006–1014
45) Helmes M, Trombitas K, Granzier H: Titin develops restoring force in rat cardiac myocytes. Circ Res 1996; **79**: 619–626
46) Winegrad S, Robinson TF: Force generation among cells in the relaxing heart. Eur J Cardiol 1978; **7**(Suppl): 63–70
47) Factor SM, Robinson TF: Comparative connective tissue structure-function relationships in biologic pumps. Lab Invest 1988; **58**: 150–156
48) Kennish A, Yellin EL, Frater RWM: Dynamic stiffness profiles in the left ventricle. J Appl Physiol 1975; **39**: 665–671
49) Rankin JS, Arentzen CE, McHale PA, Ling D, Anderson

RW: Viscoelastic properties of the diastolic left ventricle in the conscious dog. Circ Res 1977; **41**: 37–45
50) Arts T, Meerbaum S, Reneman RS, Corday E: Torsion of the left ventricle during the ejection phase in the intact dog. Cardiovasc Res 1984; **18**: 183–193
51) Gibbons, Kroeker CA, Tyberg JV, Beyar R: Effects of load manipulations, heart rate, and contractility on left ventricular apical rotation: An experimental study in anesthetized dogs. Circulation 1995; **92**: 130–141
52) Moon MR, Ingels NB Jr, Daughters GT II, Stinson EB, Hansen DE, Miller DC: Alterations in left ventricular twist mechanics with inotropic stimulation and volume loading in human subjects. Circulation 1994; **89**: 142–150
53) Solomon SB, Nikolic SD, Glantz SA, Yellin EL: Left ventricular diastolic function of remodeled myocardium in dogs with pacing-induced heart failure. Am J Physiol 1998; **274**: H945–H954
54) Stuyvers BD, Miura M, ter Keurs HE: Diastolic viscoelastic properties of rat cardiac muscle: Involvement of Ca^{2+}. Adv Exp Med Biol 1997; **430**: 13–28
55) Meisner JS, Pajaro OE, Yellin EL: Investigation of left ventricular filling dynamics: Development of a model. Einstein Quart J Biol Med 1986; **4**: 47–57
56) Yellin EL, Meisner JS, Nikolic SD, Keren G: The scientific basis for the relations between pulsed-Doppler transmitral velocity patterns and left heart chamber properties. Echocardiography 1992; **9**: 313–338
57) Thomas JD, Weyman AE: Fluid dynamics model of mitral valve flow: Description with in vitro validation. J Am Coll Cardiol 1989; **13**: 221–233
58) Garcia MJ, Thomas JD, Klein AL: New Doppler echocardiographic applications for the study of diastolic function. J Am Coll Cardiol 1998; **32**: 865–875
59) Labeit S, Kolmerer B, Linke WA: The giant protein titin: Emerging roles in physiology and pathophysiology. Circ Res 1997; **80**: 290–294
60) Granzier HL, Irving TC: Passive tension in cardiac muscle: Contribution of collagen, titin, microtubules, and intermediate filaments. Biophys J 1995; **68**: 1027–1044