The Concept of Preload and Its Evaluation in the Intact Left Ventricle

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SUMMARY

Preload affects left ventricular pump function through the Frank-Starling curve by changing sarcomere length. However, common indices of preload, such as end-diastolic volume, or pressure, or stress, do not necessarily reflect sarcomere length. Ultimately, this depends on the elastic stiffness constant (k) and end-diastolic stress (σ), which are not in simple relation with the above mentioned indices. An index of preload is proposed, $(k\sigma)^{(1/k)}$. This index has been evaluated in 148 patients with different degrees of hemodynamic overload, and in 24 normal subjects. The preload index was found to be 1.448 ± 0.034 in normal subjects. However, in the other patients evaluated preload index increased in mitral insufficiency (1.490 ± 0.035), in decompensated aortic insufficiency (1.490 ± 0.89) and in dilated cardiomyopathy (1.52 ± 0.125), and markedly decreased in aortic stenosis (1.367 ± 0.039) and in hypertrophic cardiomyopathy (1.41 ± 0.034). It was always positively related to the afterload, measured as peak systolic stress. No positive relationship was found with end-diastolic volume nor pressure. Therefore, preload as a compensatory mechanism is differently recruited in response to various degrees of hemodynamic overload and parallels the afterload, in agreement with the concept of preload-afterload mismatch.

Additional Indexing Words:

Preload Stress Strain Frank-Starling curve Heart failure

PRELOAD is usually referred to as the load imposed on the muscle fiber before contraction.¹⁾ This load stretches the fiber to a given length, and both the extent and velocity of shortening depend on this length. This fact is usually accounted for by the ultrastructure of the sarcomere.^{2),3)} As long as the sarcomere is stretched, the number of active actomyosin sites increases, so that more energy is set free at every contraction, and both the extent and

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Received for publication January 26, 1988.

Accepted May 12, 1989.

velocity of contraction increase. Thus "preload" should be ultimately best defined as the sarcomere (fiber) length before contraction, which is obviously due to the load imposed before contraction.^{4),5)}

In the intact heart preload is usually referred to as end-diastolic stress, or pressure, or volume. This definition holds true as far as a unique relation between stress, pressure or volume and sarcomere length is valid.^{4),5)} This is possibly true in inpatient comparisons and in an acute setting, but is certainly not the case in interpatient comparisons, especially if different hearts with different diseases are to be matched.

Pressure is not simply related to stress, which is the force actually stretching the sarcomere. Moreover, at the same end-diastolic stress the sarcomere length, i.e., preload, may be different because of different distensibility. Neither end-diastolic pressure nor stress, therefore, is an adequate measurement of preload in the intact heart.

At first glance, end-diastolic volume seems to reflect closely end-diastolic fiber length. Were this true, volume enlargement in chronic volume overload would simply be due to overstretching the sarcomeres. But this is absolutely not the case at least in compensated cases, where end-diastolic pressure and stress are normal, as the mass to volume ratio is quite often normal. Therefore, no additional stress is exerted upon the sarcomeres, and there is no reason to believe that they are stretched beyond normal length. Ross⁶⁾ demonstrated that this is the case through ultrastructural measurements of sarcomere length. Grossman⁷⁾ gave a plausible explanation of this enlargement without stretching, i.e., eccentric hypertrophy, with the hypothesis of series replication of sarcomeres.⁸⁾ Therefore, end-diastolic volume does not reflect adequately sarcomere length and cannot be used as a preload index for interpatient comparisons.

Another parameter frequently referred to as preload is venous return. However, venous return is identical to cardiac output in steady-state conditions. Cardiac output is the result of interaction of the preload, afterload, contractility and heart rate, not the cause. Cardiac output affects preload just in the same sense as the left ventricle affects its own afterload.

Probably the parameter that most accurately reflects fiber stretching is "strain". Natural strain is defined as

$$\varepsilon = \ln (l/l_0)$$

where ε is natural strain, l is the actual fiber length, and l_0 is the fiber length at stress=0. Lagrangian strain is defined as $(l-l_0)/l_0$.

Direct measurement of strain "in vivo" requires measurement of the length at zero stress, which never occurs during the cardiac cycle, particularly

in pathologic cases. Moreover, it has been convincingly demonstrated that systolic activity extends its influence over the rapid filling period, i.e., almost mid-diastole.⁹⁾ At that time a substantial lengthening has already occurred, and therefore it is necessary to extrapolate to a given stress reference to obtain l_0 . This entails necessarily a certain degree of error. Furthermore, direct methods currently used are rather tedious, as they require continuous pressure-volume measurement during diastole, and are not easily amenable to routine calculations. Therefore, we searched for a more practical method to evaluate preload, based on the stress-strain relationship.

METHODS

1. Calculations

Stress-strain relationship is usually described by

$$d\sigma/d\varepsilon = k\sigma + c$$

Where σ is stress, ε is strain (natural or Lagrangian), k is the elastic stiffness constant, c is elastic stiffness at zero stress and strain. This differential equation can be solved as follows:

$$\varepsilon = (1/k) \ln ((k\sigma + c)/c)$$

If we accept the “natural strain” definition, then the equation becomes

$$l/l_0 = ((k\sigma + c)/c)^{(1/k)}$$

which allows a direct computation of fiber elongation (l =actual fiber or sarcomere length; l_0 =fiber or sarcomere length at stress=0) provided k , σ and c are independently evaluated. End-diastolic stress σ is easily evaluated; k can be measured from pressure, volume and mass according to the method of Mirsky¹⁰⁾ or Fester and Samet.¹¹⁾ If we accept as a further approximation that the constant c , which represents elastic stiffness at zero stress, has a value of 0.92 as found experimentally,¹²⁾ the equation can be simplified as follows:

$$l/l_0 = (k\sigma)^{(1/k)} \quad (I)$$

We called this ratio “preload index”.

2. Patients

This parameter has been evaluated in 172 subjects who underwent cardiac catheterization for evaluation. Twenty-four subjects were normal, 40 patients had chronic aortic insufficiency, 22 mitral insufficiency, 28 aortic stenosis, 11 dilated cardiomyopathy and 9 hypertrophic cardiomyopathy.

None of the cases exhibited heart failure. Thirty-eight other patients in clinical cardiac failure, as judged by NYHA class (III or higher) and by the need for digitalis and diuretics underwent catheterization: 14 had aortic stenosis, 8 aortic regurgitation and 16 mitral regurgitation. Informed, written consent was obtained from all of them before the procedure.

All patients had biplane left ventricular angiograms quantitatively analyzed. Volume,^{12),13)} mass¹⁴⁾ and stress were computed according to known formulae. In particular, stress was computed according to Falsetti,¹⁵⁾ elastic stiffness constant according to Mirsky^{10),12)} and preload index according to equation (I). Comparisons between groups were carried out with Student's t-test. Linear correlations were calculated by the least squares method. We attempted to correlate to preload index left ventricular end-diastolic pressure, peak systolic stress, end-diastolic and end-systolic volumes, ejection fraction, and two indices of contractility: end-systolic pressure and end-systolic stress to end-systolic volume ratio.¹⁶⁾

The left ventricular function curve was traced using ejection fraction (mean value) as a performance parameter. The abscissa was double-scaled, respectively with end-diastolic pressure and preload index, and end-diastolic volume and preload index. The scale was chosen in such a way that normal values coincided. A shift of a point in respect to normal should indicate a variation in myocardial contractility, provided that the afterload is constant.

RESULTS

General hemodynamic parameters in our cases are shown in Table I. Preload index is shown in Table II. Correlation coefficients and their statistical significance are summarized in Table III.

1. Results by specific left ventricular disease

a) *Mitral insufficiency*: Preload index is, on the average, increased. End-diastolic volume is moderately increased, whereas end-diastolic pressure is still in the normal range. Contractility is about half the normal level. Left ventricular function curve, if plotted against end-diastolic pressure (Fig. 1), overestimates the contractility, and probably underestimates it if plotted against end-diastolic volume (Fig. 2). Preload index is negatively correlated to contractility, measured as end-systolic pressure-to-end-systolic volume ratio, and to ejection fraction. Note that, at least in compensated cases, it bears no relationship to end-diastolic volume. This means that the preload index is sensitive both to the overload and to left ventricular function. It is positively correlated to afterload, measured as peak systolic stress. This is probably due

Table I. General Hemodynamic Parameters

Condition	k	EDV	EF	EDP	M	P/VTs	σ /VTs
Normals	17.21	82	73	8	93	6.57	8
±SD	1.87	17	8	3	25	3.28	2.65
Mitral insufficiency	16.8	139	58	11.4	123	2.45	4.81
±SD	1.2	38	13	5	28	.8	.85
Mitral insuff., decompens.	16.5	137	53	11.5	117	2.22	4.53
±SD	1.5	32	14	4	19	.9	.92
Aortic insufficiency	18.8	179	50	15.3	197	1.88	3.6
±SD	3	70	15	7.7	77	.71	.86
Aortic insuff., decompens.	19	198	42	24.1	193	1.50	3.43
±SD	3.3	58	17	5	57	.62	.94
Aortic stenosis	21.6	84.5	58	18.8	156	8.1	8.8
±SD	3	23	15	9	53	5.8	2.85
Aortic stenosis, decompens.	22.3	81	58	21.9	151	8.30	8.52
±SD	3	17	18	11	42	6.2	3.01
Hypertrophic cardiomyopathy	19.5	77	71	13.7	118	5.55	7.18
±SD	3.5	26	16	6	66	1.1	1.56
Dilated cardiomyopathy	16.2	112	38	13.2	103	1.7	3.72
±SD		32	15	10	26	.7	1.1

Abbreviations: k=elastic stiffness constant; EDV=left ventricular (LV) end-diastolic volume; EF=LV ejection fraction; EDP=end-diastolic pressure; M=LV myocardial mass; P/VTs=end-systolic pressure to end-systolic volume ratio; σ /VTs=end-systolic stress to end-systolic volume ratio.

Table II. Preload Index in Various Conditions

Condition	Preload index	P
Normal	1.448 ± 0.034	
Mitral insufficiency	1.490 ± 0.035	<0.001*
Mitral insufficiency, decomp.	1.486 ± 0.036	<0.001* ns*
Aortic insufficiency	1.412 ± 0.076	<0.02
Aortic insufficiency, decomp.	1.490 ± 0.089	<0.005* 0.01**
Aortic stenosis	1.367 ± 0.039	<0.001*
Aortic stenosis, decomp.	1.365 ± 0.029	<0.001* ns**
Hypertrophic cardiomyopathy	1.410 ± 0.034	<0.05*
Dilated cardiomyopathy	1.520 ± 0.125	=0.05*

* With respect to normal.

** With respect to compensated cases.

to the fact that hypertrophy was slightly inadequate (mean mass to volume ratio 0.88); therefore both systolic and diastolic stress are increased. In decompensated cases no significant variation is detected.

b) *Aortic regurgitation*: In these cases the preload index seems to be diminished with respect to normal cases, but with large individual variations. Note that both end-diastolic volume and pressure are markedly increased, but

Table III. Linear Correlations between Various Parameters:
X-Axis Is Always the Preload Index

Condition	Y-Axis	r	P
Mitral insufficiency	End-systolic P/ESV	-0.542	0.00913
Mitral insufficiency	Ejection fraction	-0.38269	0.078
Mitral insufficiency	Peak systolic stress	0.477	0.0246
Mitral insuff., decompensated	End-diastolic volume	0.75	0.001
Aortic regurgitation	Peak systolic pressure	-0.4078	0.00899
Aortic stenosis	Peak systolic pressure	-0.672	0.001
Aortic stenosis	Peak systolic stress	0.5266	0.0039
Aortic stenosis, decompens.	End-diastolic pressure	-0.58	0.05
Hypertrophic cardiomyopathy	Peak systolic pressure	-0.654	0.055
Hypertrophic cardiomyopathy	Left ventricular mass	-0.789	0.011
Hypertrophic cardiomyopathy	Mass to volume ratio	-0.96	0.0003
Hypertrophic cardiomyopathy	Peak systolic stress	0.801	0.00946
Dilated cardiomyopathy	Peak systolic stress	0.768	0.0057
Dilated cardiomyopathy	Left ventricular mass	-0.59	0.054
Dilated cardiomyopathy	Elastic stiffness const.	-0.6	0.0487

Fig. 1. Left ventricular systolic performance (ejection fraction, EF) is plotted against left ventricular end-diastolic pressure (upper abscissa, open symbols) and preload index (lower abscissa, solid symbols). n=normal; hcm=hypertrophic cardiomyopathy; mr=mitral regurgitation; as=aortic stenosis; ccm=congestive cardiomyopathy. The scale has been chosen so that normal points coincide. A different evaluation of left ventricular function is particularly evident in aortic stenosis and aortic regurgitation.

Fig. 2. Left ventricular systolic performance (ejection fraction, EF) is plotted against left ventricular end-diastolic volume (upper abscissa, open symbols) and preload index (lower abscissa, solid symbols). Symbols as in Fig. 1. A different evaluation of myocardial function is especially evident for mitral and aortic regurgitation and aortic stenosis.

hypertrophy is adequate, at least in compensated cases. End-systolic pressure-to-volume ratio is diminished. Therefore, the left ventricular function curve might overestimate contractility if evaluated using the preload index in the abscissa. However, it underestimates contractility if end-diastolic volume or pressure is used (Figs. 1 and 2). There was only a negative correlation observed with left ventricular systolic pressure. In decompensated cases the preload index is markedly increased. Therefore, in these cases there is concordance between preload index and left ventricular volume and pressure.

c) *Aortic stenosis*: Preload index is markedly below normal. This is certainly due to the elevated mass to volume ratio (1.85 on the average) and to the stiff myocardium. It is negatively correlated to systolic pressure and positively to peak systolic stress. In decompensated cases a linear negative correlation exists between end-diastolic pressure and preload index. End-diastolic volume is normal, but end-diastolic pressure is markedly elevated, due to the stiff ventricle, and cannot be representative of the preload index. Left ventricular function, if evaluated through end-diastolic volume, appears to be markedly depressed; it appears quite normal if evaluated through end-diastolic volume (Figs. 1 and 2).

d) *Hypertrophic cardiomyopathy*: Similar to what is observed in aortic stenosis, preload index was markedly below normal range. It was negatively correlated to systolic pressure, mass and mass to volume ratio and positively to the afterload (measured as peak systolic stress).

e) *Dilated cardiomyopathy*: Preload was on the average much larger than usual. It was positively related to the afterload and negatively to the left ventricular mass and elastic stiffness constant. This seems to be due to the inadequate hypertrophy (0.9), which determines higher stresses, and therefore elevates both afterload and preload.

2. Analysis of left ventricular function

Left ventricular systolic performance—measured as ejection fraction—has been plotted against end-diastolic pressure and preload index (Fig. 1), and end-diastolic volume and preload index (Fig. 2). The scale of the abscissa has been chosen to make the points of normality coincide. It can be seen that the plotted ejection fraction / end-diastolic pressure underestimates left ventricular function in aortic stenosis, and overestimates it in mitral regurgitation. Table I gives a value for contractility (evaluated as end-systolic pressure or stress to end-systolic volume ratio) near to normal in aortic stenosis and half the normal value in mitral regurgitation. The plotted ejection fraction / end-diastolic volume (Fig. 2) greatly underestimates left ventricular function in aortic regurgitation and, probably, in mitral regurgitation, whereas it slightly overestimates it in congestive (dilated) cardiomyopathies.

DISCUSSION

The expression (I) should relate actual sarcomere length and its length at zero stress. It is well known that the optimal sarcomere length is 2.2 microns, both in health and in disease. This value is remarkably constant even among different species. Sarcomere length at zero stress has not yet been accurately assessed. Moreover, there seems to be a difference between end-systolic and slack length at zero stress. End-systolic length has been found to be 1.5 microns or even less in hypercontractile states.^{17),18)} Early diastolic length, at zero stress, has been shown to be 1.8 microns.¹⁹⁾ The ratio l/l_0 should therefore range from 1.2 to 1.5, and our normal cases are precisely in this range. Nakamura et al²⁰⁾ found a value of $\ln(l/l_0)=0.43$, which is close to our $l/l_0=1.448$ for normal cases ($e^{.43}=1.537$), and a slightly lower one for aortic stenosis, i.e., a variation with respect to normal of the same order as seen in our cases.

A. Preload recruitment in different disease states

An interesting finding was a difference in preload reserve recruitment in different diseases, almost irrespective of end-diastolic pressure and volume, which were not related to preload index. To summarize, it can be said that preload is recruited more when the overload is *diastolic* and hypertrophy *inadequate*. Both conditions are present in mitral insufficiency and dilated cardiomyopathy, where obviously our index of preload attains its top value. On the contrary, it is minimally recruited in concentric or inappropriate hypertrophy, i.e., as clinical examples, in aortic stenosis and hypertrophic cardiomyopathy.

In aortic insufficiency individual variability is high, probably because aortic pressure in this disease can be increased. This entails a variable degree of hypertrophy, and therefore of stress and strain.

This behavior stems naturally from the equation used in the calculations, as both constant k and stress depend on mass-to-volume ratio, but is also in agreement with a few experimental results. Ross⁶⁾ found an almost normal sarcomere length in experimentally induced diastolic overload, and an even shorter sarcomere length was found in experimental pressure (or systolic) overload,^{21),22)} as myocardial stiffness was increased.²³⁾⁻²⁸⁾

Hess^{27),28)} published results that are quite at variance with ours, especially as far as dilated cardiomyopathy is concerned. He found the value for elastic stiffness constant (k) to be much higher than normal (myocardium much stiffer than normal). As a consequence, "normalized" strain (quoting Hess^{27),28)}) is much less than normal, even less than in aortic stenosis. Preload reserve therefore does not seem to be utilized in dilated cardiomyopathy. This could well be the case if slippage and/or disruption of the myofiber had already occurred, but is not in agreement with the common thinking about this disease and its therapeutic implications. Histological data on sarcomere length, which thus far have not been published, could probably give a definite answer to this controversy.

B. Preload recruitment in heart failure

Preload is not constantly recruited in heart failure. In aortic stenosis it is even lower than normal, and a paradoxically negative linear relationship exists between end-diastolic pressure and preload index (Table III). This entails important, although well known, therapeutic indications: if preload is low and end-diastolic pressure is still elevated, diuretics or dilating agents can relieve congestion, but they can also precipitate a low output state.

On the other hand, cardiomegaly is not always the result of the dilation of the ventricle.²⁹⁾ In aortic regurgitation, for example, some enlargement of

the left ventricle and of the cardiac silhouette takes place, but preload can be increased, in the normal range or decreased. Symptoms depend more on end-diastolic pressure and preload recruitment rather than on the heart size "per se". Digitalis should probably be administered only to patients with increased preload and depressed contractility, irrespective of the heart size.

C. "Afterload mismatch" and preload reserve

In all our cases afterload was linearly related to the preload index, independent of the basic pathology. This is in agreement with clinical experience, in that an increased preload almost invariably induces an increase in afterload. As a consequence, a preload-modulating drug is expected to act upon the afterload as well, and vice-versa, although its primary site of action can be entirely different. If a linear relationship exists between preload and afterload, an increase in the latter should obviously result in an increase in the former in the short term. This is, in other words, the concept of "afterload mismatch and preload reserve".³⁰⁾ Interestingly, this relationship was not found with other parameters, usually considered to represent afterload, such as systolic pressure. Thus probably only systolic stress is a reliable measurement of afterload.

D. Concluding remarks

The concept of preload as fiber elongation, and its measurement from the stress-strain relationship is quite simple and feasible, and it clarifies definitions such as "heart enlargement", "compensation" and "failure". The availability of preload-modulating drugs allows for the selective management of various forms of heart failure according to preload recruitment. The analysis of ventricular function curves using this index of preload instead of end-diastolic pressure or volume possibly gives a better estimate of left ventricular contractility.³¹⁾

ACKNOWLEDGMENTS

The editorial assistance of Mrs. Patricia Lazzaro is gratefully acknowledged.

APPENDIX

In this section a more extensive demonstration of formula (I) will be provided. It is widely accepted that

$$d\sigma/d\varepsilon = k\sigma + c \quad (\text{IA})$$

To put this differential equation into differential form, let's suppose that $y = k\sigma + c$; thus $dy =$

$k d\sigma, d\sigma = dy/k$. Thence (IA) becomes:

$$\begin{aligned} dy/d\varepsilon &= ky \\ dy/y &= k d\varepsilon \\ \ln |y| &= k\varepsilon + \cos t \\ \ln(k\sigma + c) &= k\varepsilon + \cos t \end{aligned} \quad (\text{IIA})$$

To determine the value of the constant of integration “ $\cos t$ ”, remember that when σ is 0, ε (strain) is zero by definition (because $l=l_0$, $l/l_0=1$, $\ln(1)=0$); therefore $\cos t = \ln(c)$. Thus (IIA) becomes:

$$\ln(k\sigma + c) = k\varepsilon + \ln(c)$$

and, with rearrangement:

$$\begin{aligned} \ln((k\sigma + c)/c) &= k\varepsilon \\ \varepsilon &= (1/k) \ln((k\sigma + c)/c) \end{aligned} \quad (\text{IIIA})$$

If $c=0.92$ (12)-close to unity-, and $k\sigma \gg c$, it may be taken, as a further approximation:

$$k\sigma \equiv (k\sigma + c)/c$$

with an error not exceeding 13% for $k\sigma$ ranging from 100 to 300. Therefore (IIIA) becomes

$$\varepsilon = (1/k) \ln(k\sigma)$$

and, by definition of natural strain,

$$l/l_0 = (k\sigma)^{(1/k)}$$

It is noteworthy that (IIIA) has been already published, although in a different form and with different purposes. The result of the integration of $d\sigma/d\varepsilon = k\sigma + c$ can be written this way^{32),33)}

$$\sigma = (c/k)(e^{(k\varepsilon)} - 1)$$

This is identical to (IIIA). In fact

$$\begin{aligned} k\sigma/c &= e^{(k\varepsilon)} - 1 \\ (k\sigma + c)/c &= e^{(k\varepsilon)} \\ \ln((k\sigma + c)/c) &= k\varepsilon \end{aligned}$$

and, using ε as a dependent variable,

$$\varepsilon = (1/k) \ln((k\sigma + c)/c)$$

which is the desired result.

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