Letters To The Editor

References


Reply to the Preceding Letter

We appreciate the comments made by Drs. Poggesi and Reggiani. These authors suggest that load sensitivity of relaxation is the result of the combined effects of the rate of inactivation and the lifetime of attached cross-bridges in isotonic vs. isometric conditions. In agreement with this view, this alternative explanation was also mentioned by us in a previous paper, while discussing possible mechanisms for load dependence. Please compare p. 478, line 23 to end of paragraph, in “Relaxation of Ventricular Cardiac Muscle” (Brutsaert et al., 1978a). Evidence against an important contribution of the lifetime of attached cross-bridges, however, came from subsequent experiments on single, skinned cardiac cells, where a fixed mode of activation-inactivation was imposed; in both isotonic and isometric conditions, in atrial as well as in ventricular cells, no difference in the time course of relaxation was observed (Brutsaert et al., 1978b; Couttenye et al., 1981). On the other hand, these observations do not fully rule out the possibility that the lifetime of the cross-bridges may affect load dependence under different loading conditions. Indeed, in some experimental circumstances, such as hypoxic ventricular myocardium, relaxation of an isometric twitch can be affected independently of the isometric twitch (personal observation). Yet, the implications with respect to the results in atrial muscle can, at present, not be appreciated fully, due to lack of experimental evidence.

As to the difference in architectural structure, this is also mentioned by us on p. 355 of the paper by Couttenye et al. (1981). Arguments against the importance played by differences in architectural structure can be derived from experiments by Lecarpentier et al. (1979), where a load-dependent system was converted into a load-independent system and vice versa.

Dirk L. Brutsaert

Professor of Physiology and Medicine

University of Antwerp

Groenenborgerlaan, 171

Antwerpen, Belgium

References


Brutsaert DL, Claes VA, De Clerck NM (1978b) Relaxation of mammalian single cardiac cells after pretreatment with the detergent Brij-58. J Physiol (Lond) 283: 481–491


Comments on

“Pressure-Diameter Relations during Early Diastole in Dogs: Incompatibility with the Concept of Passive Left Ventricular Filling”

which appeared in


Sabbah and Stein (1981) observed that, during early diastole, rapid filling of the left ventricle occurred while pressure within the ventricle was declining. This is not an original observation, as Sabbah and Stein clearly note by citing six or seven previous reports by other investigators which show similar results. However, Sabbah and Stein interpret their data as being indicative of a process of active enlargement rather than passive distension of the left ventricle during early diastole. This interpretation appears to depend on an analysis of instantaneous values of ventricular diameter, ventricular pressure, and calculated ventricular distensibility. Unfortunately, the calculations presented are erroneous, thus vitiating the conclusions based on this analysis.

In calculus, a change or increment of a variable (x) is written as Δx and is called delta x. Δx designates a finite, or measurable change in x. The derivative of a function [f(x)] with respect to x is the limit approached by the ratio of the increment of the function [Δf(x)] to the increment of x (Δx) as Δx approaches zero as a limit. In symbols, this becomes:

\[ \frac{df(x)}{dx} = \lim_{\Delta x \to 0} \frac{\Delta f(x)}{\Delta x}. \]

The concept that a function can be defined even when the increment of a variable is made vanishingly small is basic to the calculus.

Sabbah and Stein identify passive filling of the ventricle with the distensibility of the heart. Instantaneous distensibility (D) of the ventricle is defined such that the relation between ventricular diameter
(V) and pressure (P) is given by their Equation 1:

\[ V = D \cdot P \]  

(1)

This equation is then differentiated (sic) to yield their Equation 2:

\[ \Delta V = \Delta P \cdot D + \Delta D \cdot P \]  

(2)

where the \( \Delta \)'s are identified as increments of the corresponding variables. Subsequently, values of \( P, \Delta P, D, \) and \( \Delta D \) are substituted into the right hand side of Equation 2 and a value for \( \Delta V \) is calculated. Since this calculation yields a negative value for \( \Delta V \) (i.e., ventricular emptying) during early diastole when, in fact, the ventricle was filling, Sabbah and Stein reject the concept of passive filling during this phase.

As should be apparent from the definitions provided above, however, Equation 2 is not a differential of Equation 1, nor is it treated as one. Far from being vanishingly small, the values of \( \Delta P \) and \( \Delta D \) used by Sabbah and Stein are as large or larger than the values of \( P \) and \( D \). This is illustrated by the example in their Figure 6, which indicates an average value for \( P = 6 \) mm Hg and a \( \Delta P = -9 \) mm Hg and an average value for \( D = 8 \) mm/mm Hg and a \( \Delta D = 11 \) mm/mm Hg, and is supported by the summary data for the experiment.

Equation 2 written as a differential is

\[ dV = dP \cdot D + dD \cdot P \]  

(3)

but is correct only for infinitesimal increments of the variables. To evaluate a finite change in V (\( \Delta V \)) the righthand side of the equation would have to be integrated. This could be carried out if D and P were approximated by continuous functions of time or by numerical techniques. A second and easier approach is to calculate \( \Delta V \) by using a finite difference expression instead of Equation 2:

\[ \Delta V = \Delta P \cdot D_i + \Delta D \cdot P_i + \Delta P \cdot \Delta D \]  

(4)

where the subscripts identify the values at the time \( t_1 \) in accordance with the notation of Sabbah and Stein. This equation results from the usual procedure of subtracting the volume at \( t_2 \) from the volume at \( t_1 \):

\[
\begin{align*}
V_1 &= P_1 \cdot D_1 \\
V_2 &= (P_1 + \Delta P)(D_1 + \Delta D) \\
\Delta V &= V_2 - V_1 = (P_1 + \Delta P)(D_1 + \Delta D) - P_1 \cdot D_1 \\
\Delta V &= \Delta P \cdot D_1 + \Delta D \cdot P_1 + \Delta P \cdot \Delta D.
\end{align*}
\]

This procedure also shows that the correct values to use for \( P \) and \( D \) are the initial values, and not the time average values as used by Sabbah and Stein. (It is interesting to note that if average values of \( P \) and \( D \) are calculated by taking the mean of the initial and final values, the equation used by Sabbah and Stein becomes the same as Equation 4 and results in correct values for \( \Delta V \)).

Integration of Equation 3 or substitution of finite increments into Equation 4 results in values of \( \Delta V \) that are identical to the observed values. Moreover, this result is inevitable, since \( D \) was calculated from values of \( V \) and \( P! \) In the experiment, measurements were made of pressure and diameter. Distensibility then was derived from these measurements. Finally, values for the diameter was calculated from values of pressure and the derived parameter, distensibility. The same values that went into the calculation had to come out, since no new data were generated during the process.

Finally, it should be pointed out that it is inevitable that early diastolic filling of the left ventricle will occur while pressure within the ventricle is declining. At the end of ejection, ventricular pressure is high; later, pressure declines to a minimum in diastole. At some point between these two times, ventricular pressure falls below atrial pressure. Unless the mitral value remains closed until ventricular pressure reaches its minimum, for reasons that would be difficult to envision, or unless the ventricular pressure declines instantaneously, flow will occur from the atrium into the ventricle, i.e., filling will occur. This must be so, regardless of the factors contributing to the decline in ventricular pressure. Thus, ventricular filling during this phase, per se, provides no clue as to the underlying mechanisms.

Edward S. Kirk
Cardiovascular Research Laboratories
Division of Cardiology
Albert Einstein College of Medicine
Bronx, New York 10461

References


Reply to the Preceding Letter

We believe, contrary to Dr. Kirk's last statement, that ventricular filling in the presence of a falling pressure provides a major clue to the underlying filling mechanism during early diastole. We disagree with Dr. Kirk that early diastolic filling is "inevitable" only because the pressure in the ventricle is declining. In considering the cause of distension of the ventricle during early diastole, it is incorrect to consider the pressure in the atrium or the pressure drop across the mitral valve. It is only the pressure within the ventricle that could produce passive distension. Consequently, only ventricular pressure should be considered. A declining pressure in the left ventricle, irrespective of the compliance, would be associated with an equalization of atrial and ventricular pressure, and would not involve a change of volume. A change of volume with a passive ventricle would occur only as the pressure increased.

Dr. Kirk's preferred solution in no way negates the validity of the mechanism that we demonstrated. Rather than use the instantaneous pressure volume relation to define a time-varying distensibility, the definition of distensibility used by Mirsky would have been more appropriate (1). That is, distensibility may be defined as a change in volume (V) relative to a change in pressure (P), namely \( D = dV/dP \). Consequently, \( dV = D \cdot dP \). From this equation it is clear
Comments on "Pressure-diameter relations during early diastole in dogs: incompatibility with the concept of passive left ventricular filling" which appeared in Circ. Res. 48: 357-365, 1981.

E S Kirk

Circ Res. 1982;50:441-443
doi: 10.1161/01.RES.50.3.441

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/50/3/441.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/