Right ventricular diastolic function in canine models of pressure overload, volume overload and ischemia

(RV diastolic mechanics & myocardial compliance)

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ABSTRACT

By limiting filling, abnormalities of right ventricular (RV) diastolic function may impair systolic function and affect adaptation to disease. To quantify diastolic RV pressure-volume relations and myocardial compliance a new sigmoidal model was developed. RV micromanometric and sonomicrometric data in awake dogs at control (CL: n=16) and under surgically induced subacute (2-5 weeks) RV pressure overload (PO: n=6), volume overload (VO: n=7), and ischemia (IS: n=6) were analyzed. The conventional exponential model detected no changes from CL in the passive filling pressure-volume ($P_{pf}-V$) relations. The new sigmoidal model revealed significant quantifiable changes in $P_{pf}-V$ relations. Maximum RV myocardial compliance ($M_{C_{max}}$), attained during early filling, is reduced from control in pressure overload ($p=0.0016$), while filling pressure at maximum compliance ($P_{M_{C_{max}}}$) is increased ($p=0.0001$). End-diastolic RV myocardial compliance increases significantly in volume overload ($p=0.0131$), while end-diastolic pressure is unchanged. In ischemia, $M_{C_{max}}$ is decreased ($p=0.0102$), with no change in $P_{M_{C_{max}}}$. We conclude that the sigmoidal model quantifies important changes in RV diastolic function in awake dog models of PO, VO, and IS.

Key Words: diastole, dynamics, heart failure, myocardial compliance, right ventricle
INTRODUCTION

Right ventricular (RV) diastolic abnormalities such as reduced myocardial compliance may impair systolic function by limiting filling and play an integral role in cardiac adaptations to disease. Nevertheless, development of indexes for RV function has evolved slowly, and numerous gaps remain in our understanding of RV diastolic function (10,13,28). Limitation of our understanding of the right ventricle can be attributed to the paucity of information from animal analogs of human RV disease and the lack of mathematical models for the analysis of RV performance. In contrast, comparable aspects relating to the left ventricle (3,9,17,23) are much more highly developed. However, simple application of indexes developed for the left ventricle to RV function has led to confusing and conflicting results.

The primary aim of the current study is to derive and validate new mathematical models and indexes specifically for the analysis of RV diastolic dynamics and the quantitative assessment of diastolic RV dysfunction and failure. Recognizing that a consensus has not been reached on what constitutes a correct mathematical descriptor of diastolic pressure-volume relations even for the extensively studied left ventricle, we propose that these new conceptual approaches will contribute to the study of LV function too. Our present focus, however, is on RV diastolic pressure-volume relations and corresponding myocardial properties utilizing newly developed, chronically instrumented, awake dog models of RV volume overload (VO) and RV free wall ischemia (IS), and a conventional model of RV pressure overload (PO).

METHODS

Sensor implantation. Experimental animals (20 – 30 kg dogs) were premedicated with cefazolin (500 mg) and iron dextran (100 mg) and anesthetized with intravenous pentobarbital (20 mg/kg) and succinylcholine (1 mg/kg). They were ventilated with a Bennett MA 1™ respirator (Puritan-Bennett, Los Angeles). At thoracotomy, silastic tubes were positioned for later introduction of micromanometric catheters into the right atrium and ventricle. Sonomicrometric transducers were sewn across the base-apex, anterior-posterior and septal-free wall axes of the left ventricle, and across the RV septal-free wall.
axis, as shown in Figure 1, for derivation of dimensional data to use with the shell subtraction model (6,18,29). All connectors, tubes, and cables exited the chest wall through a dorsal Teflon skin button. Each dog recovered for 7-10 days before control data acquisition and induction of RV PO and VO. IS was actually induced at the end of sensor implantation.

**Control (CL) data acquisition.** Lying on its right side, each dog was sedated with morphine (0.7 mg/kg) and the ultrasonic transducers were connected to a sonomicrometer (Physiologic Systems Inc, Durham, NC), (29). Through a jugular vein cutdown, a 30 cm, 8 Fr. sheath was introduced into the right ventricle to allow passage of a custom right-heart Millar™ catheter (Millar Instruments, Houston, TX) with two micromanometers, 5 cm apart. The distal micromanometer is at the tip.

Attenuation of autonomic reflexes was accomplished by intravenous propranolol and atropine. The catheter was advanced, under fluoroscopy, ensuring that the two micromanometers were located inside the right atrium and ventricle. Multiple data sets were recorded under steady-state conditions, and digitized at 400 Hz. Each set was 20 - 30 s long, to provide sufficient beats for analysis. After control data acquisition, RV PO or VO was induced.

**Induction of PO.** At thoracotomy, each animal was instrumented with a silicone rubber pneumatic occluder. The pulmonary trunk beneath the occluder was wrapped with Gore-Tex™ (WL Gore & Associates, Inc, Flagstaff, AZ) to prevent rupture. The occluders were filled with hypertonic glycerin. This kept balloon volumes very stable, few leaked, a few even swelled by drawing in fluid. We recorded the inflation volume and checked the balloon volume weekly to maintain inflation. If any leak was detected, the degree of occlusion was readjusted using either echocardiography or catheterization. An additional check was on the volume of glycerin in the balloon which could be briefly deflated, then reinflated with the original volume found to provide the desired RV systolic pressure. At the time of study, echocardiography and right heart catheterization confirmed stable pulmonary artery stenosis. The occluder was inflated until the peak RV systolic pressure was at least 8 kPa (60 mm Hg), or
approximately twice the control level. It remained inflated throughout the study. PO data were collected 3-5 weeks after its induction.

**Induction of VO.** At thoracotomy, an 8 Fr. 25 cm sheath was advanced into the right ventricle via the right jugular vein under fluoroscopy. A 6 Fr. urologic biopsy forceps (Circon Instruments, Santa Barbara, CA) was placed into the right ventricle through it and multiple passes taken to sever chordae, until 3-4+ tricuspid regurgitation (TR). TR yielded complete contrast-medium filling of the atrium within several cycles (29) and an elevation of peak RA pressures to over 15 mmHg. This was accompanied by x-y descent obliteration, elevated v-waves, and/or *ventricularization* of the atrium (Figure 2). The hemodynamic data were collected 2-3 weeks after TR.

**Induction of IS.** As noted above, IS was induced at the end of sensor implantation. This enhanced the surgeon’s ability to produce controllable ischemia of only the RV free wall without affecting the LV. Lidocaine 50 mg I.V. was administered and the right coronary artery ligated. After stabilization, multiple branches off the left anterior and posterior descending coronary arteries were ligated to limit collateral flow. IS data were collected in the second week following induction. At the time of autopsy, the condition of ischemia was assessed by visual inspection of infarcted myocardium. Ischemia was confirmed by histopathologic (hematoxylin and eosin) staining (Figure 2), showing a 35% or greater infarcted cross-sectional myocardial region of the RV free wall (20).

**Mathematical modeling of RV filling pressure – volume relations**

Hemodynamic data processing began with selection of steady-state beats and ensemble averaging (20). Representative ensemble averages, with individual beat tracings superposed, are presented in Figure 3. Using the ensemble-averaged RV pressure waveform, the relaxation pressure was first determined using the exponential model with asymptote, which accurately described RV isovolumic pressure decay (20). The passive filling pressure ($P_{pf}$) was then calculated (Figure 1, insert) using the following formula: $P_{pf} = P_M - P_R$, where $P_M$ and $P_R$ are the measured and the relaxation pressure, respectively (8,17,21-23,25). Once the passive filling pressure vs. RV volume ($P_{pf}$-$V$) relationship was calculated,
regression was performed for parameter estimation in both the conventional exponential (Eq. 1) and the new sigmoidal model (Eq. 2). Sigmoidal model symbols definitions and explanations, including parametric variations of coefficients are provided in Figures 4, 6, 7 and 8 and Tables 2 and 3.

\[
P_{pf} = \beta \times \exp(\alpha \times V) \quad \text{(Eq. 1)}
\]

\[
P_{pf} = -B + \sqrt{\frac{A}{C} - \frac{1}{C} \times \ln\left[\frac{K_2}{V - K_1} - 1\right]} \quad \text{(Eq. 2)}
\]

The new sigmoidal function was derived from the logistic equation \( V = K_1 + K_2 / (1 + e^{-(C(P_f + B)^2 + A)})\), by solving for \( P_{pf} \) in terms of \( V \). A logistic curve is a sigmoidal (S-shaped) growth curve that can be used to model functions that increase gradually at first, more rapidly in a middle growth period, and slowly at the end, leveling off at an asymptotic maximum value after some time. Such a curve is classically applied to the growth of a bacterial population, \( p(t) \), in culture as a function of time—cf. the left plot of panel III. in Figure 4. The rate of growth accelerates as it approaches the inflection point of the curve. At the inflection point it begins to decelerate but continues to grow until it reaches an asymptote, the "carrying capacity" for the culture environment. This forms the mechanistic basis for the Sigmoidal Model. Substituting pressure, \( P \), for time and volume, \( V(P) \), for population, \( p(t) \), we obtain the Sigmoidal \( P(V) \) curve in the right plot of panel III, after a 90° counterclockwise rotation (middle plot) followed by a horizontal 180° flip. In the \( P(V) \) plot the slope, \( \alpha = dP/dV \), is now at its minimum (\( \alpha_{min} \)) at the inflection point, and this corresponds to a myocardial compliance (MC) maximum (cf. Figure 8, insert).

**Calculation of myocardial compliance.** The global myocardial compliance (MC) (17) was defined as \( \frac{1}{P} \cdot \frac{dV}{dP_{pf}} \), obtained by taking the derivative of the inverse function of Eq. 1 and 2. For the simple exponential model, MC can be modeled using Eq. 3:

\[
MC = \frac{1}{V} \cdot \frac{dV}{dP_{pf}} = \frac{1}{\alpha \cdot P_{pf} \cdot V} \quad \text{(Eq. 3)}
\]

Similarly, for the sigmoidal model, MC is:
Throughout the passive-filling process, both V and Ppf are positive and increasing. Eq. 4, therefore, is always positive. On the right-hand side of Eq. 4, the exponential terms in the numerator and the denominator are both positive. To keep its right side positive, the signs of $K_2$, C, and $(P_{pf}+B)$ had to be selected properly and consistently, so as to fall into one of the four categories outlined in Table 4. This allowed direct comparability of the estimated model parameters.

For each condition, once the sigmoidal model coefficients were obtained, RV myocardial compliance was calculated point-by-point for the same $P_{pf}$ range as in the $P_{pf}$-V relationship. The following diastolic properties were evaluated: the maximum myocardial compliance ($MC_{max}$); the passive filling pressure at maximum compliance ($P_{MC_{max}}$), which demarcates the region of the curve that is concave downwards from that which is concave upwards; the myocardial compliance at end diastole ($MC_{ed}$); and, the corresponding passive filling pressure at end diastole ($P_{MC_{ed}}$), which generally coincides with the clinically measured end-diastolic pressure, EDP.

**Regression and statistics methods**

Regression was performed (4) using SAS™ (SAS, Inc., Cary, NC). All data sets are presented as mean±SD. ANOVA was performed, with four groups of data being CL (n=16), PO (n=6), VO (n=7) and IS (n=6). Student’s unpaired t-test was used for significance of differences between CL and each disease state. The α-level for Student’s t-test was adjusted first with the Bonferronian inequality (2), thus using a conservative critical value for the t-statistics, to accommodate the fact that 3 comparisons were made against the control set for each variable. With this adjustment, the critical level for significance, $P_{BONF}$, was reduced from the usual 0.05 to 0.0167 (i.e., 0.05/3). After the first comparison at 0.0167, a subsequent comparison at $P_{HOLM}= 0.0250$ (0.05/2) was performed according to the Holm modification.
(11) of the Bonferroni procedure, which may reduce Type II error compared to Bonferroni while moderating Type I error compared to unmodified $\alpha$-levels.

**RESULTS**

**RV hemodynamics**

Representative steady-state RV pressure pulse tracings from CL, PO, VO, and IS are presented in the insert panels of Figure 3. The most distinctive difference between PO and CL was in pressure levels. While at CL the measured RV pressure decayed to around 0-kPa, the lowest level under PO remained above 1.3 kPa (10 mm Hg). In addition, peak RV systolic pressure exceeded 12 kPa (90 mm Hg) compared to less than 4.7 kPa (35 mm Hg) at CL. Although peak RV systolic pressure in VO was not significantly higher than CL, the pressure minimum was significantly elevated to about 1.3 kPa (10 mm Hg). There was also a steeper rising pressure slope during filling. In VO, the pressure difference between the peak of the a-wave and the nadir of diastolic pressure was about 5 mm Hg, or twice CL. The peak RV systolic pressure in ischemia was significantly depressed compared to CL. The magnitude of the pressure rise during diastolic filling was similar to CL.

**Passive filling pressure-volume relations and myocardial compliance**

The diastolic $P_{pf}$-$V$ relationship was obtained by plotting passive filling pressure, $P_{pf}$, against volume. Figure 4 displays the two primary types of $P_{pf}$-$V$ relationships observed. One is strongly sigmoidal (panel I.) while the other appears exponential (panel II.). The sigmoidal curve is the result of a sharp rise in $P_{pf}$ during early filling while the change in volume is disproportionately small. In the exponential $P_{pf}$-$V$ relationship the change in volume in early filling is large compared to that in $P_{pf}$. It is essential to note that the portion of the sigmoidal curve for $P_{pf} > 5$ mm Hg appears similar in shape to the exponential curve. Therefore, the exponential curve may be regarded as a sigmoidal curve partially submerged below the x-axis (cf. Figure 8).

Figure 4 also shows representative curves of RV myocardial compliance, calculated using the results obtained from the $P_{pf}$-$V$ relationships for CL, PO, VO, and IS. Panel IV. shows the curve resulting from the
sigmoidal model (Eq. 4); Panel V, the curve using a simple exponential model (Eq. 3). The most striking difference between these curves is the chamber volume at which the maximum myocardial compliance occurs. For an exponential $P_{fr}$-$V$ relationship, the maximum is found right at the beginning of the process, and declines throughout the entire filling period. With the sigmoidal relationship, the myocardial compliance reaches a maximum well into the filling process. The maximum in compliance corresponds to the inflection point of the sigmoidal curve. The curves derived from both models show a continuous decline in myocardial compliance after their respective maxima.

We compared the sensitivity of the conventional simple exponential model and the new sigmoidal model in detecting the changes in the $P_{fr}$-$V$ relationship resulting from RV disease. As shown in Figure 5, substantially better fits to the data points were obtained with the Sigmoidal model than with the conventional exponential. The sum of the squares of the residuals with the former was smaller by one order of magnitude than with the latter. Moreover, as shown in the panels with the residual plots, the residuals of the exponential (but not of the sigmoidal) fit are characterized by a strong correlation of sequential observations, indicating that a systematic effect is neglected by the exponential model. Statistical analysis summarized in the top portion of Table 1 showed that, in contradistinction to the sigmoidal model (bottom portion of Table 1), the simple exponential model was not sensitive enough to detect the important $P_{fr}$-$V$ alterations ensuing in RV disease. These included changes in sigmoidality and in relative elevation or depression of the $P_{fr}$-$V$ data in the midrange of operating volume, leftward rotation, and shift to higher operating volumes. Accordingly, data for myocardial compliance derived from the exponential model were not included in further analyses. Figures 6 and 7 summarize significant changes from control that were brought about by the three RV disease modes in the sigmoidal model parameters and compliance values.

**Control condition.** Table 2 shows the values of each parameter of the sigmoidal $P_{fr}$-$V$ model. Table 3 shows the maximum and end-diastolic compliances, as well as the corresponding levels of $P_{fr}$. The end-diastolic myocardial compliance showed relatively wide variation. The same is true for the ratio of maximum to end-diastolic compliance. The minimum of this ratio in an individual animal was
approximately 3. The levels of $P_{pf}$, both at the point of maximum myocardial compliance and at end diastole, were low.

**Pressure overload.** Table 2 shows the values of each parameter of the sigmoidal model. It summarizes data for six PO animals. Similarly to control, the signs of $C$, $K_1$, and $K_2$ are negative, positive, and negative, respectively. However, in contrast to CL, the values for $B$ were *uniformly negative* in all animals. Table 3 shows diastolic properties in PO. The maximum compliance level decreased from CL. Other significant changes include the elevated $P_{pf}$ at both maximum compliance and end diastole.

**Volume overload.** Table 2 summarizes the parameters of the sigmoidal model for the $P_{pf}$-V relationship. It summarizes data for seven VO animals. Similarly to control and PO, the signs of $C$, $K_1$, and $K_2$ are negative, positive, and negative, respectively. In contrast to control for which the signs in individual animals were *mixed*, individual values for $B$ were *uniformly positive*. This is in even sharper contrast to PO, in which $B$ was *uniformly negative*. Table 3 summarizes the findings for diastolic properties in VO. Similarly to CL, the levels of $P_{pf}$ at both maximum myocardial compliance and end diastole are low. The end-diastolic compliance shows a strongly significant increase from CL. However, noticeable variation exists in end-diastolic myocardial compliance and in $P_{pf}$ at maximum compliance.

**Ischemia.** Table 2 displays sigmoidal model parameter values for the $P_{pf}$-V relationship. Unlike control and the other two disease states, data for all five parameters in individual cases were uniform in sign. With the exception of $K_1$, all parameters were negative. Similarly to PO, $B$ values in individual animals were uniformly negative. In addition, the mean value of $C$ is the most negative of all the RV disease models studied. It also appears that both $K_1$ and $K_2$ tend to increase in IS. Table 3 summarizes the analysis of myocardial compliance in IS. Levels of $P_{pf}$ at maximum myocardial compliance and at end diastole are very similar to CL. The maximum compliance is decreased significantly from CL. With the exception of end-diastolic myocardial compliance, the diastolic properties exhibited relatively limited variation.
In summation, statistical analyses were performed on the impact of each RV disease modality on model parameters and indexes of RV diastolic function. ANOVA and Bonferroni-Holm statistics (Table 1 and top panels of Figure 6) show that significant differences exist for three of the model coefficients: B, C, and K₁. PO induced significant increases from CL in C and K₁, and a decrease in B. VO provoked increases in B, C, and K₁. IS caused a decrease in B and C from CL and an increase in K₁. A and K₂ did not differ significantly from CL for any disease modality. The bottom panels in Figure 6 illustrate the effects of parametric changes in each of these model coefficients on the shape and location of the sigmoidal curve on the P_{pf}-V plane.

Important changes in P_{pf}-V relations and diastolic properties are induced by the three RV failure modes (Table 3 and Figure 7.) PO alters RV myocardial compliance properties more significantly than the other two conditions. It caused a decrease in RV maximum myocardial compliance, as well as an increase in passive filling pressure levels at both maximum myocardial compliance and end diastole. VO exhibited a strong increase in end-diastolic myocardial compliance and a somewhat decreased maximal compliance compared to control values. IS decreased the maximum compliance that was attained during the early filling process.

**DISCUSSION**

The material properties of working myocardium during diastolic filling are important in assessing both diastolic and systolic function (24), but their determination presents challenging difficulties (8,12,15,17,21-26). A consensus has not been reached on what constitutes a correct mathematical descriptor of diastolic pressure-volume relations even for the extensively studied left ventricle. It is common practice to curve-fit diastolic pressure-volume data in exponential form. Ostensibly, the reason behind the practice is that since papillary muscle exhibits an exponential stress-strain relationship, so should the pressure-volume relations for the intact ventricle. This approach was adopted in 1969 by Noble et al. (19), whose work was often cited by subsequent early investigators. However, even Noble cautioned
in that frequently cited article that “pressure often differed from that predicted by the exponential
equation,” suggesting that it is not a reliable descriptor of ventricular diastolic dynamics. In a
comprehensive survey on the clinical assessment of diastolic ventricular function, Mirsky and
Pasipoularides (17) noted several drawbacks of using an exponential model for pressure-volume relations
during the filling period. In the present study, RV $P_{pf}$-V relations were examined on awake dogs at control
and in three models of RV disease.

The sigmoidal model for RV $P_{pf}$-V relations

The sigmoidal gave much better curve fits to the $P_{pf}$-V data than the exponential model. The sigmoidal
curve models fittingly the dynamics of RV chamber volume, which increases gradually at first, more
rapidly in the middle of its operating range, and slowly at the end, tending to level off toward a maximum
value. Initially, the rate of change of volume with respect to pressure is low but it accelerates as it
approaches the inflection point of the curve. At that point, the rate of change of volume begins to
decelerate as the chamber volume continues to grow toward an asymptotic value. Sigmoidal pressure-
volume relations had been in evidence, but not described mathematically in numerous studies involving
P-V data on excised blood vessels (1,5,16). Such sigmoidal end-diastolic pressure-volume relations are
similarly not described explicitly but in plain evidence for both the right and the left ventricle in isolated,
atrially paced, isovolumically (thin latex balloons) beating pig hearts undergoing retrograde aortic
perfusion (Figure 5 in ref. 14).

The most significant difference between the sigmoidal and the exponential model is that the sigmoidal
model is *concave* toward the abscissa in the lower range of operating volume. The exponential model
corresponds to the upper portion of the *universal sigmoidal* curve depicted in Figure 8. Adjusting the
values of the sigmoidal parameters shifts the portion of the sigmoidal curve that is concave toward the
abscissa higher above or lower below the zero-$P_{pf}$ level. As illustrated in Figure 8, submerging the
sigmoidal curve below the x-axis is equivalent to *removing* the lower-operating-volume segment of the
sigmoidal curve. Therefore, the general sigmoidal model is robust and can describe specific \( P_{pf} - V \) curves manifesting an exponential form.

**Quantitative analysis of RV diastolic physiology.** Significant changes from control were detected and quantified in all three RV disease states by the sigmoidal model, whereas none was detected by the exponential. The increase in \( K_1 \) in all three states indicates that the diseased right ventricle has increased its preload (Figure 6) in an effort to maintain pumping, a manifestation of the Frank-Starling mechanism. Under RV PO and VO, \( C \) increased. This indicates an elevation of the \( P_{pf} - V \) relations in the midrange of operating volume (Figure 6). In IS, \( C \) decreased, indicating a depression of the \( P_{pf} - V \) relations over the same range.

An essential advantage of using the sigmoidal equation to model the \( P_{pf} - V \) relation is the inclusion of the pressure-shift parameter \( B \), which effectively determines the vertical position of the curve. An upward shift (decreased \( B \)), regardless of compliance, indicates that a higher pressure is required to fill the ventricle. In the present study, most interesting changes were quantifiable by the parameter \( B \). The decrease in \( B \) in RV PO reflects a \( P_{pf} - V \) relationship with strongly manifest sigmoidality accruing from the rise of the universal sigmoidal curve out of the abscissa (Figure 6). On the other hand, the increased \( B \) in VO reflects a less pronounced sigmoidality resulting from a submersion of the concave portion of the universal sigmoidal curve below the abscissa (Figure 6). In IS no significant change occurred in \( B \).

In PO higher filling pressure was required to force blood into the hypertrophied RV chamber in early filling, resulting in the increased sigmoidality of the \( P_{pf} - V \) relation. In VO, the change in the \( P_{pf} - V \) relation accrued from the increase in operating volume range, which caused a reduction in relative wall thickness. This reduction makes the right ventricle more compliant during early diastole, as manifested in the submersion of the \( P_{pf} - V \) curve below the abscissa (Figure 8).

In IS, the factors considered in the previous two states work in directions opposite to each other. On one hand, there is an increase in the operating volume (i.e., reduction in relative wall thickness), resulting in a submersion of the \( P_{pf} - V \) relation. On the other, previous studies (8,9,17) have shown that regional
hypertrophy eventually ensues under ischemia, as nonischemic muscle compensates for pumping capability lost due to ischemic regions. On balance there was a statistically significant elevation of the $P_{pl}$-$V$ relation, viz., a decrease in $B$.

The impact of any individual sigmoidal parameter on the overall shape of the curve depends not only on its own value, but also on the values taken by the other parameters. To obtain comparability and a consistent interpretation of changes in the sigmoidal parameters, investigators must commit to one of the four parameter-combination cases shown in Table 4, since the impact of individual parameters on the overall curve is case-dependent. This is another manifestation in cardiac mechanics of the critical need to pay attention to the range of applicability of model parameters (22). In the present study, the sign combination of parameters $B$, $C$, and $K_2$ corresponded to case 2.

**Myocardial compliance**

*Myocardial viscoelastic creep and compliance.* The aspect differentiating the sigmoidal from the exponential model is that the sigmoidal curve is concave toward the abscissa in the lower range of operating volume. The behavior evident in the lower portion of the sigmoidal curve may be conceived as a manifestation of *viscoelastic creep.* In general, viscoelastic behavior may be imagined as a spectrum having the elastic deformation as one limiting case and viscous flow the other extreme, with changeable combinations of the two spread over the intervening range. Thus, viscoelastic creep embodies response patterns that characterize behavior blends of elastic deformation and viscous flow. According to the *Boltzmann superposition principle* (7), the behavior of a viscoelastic material loaded in a series of steps can be analysed by summation of the time dependent effects of each step. The creep deformation $\varepsilon(t)$ is thus determined for incremental loads $\Delta\sigma_1$, $\Delta\sigma_2$, $\Delta\sigma_3$, ... applied at times $t_1$, $t_2$, $t_3$, ..., as:

$$
\varepsilon(t) = \Delta\sigma_1 \cdot J(t-t_1) + \Delta\sigma_2 \cdot J(t-t_2) + \Delta\sigma_3 \cdot J(t-t_3) + \ldots \quad (\text{Eq. 5})
$$

where, $J(t-t_i)$ is the creep response function that is analogous to compliance. Therefore, the deformation response of the viscoelastic myocardium is not manifested instantaneously in response to
applied load; moreover, at any time $t$ it depends on all of the foregoing series of loading steps up to that time. Figure 9 provides a simplified depiction of the phenomenon using two pressure loading steps in time, the incremental viscoelastic response to each of them (insert), and the resulting chamber volume response in the P-V diagram. In view of these considerations, it is to be expected that evaluation of myocardial diastolic properties is more likely to be clinically useful when it involves compliance curves spanning the entire diastolic period, as is exemplified in Figures 4 and 6. With this in mind, examination of specific indexes derived from such curves ($MC_{max}$, $MC_{ed}$, etc) is operationally helpful in evaluating diastolic function in a clinical setting, as is illustrated in a subsequent segment.

**Morphomechanical correlations.** It is premature at present to attempt to identify structural components of the RV muscle with the exhibited viscoelastic response, because much more information is required for such an identification. A very broad interpretation of the viscoelastic relaxed myocardial response may, however, be offered: the viscoelastic creep embodies response patterns that characterize the interactions of elastic myocyte, elastin and collagenous connective tissue formed elements with the viscous cardiac myocyte intracellular and tissue fluids. Furthermore, it is instructive to recall the demonstration by H.B. Bull in Remington’s classic book on tissue elasticity (27) that although a single nylon fiber is elastic, a stocking woven from nylon fibers exhibits viscoelastic behavior. Viscoelasticity may result from the histo-architectonic rearrangement of elastic and viscous structural elements of RV muscle in response to the imposed pressure load.

**Clinical implications of myocardial compliance changes.** The present work showed that the passive compliance of RV muscle changed significantly as a result of PO, VO, and IS. PO and IS resulted in decreased maximum myocardial compliance. Decreased maximum myocardial compliance in early diastole will have the direct clinical consequence of increasing central venous pressure and, in turn, decreasing cardiac output. Both of these effects will be exacerbated at higher heart rates. Since the $P_{p}V$ relations were shifted upward in PO, the pressure levels applying at maximum myocardial compliance and at end diastole were both significantly increased, again tending to elevate central venous pressure
clinically. In VO, a significant increase in operating end-diastolic compliance was observed, while the level of end-diastolic pressure remained unchanged. This is consistent with the increase in parameter $C$ observed in the $P_e$-$V$ relations, which causes an elevation of the middle segment of the sigmoidal curve. This is complemented by a reduction in the slope of the final segment of the curve and an increased end-diastolic compliance. Because of this diastolic compliance rise in VO there may be less of a tendency to elevate central venous pressure than in PO or IS. In VO due to tricuspid regurgitation it may be the regurgitant tricuspid flow ($v$-wave) itself that will directly elevate central venous pressure and impair forward cardiac output.

**Conclusions**

This study is the first to characterize RV passive filling pressure-volume relations throughout diastole and the first to fit the relations with a sigmoidal function. Myocardial compliance curves were calculated from the sigmoidal function over the entire filling period. The new model parameters and related diastolic properties allowed accurate quantitative assessment of RV diastolic function abnormalities in canine surgical models of subacute RV free wall ischemia, pressure and volume overload. The method allows for a more complete evaluation of the diastolic properties of viscoelastic myocardium in the beating heart. Application of the new Sigmoidal model to clinical investigations of ventricular diastolic function should provide a more sensitive diagnosis and a more thorough and quantitative pathophysiologic characterization of diastolic property changes attendant to normal (ageing) and abnormal disease states, involving both the right and the left ventricle, than those possible using the conventional exponential approach.

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FIGURE LEGENDS

Figure 1. Diagram of the instrumented dog heart demonstrating the sonomicrometric implanted sensors and measured dimensions of the SSM. $V_{RVFW}$ denotes the RV free wall volume, determined by water displacement during autopsy. The middle insert illustrates the derivation of the passive filling pressure, $P_{pf}$, from the measured pressure, $P_M$, by subtracting the relaxation pressure, $P_R$.

Figure 2. Top panel: pressure waveforms at the time of induction of RV volume overload through surgical tricuspid chordal rupture. Note the elevation of the right atrial pressure level, and the striking shape similarity between right atrial and ventricular pressures. Bottom panel: hematoxylin/eosin histopathologic staining; the arrows point to infarcted myocardium.

Figure 3. Representative ensemble-averages of measured diastolic RV pressure obtained under control (CL), pressure overload (PO), volume overload (VO), and ischemia (IS) conditions. Superposed on each ensemble average are the individual diastolic pressures in the ensemble. The inserts illustrate typical RV pressure pulse trains.

Figure 4. Representative shapes of $P_{pf}-V$ relationships. Panel I shows a sigmoidal $P_{pf}-V$ in PO. Panel II shows a $P_{pf}-V$ in VO fitted as an exponential; this can also be viewed as the upper portion of a sigmoidal curve. Experimental data points are displayed along with the fitted curves. Panels IV and V, respectively, exhibit representative myocardial compliance data and curves calculated using curve-fit parameters from a sigmoidal and an exponential $P_{pf}-V$ relationship. Approximate maximum and end-diastolic myocardial compliances are labeled. Panel III demonstrates how the sigmoidal $P(V)$ curve is derived from the logistic curve after substituting pressure, $P$, for time and volume, $V(P)$, for population, $p(t)$, by a 90° counterclockwise rotation and a horizontal 180° flip.

Figure 5. The main panel shows the much closer agreement between the $P_{pf}-V$ data points and the least-squares fitted curve when the Sigmoidal model is used, compared to the exponential. The Residual Sum of Squares (SSRes) for the former was smaller by one order of magnitude than for the latter. As shown in the residual plot inserts, the residuals of the exponential fit are characterized by a strong correlation of sequential observations.
Figure 6. As shown in the top panels, all three of the RV disease modalities studied changed significantly parameters $B$, $C$ and $K_1$ of the Sigmoidal model. The lower panels show the impact of corresponding parametric changes on the overall shape of the sigmoidal curve. The left lower panel shows an increase in $B$ resulting in a submersion of the lower portion of the curve. As a result, the portion of the sigmoidal curve remaining above the zero pressure line may resemble an exponential. The middle panel shows an increase in $C$ resulting in elevation with leftward rotation of the middle portion of the curve without altering the position of the asymptotes; as a result, the slope $dP/dV$ increases, implying reduced myocardial compliance. Finally, the lower right panel shows an increase in $K_1$ resulting in a parallel, rightward displacement of the entire curve to higher operating volumes.

Figure 7. The top panels show representative shapes of RV $P_{pf}$-$V$ relationships and corresponding global curves of myocardial compliance at control, RV pressure overload, volume overload and RV free wall ischemia. The middle panels show changes in maximum myocardial compliance ($MC_{max}$) and the associated filling pressure ($P_{MC_{max}}$ at the inflection point). The bottom panels show changes in myocardial compliance ($MC_{ed}$) and the associated pressure ($P_{MC_{ed}}$) at end-diastole.

Figure 8. The universal sigmoidal curve: If a sigmoidal curve is displaced as shown from A to B, the portion of the overall sigmoidal $P_{pf}$-$V$ relation actually manifested above the abscissa may appear to be quasi-exponential. The insert shows that the maximum myocardial compliance ($MC_{max}$) corresponds to the inflection point of the universal sigmoidal curve, where $\alpha = dP/dV$ is at its minimum.

Figure 9. Schematic representation of how a highly nonlinear P-V curve embodies superposition of consecutive viscoelastic (time-dependent) responses to successively imposed pressure steps.
Table 1 A. Lack of significant changes in the exponential parameter values.

<table>
<thead>
<tr>
<th></th>
<th>$\beta$</th>
<th>$\alpha$</th>
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<tbody>
<tr>
<td>ANOVA</td>
<td>F-statistic</td>
<td>0.77</td>
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<tr>
<td></td>
<td>P-value</td>
<td>0.5178</td>
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<tr>
<td>PO vs. Cl</td>
<td>$P_{BONF}$</td>
<td>0.4352</td>
</tr>
<tr>
<td>IS vs. Cl</td>
<td>$P_{HOLM}$</td>
<td>0.0773</td>
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</table>

1B. Significant changes* in the sigmoidal model parameter values.

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>$K_1$</th>
<th>$K_2$</th>
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<tr>
<td>ANOVA</td>
<td>F-statistic</td>
<td>1.30</td>
<td>14.60</td>
<td>9.59</td>
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<td></td>
<td>P-value</td>
<td>0.2889</td>
<td><strong>0.0001</strong></td>
<td><strong>0.0001</strong></td>
<td><strong>0.0001</strong></td>
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<tr>
<td>PO vs. Cl</td>
<td>$P_{BONF}$</td>
<td>0.4007</td>
<td><strong>0.0001</strong></td>
<td><strong>0.0017</strong></td>
<td><strong>0.0065</strong></td>
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<tr>
<td>IS vs. Cl</td>
<td>$P_{HOLM}$</td>
<td>0.1514</td>
<td><strong>0.0001</strong></td>
<td><strong>0.0125</strong></td>
<td><strong>0.0007</strong></td>
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* Bold script
Table 2. Changes from control in the sigmoidal model parameter values.

<table>
<thead>
<tr>
<th>CONDITION (Mean ± SD)</th>
<th>A</th>
<th>B (Pa)</th>
<th>C (kPa⁻²)</th>
<th>K₁ (ml)</th>
<th>K₂ (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl</td>
<td>-0.438 ± 2.67</td>
<td>101 ± 170</td>
<td>-12.4 ± 7.10</td>
<td>76.1 ± 22.0</td>
<td>-92.4 ± 80.8</td>
</tr>
<tr>
<td>PO</td>
<td>-0.747 ± 2.08</td>
<td>-297 ± 216</td>
<td>-1.91 ± 1.68</td>
<td>106.5 ± 27.0</td>
<td>-46.3 ± 35.0</td>
</tr>
<tr>
<td>VO</td>
<td>-1.817 ± 3.66</td>
<td>572 ± 301</td>
<td>-5.29 ± 4.53</td>
<td>115.4 ± 29.8</td>
<td>-102 ± 110</td>
</tr>
<tr>
<td>IS</td>
<td>-2.086 ± 1.76</td>
<td>-60 ± 90</td>
<td>-22.3 ± 13.2</td>
<td>165.2 ± 28.1</td>
<td>-29.7 ± 14.6</td>
</tr>
</tbody>
</table>

Bold scripted values are significantly changed from Cl.
Table 3. RV myocardial compliance in PO, VO and IS.

<table>
<thead>
<tr>
<th>CONDITION (Mean ± SD)</th>
<th>MC&lt;sub&gt;MAX&lt;/sub&gt; (kPa⁻¹)</th>
<th>PMC&lt;sub&gt;MAX&lt;/sub&gt; (Pa)</th>
<th>MC&lt;sub&gt;ED&lt;/sub&gt; (kPa⁻¹)</th>
<th>PMC&lt;sub&gt;ED&lt;/sub&gt; (Pa)</th>
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</thead>
<tbody>
<tr>
<td>Cl</td>
<td>0.7276 ± 0.217</td>
<td>315 ± 226</td>
<td>0.0466 ± 0.0633</td>
<td>773 ± 346</td>
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<tr>
<td>PO</td>
<td>0.2850 ± 0.382</td>
<td>1507 ± 785</td>
<td>0.0235 ± 0.0254</td>
<td>2427 ± 973</td>
</tr>
<tr>
<td>VO</td>
<td>0.502 ± 0.263</td>
<td>137 ± 168</td>
<td>0.1770 ± 0.1935</td>
<td>760 ± 453</td>
</tr>
<tr>
<td>IS</td>
<td>0.502 ± 0.120</td>
<td>352 ± 227</td>
<td>0.0563 ± 0.0689</td>
<td>680 ± 187</td>
</tr>
</tbody>
</table>

ANOVA

<table>
<thead>
<tr>
<th></th>
<th>F-statistic</th>
<th>P-value</th>
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<td>5.02</td>
<td>0.0060</td>
<td>18.73</td>
<td>0.0001</td>
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<td></td>
<td>3.38</td>
<td>0.0306</td>
<td>18.52</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

| P<sub>BONF</sub> = 0.0167 | PO vs. Cl | 0.0016 | 0.0001 | 0.2020 | 0.0001 |
| P<sub>HOLM</sub> = 0.0250 | VO vs. Cl | 0.0232 | 0.0407 | 0.0131 | 0.4768 |
| IS vs. Cl      | 0.0102 | 0.3619 | 0.3731 | 0.2714 |

Bold scripted values are significantly changed from Cl.
Table 4. Sign combinations of parameters in the sigmoidal model.

<table>
<thead>
<tr>
<th>Case #</th>
<th>$P_{pr+B}$</th>
<th>C</th>
<th>$K_2$</th>
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<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>-</td>
<td>-</td>
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<tr>
<td>3</td>
<td>-</td>
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</tr>
<tr>
<td>4</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>
Figure 1

\[ V_{RV} = \frac{1}{6} \cdot \pi \cdot a \cdot b \cdot d - V_{RVFW} \]

\[ V_{LV} = \frac{1}{6} \cdot \pi \cdot a \cdot b \cdot c - V_{LVFW} \]

\[ V_{total} = \frac{1}{6} \cdot \pi \cdot a \cdot b \cdot (c+d) \]
Figure 2
Figure 3
Figure 4
Figure 5
Figure 6
Figure 7
Figure 8
Figure 9