**REVIEW**

**Right ventricular myocardial stiffness and relaxation components by kinematic model-based analysis**

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Abstract: Right ventricle (RV) has frequently been described as the forgotten ventricle in the circulation. However, its importance in various cardiac diseases is now unquestioned. This recognition has led to improved risk stratification and development of algorithms for intervention, which incorporate measurements of RV function as key components of the assessment of many conditions. The diastolic function plays an important role in determining ventricular filling and stroke volume. Abnormal left ventricular (LV) diastolic function has been recognized in many cardiovascular diseases and is associated with worse outcomes, including total mortality and hospitalizations due to heart failure. In this review, we define what global RV diastolic function is, and how to measure it. This article indicates the validation of kinematic model parameters for assessing RV diastolic function. J. Med. Invest. 67:11-20, February, 2020

**Keywords**: right ventricle, diastolic function, stiffness, relaxation, pressure phase plane

### INTRODUCTION

Systemic hypertension is recognized as one of the major causes of diastolic dysfunction in the left ventricle (LV) (1). However, there is limited knowledge regarding the effect of chronic pressure overload on the right ventricular (RV) diastolic function. Since the assessment of the RV diastolic function is challenging (2, 3), Patients with pulmonary arterial hypertension (PAH) ultimately develop right heart failure (4). Previous studies have demonstrated that PAH patients have reduced systolic function as measured by the right ventricular (RV) ejection fraction. Although most clinical research has focused on systolic function, normal RV filling is also essential to maintain exercise activity and adapt to acute and chronic overload. However, knowledge of the role of RV diastolic function in PAH is limited (3-5). Abnormalities in both active cross-bridge relaxation and passive elastic recoil are observed in the hypertrophied RV myocardium, eventually leading to RV diastolic dysfunction, which results in increases in RV filling and right atrial pressures. Indeed, they are associated with disease progression and increased mortality in both adults and children with PAH (5-7). However, assessment of RV diastolic function is challenging (3-5). Consequently, few studies have investigated RV diastolic function, particularly in pediatric PAH patients (9). Accurate measurement of RV diastolic function could contribute to improved clinical management of these patients.

The time constant (τ) is considered the best empirical standard for estimating the rate of pressure decrease in the assessment of both ventricular (LV) diastolic function (10, 11). However, the pattern of RV pressure decrease is quite different from that of LV pressure decrease (12). The peak rate of pressure decrease (dP/dt_min) is not a reliable reference point for evaluating the onset of RV diastole, because it appears when the major portion of RV pressure decrease has already occurred (12). The time constant (τ) evaluates a relatively much shorter segment in the RV than in the LV.

On the other hand, noninvasive assessment of diastolic function is commonly achieved through the use of pulsed Doppler echocardiography. Although conventional echocardiographic parameters are often indicative of dysfunction, their utility in characterizing the relaxation and stiffness/elastic recoil is limited (13). To overcome the limitations of these parameters, Kovács et al. quantified LV diastolic function using a mechanistic model of filling that was determined by cross-bridge uncoupling relaxation, elastic recoil/restoring forces, and initial displacement (load) (14-16).

We recently demonstrated the feasibility and usefulness of kinematic model parameters obtained from RV pressure waveform for evaluating RV diastolic function (17). Furthermore, we have shown that the physical and physiological principles govern the transtricuspid flow pattern and that a mathematical model would be able to correctly quantify the pathological RV diastolic property in children and adolescents with PAH (18).

### PRESSURE MEASUREMENT AND DIASTOLIC FUNCTION

The ventricular pressure (P(t)), the time derivatives of pressure (dP/dt), LV and RV end-diastolic pressures (LVEDP and RVEDP), maximum and minimum pressures and pressure derivatives (Pmax, Pmin, dP/dt_max, and dP/dt_min), and the IVR pressure inflection point are determined. The pressure phase plane (PPP), where dP/dt is plotted against P(t), is delineated (Fig. 1) (19-21). LVEDP is defined by the LV pressure at the ECG R-wave peak. The mitral valve opening (MVO) and tricuspid valve opening (TVO) times are determined as the time points where the decaying pressure contours are closest to the LVEDP and RVEDP, respectively, of the subsequent filling beat (22, 23).
Assessment of monoexponential and logistic time constants

Diastolic function has traditionally been evaluated using the IVR time constant, which describes the pressure decrease. In the monoexponential model of pressure decay, it is assumed that the time derivative of pressure decay is proportional to pressure. The governing differential equation for the monoexponential model is

\[
\tau_E \frac{dP(t)}{dt} + (P_0 - P_\infty) e^{-\tau_E / P_\infty} = 0 \quad (1A)
\]

or

\[
P(t) = (P_0 - P_\infty) e^{-\tau_E / P_\infty} + P_\infty \quad (1B)
\]

where \(\tau_E\) is the monoexponential time constant of IVR pressure, and \(P_\infty\) is the pressure asymptote \((10, 11)\). A convenient way to determine it is to plot Eq. 1A in the PPP, where a straight line with a slope of -1/\(\tau_E\) and an intercept on the dP/dt axis is inscribed, and it is then fit to the IVR portion of the loop that is inscribed by P(t) for the cardiac cycle (Fig. 1E, F) \((20, 21)\). However, because there are curvilinear IVR segments, a straight-line fit to the IVR portion of the loop is not always physiological (Fig. 1F). In addition, RV pressure decay in particular has been shown to have curvilinear IVR segments \((12)\). Thus, \(\tau_E\) may not be suitable for evaluating RV diastolic function.

Another empirical constant has been proposed as an alternative to fit these common curved IVR segments of PPP trajectories \((21)\). The logistic time constant \(\tau_L\), which is similar to \(\tau_E\), provides an empirical fit, in which the rate of pressure decrease is proportional to the square of the pressure and is given by

\[
P(t) = \frac{P_0^2}{P_\infty} \frac{dP}{dt} + P(t) - P_B = 0 \quad (2A)
\]

or

\[
P(t) = \frac{P_0}{1 + e^{\tau_L / P_\infty}} + P_B \quad (2B)
\]

where \(\tau_L\) is the logistic time constant of IVR, and the pressure asymptote is given by the sum of \(P_\infty\) and \(P_B\). This logistic relationship is quadratic in P(t), and it can only produce, and, therefore, best fit, curvilinear PPP IVR contours in the PPP.

The slope of the dP/dt versus P(t) plot over the interval between 10 ms after dP/dt_min and 10 ms before the estimated MVO time determined by the least-squares method is equal to -1/\(\tau_E\) \((10, 11, 19)\). \(\tau_L\) is obtained using the methods of Matsubara et al. with a customized Levenberg-Marquardt algorithm \((21, 24)\).
KINEMATIC MODELING OF VENTRICULAR PRESSURE DECAY

Chung and Kovács previously showed that LV pressure decay is accurately determined mathematically by the interactions of inertial, stiffness, and relaxation forces using physiological-kinematic arguments, and they published their experimental results (25). The relative contributions of stiffness and relaxation to IVR pressure are characterized by a stiffness parameter and a damping or relaxation parameter. (25, 26) In the kinematic model, IVR pressure is predicted from before dP/dt_min to near MVO. Their theory applies the kinematics of the damping oscillator governed by the (mass normalized) equation of motion:

\[
\frac{d^2x}{dt^2} + c \frac{dx}{dt} + kx = 0 \tag{3a}
\]

where \( k \) is stiffness and \( c \) is damping (25, 26). The parameters of this model are stiffness/restoring \( E_k \) and damping/relaxation \( \mu \). The equation for LV pressure during this IVR phase is

\[
\frac{d^2P}{dt^2} + \frac{1}{\mu} \frac{dP}{dt} + E_k(P - P_\infty) = 0 \tag{3b}
\]

The solution for this equation in the underdamped regime (1/\( \mu^2 < 4E_k \)) for pressure or for the time derivative of pressure is given by

\[
P(t) = e^{\nu_2\mu} \left[ \frac{P_0 + P_\infty}{\nu_1} \sin(\omega t) + P_\infty \cos(\omega t) \right] + P_\infty \tag{4}
\]

\[
\frac{dP}{dt}(t) = e^{\nu_2\mu} \left( -\left( \frac{P_0 + P_\infty}{\nu_1} \right) \sin(\omega t) + P_\infty \cos(\omega t) \right) \tag{5}
\]

where \( P_0 \) is the initial pressure assuming a zero pressure asymptote, \( P_\infty \) is the initial time derivative of pressure, and

\[
\omega = \sqrt{4E_k - 1/\mu^2}/2
\]

The critically damped (1/\( \mu^2 = 4E_k \)) and overdamped (1/\( \mu^2 > 4E_k \)) solutions are provided by evaluating Eqs. 4 and 5 at the \( \omega = 0 \) (critically damped) or \( \omega = i\beta \) (overdamped) limits.

When 1/\( \mu^2 = 4E_k \) (critically damped kinematics):

\[
P(t) = P_\infty e^{i2\mu} \left( P_0 + P_\infty/2\mu \right) e^{i2\mu} t + P_\infty \tag{6}
\]

When 1/\( \mu^2 > 4E_k \) (overdamped kinematics):

\[
P(t) = e^{i2\mu} \left( \frac{P_0 + P_\infty}{\beta} \sinh(\beta t) + P_\infty \cosh(\beta t) \right) + P_\infty \tag{7}
\]

\[\beta = \sqrt{1/\mu^2 - 4E_k}/2\]

To extract \( E_k \) and \( \mu \) from an isovolumic pressure contour, which is the equivalent to solving the “inverse problem of IVR pressure,” the procedure is as follows.

With a custom-automated Java program (Pressure Decay Analysis Tokushima (PDA-Tokushima) ver. 1.05) (17), hemodynamic data were analyzed (Fig. 2). \( E_k \), \( \mu \), \( P_0 \), and \( P_\infty \) were extracted for each IVR pressure contour in each subject via Eq. 5 from dP/dt versus t data by a Levenberg-Marquardt fitting algorithm to the dP/dt data (17, 25-27). The initial point for the fitting is from the inflection point in the IVR pressure contour before dP/dt_min, while the endpoint was taken to be 10 ms prior to the estimated MVO or TVO time. Having found \( E_k \), \( \mu \), \( P_0 \), and \( P_\infty \), Eq. 4 is used to determine \( P \) with the Levenberg-Marquardt algorithm and the other 4 parameters held constant. Since IVR pressure contours are non-physiological and noisy, they generate high root mean square error (RMSE) values between the raw

Fig. 2  Appearance of the custom-automated Java program (Pressure Decay Analysis Tokushima (PDA-Tokushima) ver. 1.05) for the calculation of the kinematic model parameters. Pressure, dP/dt, and d²P/dt² of several cardiac cycles are shown (A). One cardiac cycle of these waves is shown as an enlarged display (B). The actual measured pressure and dP/dt are shown as dots, and fitting curves for P and dP/dt obtained from equations 4 and 5 are shown as the curvilinear lines (C). PPP trajectories are shown by the black curvilinear portion. The actual measurements are shown by the red dots. The calculated kinematic model fitting curve using \( E_k \) and \( \mu \) is shown by the red curvilinear portion (D). Figure modifies from Haybuchi Y, et al. (17) with permission.
dP/dt data and the model fit dP/dt when they are compared with acceptable physiological data. Therefore, beats having the largest 50th percentile RMSE values are to be discarded. Thus, only physiological smooth data are included in the final analysis, and this had the additional advantage of being automated, which minimized observer bias in beat selection.

RIGHT AND LEFT VENTRICULAR PRESSURE DECREASES IN NORMAL SUBJECTS

Representative examples of cardiac cycles in the control group are shown as LV and RV pressures, dP/dt time courses, and PPP (Fig. 1). The pattern and rate of RV pressure decay can be compared with those of LV pressure decay. Both ventricles show two distinct phases of pressure decrease, an initial accelerative phase and a subsequent decelerative phase separated by the corresponding dP/dt_min. In the LV, the initial accelerative phase (until LV-dP/dt_min) encompasses 25.05% ± 3.1%, while the major part of the LV pressure decreases during the subsequent phase in a decelerative fashion. In contrast, the accelerative phase of the RV is 67.5% ± 4.9% of its course, significantly shorter than that of the LV (p < .001). The dP/dt_min of the LV and RV were -1013.7 ± 188.1 mmHg/s and -402.2 ± 165.3 mmHg/s, respectively (p < .0001). The ratio of pressure at dP/dt_min to Pmax (P at dP/dt_min / Pmax) was significantly lower in the RV than in the LV (28.6% ± 14.8% and 58.3% ± 7.5%, respectively; p < .0001).

DIASTOLIC PARAMETERS OF THE LV AND RV IN THE CONTROL GROUP

The obtained parameter values for τE, τL, and the kinematic model parameters Ek and μ were compared between the LV and RV in the control group to assess the characteristics of normal RV diastolic physiology. Thereafter, the results obtained from RV pressure in the PAH group were compared with those of the normal RV to elucidate the RV diastolic pathophysiology in pressure overload (Fig. 3). In the control group, τE and τL were not significantly different between the LV and RV (33.1 ± 6.9 ms vs. 32.5 ± 14.6 ms, and 12.6 ± 2.4 ms vs. 14.5 ± 7.2 ms, respectively). Furthermore, τE and τL of the PAH RV were 46.8 ± 15.5 ms and 19.6 ± 6.0 ms, respectively, and they were not significantly different from those of the normal RV. In the analysis of the kinematic model, Ek was significantly lower in the normal RV than in the normal LV (487.0 ± 99.6 s² vs. 858.1 ± 162.7 s², p < .0001), whereas μ was significantly higher in the RV than in the LV (41.1 ± 10.4 ms vs. 21.5 ± 3.8 ms, p < .0001). These results indicate that the normal RV has lower stiffness/elastic recoil and superior cross-bridge relaxation.

DIASTOLIC PARAMETERS OF THE RV IN THE PAH GROUP

Measured τE and τL were not significantly different between the PAH and Control groups (46.75 ± 15.51 ms vs. 32.5 ± 14.6 ms, and 19.6 ± 5.9 ms vs. 14.5 ± 7.2 ms, respectively). The PAH group had significantly higher Ek than the control group (915.9 ± 84.2 s² vs. 487.0 ± 99.6 s², p < .0001) and significantly lower μ than the control group (16.5 ± 4.3 ms vs. 41.1 ± 10.4 ms, p < .0001). These results demonstrate that the PAH RV has higher stiffness/elastic recoil and lower active relaxation in diastole.

ECHOCARDIOGRAPHIC MEASUREMENT

The conventional echocardiographic parameters that are measured included: E-wave acceleration time (AT), deceleration...
time (DT), peak E- and A-wave velocities (E-peak and A-peak, respectively), and the E/A ratio. Peak early mitral and tricuspid annular velocity (e’) and peak late annular velocity (a’), E/e’, and e'/a’ are similarly calculated from the Doppler tissue recordings.

DOPPLER E-WAVE ANALYSIS USING KINEMATIC MODEL

Transmitral and tricuspid E-waves can be assessed as follows. Using a custom MATLAB release 2015a (MathWorks, Natick, MA, USA) program, beats with clear contours are selected, digitized, and cropped. The maximum velocity envelope is determined from the digitized E-wave image and then used to obtain the automated parametrized diastolic filling (PDF) fit. For the purpose of detecting the appropriate velocity profile, the program searches each time point of the image from the top down for the first pixel having a brightness higher than or equal to a user defined threshold level, matching each time point with a velocity. Furthermore, it is assumed that there must be an upper limit to the velocity difference between two time points a few milliseconds apart. The algorithm accordingly discards a detected velocity that differs too much from the previous velocity. Discarded velocities are displayed for reference and transparency as to the behavior of the algorithm.

The E-waves are then used to compute the PDF parameters. The PDF formalism characterizes the suction-initiated transmitral or tricuspid flow. This is analogous to the kinematics of a previously displaced, damped, harmonic oscillator after it recoils from a resting state. This methodology utilizes Newton’s Second Law, with the predictions of the E-wave contours parametrized on the basis of the chamber stiffness, relaxation/viscoelasticity, and the load. The equation that describes the balance of forces in a damped harmonic oscillator is:

\[ m \frac{d^2x}{dt^2} + c \frac{dx}{dt} + kx = 0 \quad (8) \]

where \( m \) (g), \( c \) (g/s) and \( k \) (g/s²) represent inertia, relaxation (damping) and ventricular stiffness/elastic recoil (spring constant), respectively. The parameter \( x_0 \) (cm) indicates the load and represents the initial displacement of the spring before motion, which corresponds to the elastic strain stored in the myocardium and surrounding structures available at the mitral or tricuspid valve openings that facilitate the mechanical recoil (14-16). When the initial velocity \( (dx/dt) \) of the system is zero, this corresponds to no transmitral or tricuspid flow prior to the valve opening. The inertial term \( m \) is normalized to 1 in order to enable the computation of \( c \) and \( k \) per unit mass. These parameters \( (k, c, \text{ and } x_0) \) can be directly determined from the clinical E-wave contour. The estimated model parameters are averaged values within the cardiac phase of interest. Expressions describing the velocity of motion as a function of time (t) is

\[ v(t) = \frac{-kx_0}{\omega} \exp(-c \cdot t/2) \sin(\omega \cdot t) \quad (9) \]

where

\[ \omega = \sqrt{4k - c^2}/2 \]

For underdamped cases, which are defined by \( c^2 - 4k > 0 \), the expression is

\[ v(t) = \frac{-kx_0}{\beta} \exp(-c \cdot t/2) \sin(\beta \cdot t) \quad (10) \]

where

\[ \beta = \sqrt{c^2 - 4k}/2 \]

For critically damped cases, which are defined by \( c^2 - 4k = 0 \), the expression is

\[ v(t) = -kx_0 \cdot t \cdot \exp(-c \cdot t/2) \quad (11) \]

The output of the Levenberg-Marquardt algorithm is used to determine the PDF parameter values for \( k \), \( c \), and \( x_0 \). We compared the kinematic model parameters \( c \), \( k \), and \( x_0 \) between the LV and the RV in the control group in order to assess the characteristics of the normal RV diastolic physiology. Subsequently, results from the E-waves in the PAH group were compared with those obtained from the normal RV to elucidate the RV diastolic pathophysiology during the RV pressure overload. Figure 4 shows 2 representative examples of tricuspid Doppler E-wave velocity profile edge detection and fitted curves. These examples demonstrate the method and process on how the digitized E-wave image was used to determine the maximum velocity envelope, from which the automated PDF fit was obtained.

KINEMATIC MODEL-BASED DIASTOLIC PARAMETERS OF THE RV IN THE PAH GROUP

As compared to the control group, the PAH group exhibited significantly greater values for the parameters \( k \) (182.5 ± 72.4 g/s² vs. 135.7 ± 49.5 g/s², p = 0.0232) and \( c \) (21.9 ± 6.5 g/s vs. 10.6 ± 5.2 g/s, p < 0.0001). These results demonstrate that the PAH RV has a higher stiffness and inferior active relaxation in diastole. The PAH and control groups had an indistinguishable initial load prior to the tricuspid valve opening \( (x_0 = 7.7 ± 2.4 \text{ cm in PAH; } 8.2 ± 2.9 \text{ cm in the control group}) \) (Fig. 5). The PAH group also exhibited greater values of cE-peak, kxo, and 1/2kxo².

CORRELATION BETWEEN KINEMATIC PARAMETERS AND RV PERFORMANCE IN THE PAH GROUP

In order to analyze the relationships between the kinematic-based parameter values and PAH severity and RV systolic performance, we evaluated the correlation between kinemat-
ic parameters and RVFAC (right ventricular fractional area change) and TRPG (tricuspid regurgitation peak gradient) (Fig. 6). RVFAC did not have significant correlation with k, c, and x₀. Although there was significant correlation between TRPG and k (r = 0.778, p = 0.0008), TRPG did not have significant correlation with c and x₀.

![Fig. 4](image1)

**Fig. 4** Quantitation of diastolic function via the PDF formalism. Representative transtricuspid E-wave Doppler images from a normal subject (A, B) and a PAH patient (C, D) are shown. Doppler E-wave velocity profile edge detection and fitted curves were shown. The digitized E-wave maximum velocity envelope is identified (A, C) and fitted using the Levenberg-Marquardt method by the solution to the PDF model (B, D), which yielded the 3 unique best fit PDF parameters of chamber stiffness k, relaxation c, and initial load x₀.

Control subject (A, B) parameters: x₀ = 11.4 cm, c = 10.1 g/s, k = 88.6 g/s²; MSE 5.3 cm²/s².
PAH patient (C, D) parameters: x₀ = 9.2 cm, c = 27.7 g/s, k = 148.1 g/s²; MSE 5.1 cm²/s².
Figure modifies from Haybuchi Y, et al. (18) with permission.

![Fig. 5](image2)

**Fig. 5** Conventional and kinematic model-based RV diastolic parameters. The values of E/A (A), E/e′ (B), DT (C), k (D), c (E), and x₀ (F) were compared between the control and the PAH groups. Boxes, IQR; Central line, median; Whiskers, minimum and maximum.

Figure modifies from Haybuchi Y, et al. (18) with permission.
ASSESSMENT OF RV DIASTOLIC FUNCTION USING BY KINEMATIC MODEL-BASED ANALYSIS

Our clinical investigation demonstrates that the causality-based kinematic parameters, Ek and μ, could precisely characterize load-independent RV diastolic function, whereas τE and τL of the RV did not show significant differences between the control and PAH groups. Furthermore, the analysis of the tricuspid E-waves via the PDF method also generates the parameters of chamber stiffness/elastic recoil and relaxation/viscosity that is useful for non-invasive diagnosis.

We have shown that the RV has significantly different diastolic properties, including stiffness/elastic recoil and active relaxation, from the LV. The kinematic model demonstrated that the normal RV has lower passive stiffness/restoring and higher active relaxation than the normal LV. Moreover, the RV in the PAH group was significantly stiffer and had slower cross-bridge detachment relaxation than the RV in the control group. This method is found to be quite useful way for evaluating RV diastolic dysfunction in PAH patients. Although some previous reports suggest the usefulness of τE and τL for the assessment of RV diastolic dysfunction in PAH patients (5, 9, 31), this issue has remained controversial. Our results do not show significant differences in these indices between the normal and PAH groups. This discrepancy might result from the subjects’ age, disease duration, and severity. The progression of deterioration of RV diastolic function, which consists of active relaxation and stiffness/elastic recoil, might differ between children and adults.

Furthermore, the RV and LV pressure decreases were found to follow distinct time courses. The initial accelerative phase until dP/dt_min is relatively longer, and the subsequent decelerative phase is shorter in the RV than in the LV. In this respect, the RV time constants τE and τL evaluate a quite short segment of RV pressure decay. However, on the molecular level, both τE and τL have been shown to correlate with active relaxation as defined by deactivation events, such as cross-bridge cycling, calcium handing, or lusitropism (32, 33), but neither can fully characterize the full range of the IVR pressure decrease. We should, therefore, be aware that the RV time constant only evaluates a minor portion of the RV pressure fall and has low reproducibility. When compared with τE and τL, models in the kinematic model parameters Ek and μ provides a superior fit to IVR pressure and higher reproducibility.

Previous work by Chung and Kovács demonstrated that IVR pressure is precisely determined by the interplay of stiffness/elastic recoil and damping/relaxation forces (25). The relative contributions of stiffness and relaxation to IVR pressure decay are characterized by the stiffness/restoring parameter Ek and the damping/relaxation parameter μ. This kinematic model successfully unifies the previously unrelated τE and τL models of isovolumic pressure decay in a parametric limit sense. The model proposed in Eq. 3B explains why PPP contours can change shape. A linear IVR PPP segment is one where the relaxation parameter (1/μ) is large compared with the elastic term (Ek) (31). As the elastic term increases, the IVR PPP segment becomes more curvilinear (31). A recent study involving humans demonstrated RV hypertrophy with collagen deposition, increased sarcomeric stiffness, and changed titin isoform and phosphorylation (3, 32). RV diastolic behavior should be evaluated from the perspectives of stiffness and relaxation. In this respect, the kinematic model established the parameters conforming to the pathophysiological state.

The load dependence of τE and τL is well established (33-35), and, therefore, the variations in τE and τL between subjects may be the result of intrinsic chamber property differences or may be caused by extrinsic load effects in the assessment of LV diastolic function. We had shown that RV τE and τL are significantly correlated with RVEDP (17). Thus, a load-independent index that overcomes the limitations of τE and τL would be advantageous. The kinematic parameters Ek and μ were relatively independent of preload (17). Furthermore, Shmuylovich and Kovács applied this kinematic model and derived a load-independent parameter.
named $MLHVPP$, which is the constant slope between the effective peak elastic recoil forces that drive pressure decline during isovolumic relaxation and the peak resistive forces that oppose cross-bridge uncoiling and pressure decline (36).

With the combined pressure conductance catheter, it has become possible to determine ventricular pressure and volume simultaneously. The gold standard for measuring load-independen
diastolic stiffness by pressure-volume (PV) analysis is not without risk in PAH patients because it requires temporal pre-
load reduction (37, 38). In left heart failure, this is circumvented
by the development of single-beat analyses of the diastolic PV
relationship (39, 40). However, it is unclear whether this analysis
could also be used for the RV in PAH. Furthermore, since precise
RV volumetric measurement is challenging, it would be quite
difficult to assess RV diastolic function using PV analysis.

In the echocardiographic study, the parameter $k$ represents
the chamber stiffness/elastance recoil property. As described above,
chamber stiffness (dP/dV) as evaluated by invasive cardiac cath-
erization, has been shown to be linearly related to the spring
constant $k$ (g/s$^2$) (29-30). It has been shown that PDF analysis of the Doppler E-wave can accurately determine the LV diastatic
passive chamber stiffness (41). The higher $k$ value for the RV in
the PAH group is consistent with an elevated RV filling pressure.

Kinetically, the lumped viscoelastic (resistive) properties of
the system are represented by the $c$ parameter. Thus, any
source of energy loss that opposes motion during the filling are
considered to be a part of the physiological analog. Increased
values of $c$ can be manifested by various factors that can influ-
ence filling via an energy loss. These factors can include blood
viscosity, delayed relaxation, dynamic friction during sarcomere
lengthening that occurs as the detached myosin heads slide past
the thin filaments, pericardial effects, and the viscosity of the
extracellular matrix (42-44). Changes in intracellular calcium
handling and high myofilament calcium sensitivity in PAH have
been reported to impair proper relaxation of cardiomyocytes (2).
Moreover, these pathological conditions are known to affect the
kinematic model parameters.

The $x_0$ value is related to the load responsible for compressing
the elastic myocardium at the end of systole, which is a prerequi-
site in order for the restoring force to arise. The $x_0$ value is also
closely related to the velocity time integral (VTI) of the E-wave.
In normal subjects, the parameter $x_0$ was lower in the RV versus
the LV. This might be because of the difference of the area at the
tip of the valve leaflets found between them. Furthermore, this
could possibly be due to the difference of the E/A ratio, Doppler
beam angle, and respiratory condition present at the time of the
recording. There was no significant difference in the volumetric
preload parameter $x_0$ between the control and PAH groups. This
value is specifically determined by several factors, including
stroke volume, volumetric E/A ratio, RV filling pressure, and
right atrial pressure. This finding suggests that during patho-
logical conditions, these PAH patients maintained the stroke
volume while at rest.

The initial maximum recoil force ($kx_0$) and the stored poten-
tial elastic energy $(1/2kx_0^2)$ were significantly higher in the PAH
versus the control group. The product $kx_0$, which is analogous to
the maximum atrioventricular pressure gradient that generates
the E-wave by mechanical suction, represents the initial peak
force in the spring. The results of a previous investigation that
found the $kx_0$ was more consistent than the modified Bernoulli
equation (PG = 4V$^2$; PG, pressure gradient; $V$, blood flow veloci-
ty) with regard to predicting the instantaneous maximum pres-
sure gradient also validates the above predictions (15).

Kinematically, the potential energy in the spring prior to
its release is represented by $1/2kx_0^2$. The physiological analog
for this factor is the stored elastic strain energy that is avail-
able at the tricuspid valve opening. This energy generates the
chamber recoil, which leads to the generation of the E-wave. The significantly greater values for $kx_0$ and $1/2kx_0^2$ in the PAH
group suggest that an adaptive mechanism via the hypertrophic
RV chamber is required in order to maintain a stroke volume.
This is shown by our results that indicated that there was no significant difference for the load $x_0$ between the control and
PAH groups. However, this occurs at the cost of increased en-
ergy utilization. In addition, our data also indicated that the
E-peak was significantly higher in the PAH patients versus the
control subjects, which indicates a higher resistance (impaired
relaxation) to the RV filling. A greater atrioventricular pressure
gradient $kx_0$ (and consequently, $1/2kx_0^2$) would be expected to be
generated in response to increased damping (resistive losses) of
the tricuspid flow, as is manifested by greater values of $c$
and $cE$-peak, in order to maintain the load $x_0$ or stroke volume.

Although previous reports and the ASE guidelines have sug-
gested the usefulness of conventional parameters in the assess-
ment of RV diastolic dysfunction (9, 31, 46, 47), the utilization
of these parameters has remained controversial (31, 46, 47). The
present study revealed that $E/e’$ and DT of the tricuspid E-wave did not exhibit any significant differences between
the control and PAH groups, whereas there was a significant differ-
ence for the E/A. This discrepancy regarding the usefulness of
the conventional indexes might be associated with the subjects’
age, disease duration, and pathological severity. Moreover, the
progression of the RV diastolic function deterioration, which
consists of active relaxation and stiffness/elastance recoil, might
differ between children and adults. In most of the studies that
have examined these differences, results indicated there was
a modest correlation between the E/A ratio and increasing age (48, 49).
Since the peak velocity of E-wave increases during inspira-
tion, this causes an increase in the E/A ratio. Furthermore, while
increases in the E-peak are caused by tachycardia, a relatively
greater increase in the A-peak will result in a decrease in the
E/A ratio (49, 50). These parameters are also sensitive to chang-
es in preload. Thus, while a reduction in the preload will lead to
a decrease in E, there will be a relatively smaller decrease in A,
thereby causing the E/A to decrease (51-53). However, it should be
noted that since the conventional echocardiographic diastolic
function indexes are empirical, these values will not provide any
mechanistic information on the chamber property, e.g., stiffness
and relaxation. Moreover, since E-wave parameters are not de-
lected from basic physiologic principles that govern filling, these
parameters are considered to be load dependent (54-56). In add-
ition, the complex interplay of simultaneous physiologic deter-
minants and chamber properties are responsible for generating
these indexes. Moreover, a previous study has demonstrated that
E-wave DT was specifically dependent upon both the chamber
stiffness and the chamber relaxation/viscoelasticity (57).

All the global physiologic determinants of the contour were
accounted for by the lumped parameters $c$, $k$, and $x_0$. RV dia-
stolic dysfunction determines ventricular performance and pa-

tient outcomes for many conditions. Moreover, this dysfunction
may preclude the apparent systolic dysfunction (31, 45, 58, 59).
Overall, we believe that our current findings indicate that there
are great clinical implications for this method with regard to the
management of PAH patients.

CONCLUSION

This review article indicated the validation of kinematic model
parameters for assessing RV diastolic function in PAH patients.
The PAH patients have higher stiffness/restoring and lower
cross-bridge relaxation than the Control group.
DISCLOSURE

The authors declare that they have no conflicts of interest.

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