What does the time constant of the pulmonary circulation tell us about the progression of right ventricular dysfunction in pulmonary arterial hypertension?

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Abstract: Compliance (C) and resistance (R) maintain a unique, inverse relationship in the pulmonary circulation, resulting in a constant characteristic time $\tau = RC$ that has been observed in healthy subjects as well as patients with pulmonary arterial hypertension (PAH). However, little is known about the dependence of right ventricular (RV) function on the coupled changes in R and C in the context of this inverse relationship. We hypothesized three simple dependencies of RV ejection fraction (RVEF) on R and C. The first model (linear-R) assumes a linear RVEF-R relation; the second (linear-C) assumes a linear RVEF-C relation; and the third one combines the former two in a mixed linear model. We found that the linear-R model and the mixed linear model are in good agreement with clinical evidence. A conclusive validation of these models will require more clinical data. Longitudinal data in particular are needed to identify the time course of ventricular-vascular impairment in PAH. Simple models like the ones we present here, once validated, will advance our understanding of the mechanisms of RV failure, which could improve strategies to manage RV dysfunction in PAH.

Keyword: mathematical model, right ventricular failure, RC time constant, pulmonary circulation.

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In understanding the progression of right ventricular (RV) failure in pulmonary arterial hypertension (PAH), a key knowledge gap is the mechanisms that underlie the transition from normal RV function to RV dysfunction and failure and how these transitions are dependent on changes in pulmonary vascular function as the disease progresses. Clinical studies have shown that the mechanical properties of the pulmonary vasculature (i.e., resistance [R] and compliance [C]) correlate with mortality in PAH.[1-3] In addition, an inverse relationship exists between C and R in the pulmonary circulation.[4] The time constant $\tau = RC$ has been found to be equal to ~0.5 s in a large clinical population, including patients with and without PAH, patients with different types of PAH, and patients before and after treatment.[4-7] However, it is unclear how pathological changes in vascular R and C mediate RV dysfunction.

Here we formulate three hypothetical models to describe the dependence of RV function on the metrics of pulmonary vascular function R and C. We hypothesize that RV function, expressed as RV ejection fraction (RVEF), depends linearly on R or C or on a combination of both. The results from the three models are evaluated on the basis of relevant clinical evidence.

METHODS

To describe the dependence of RV function on R and C, we chose a single metric of RV function. Under normal physiological conditions, known mechanisms of RV autoregulation preserve stroke volume (SV) and cardiac output (CO) in the face of increased afterload.[8] The maintenance of SV or CO may persist in the adaptively functioning RV in mild or moderate PAH; thus, it would be difficult to correlate these parameters with the early phase of disease. RVEF may be a more sensitive metric of PAH progression than SV and CO.[9] RVEF correlates with mean pulmonary artery pressure[10] and pulmonary vascular R[11] and has a strong prognostic value in PAH.[12] Therefore, here we chose RVEF as a metric of RV function for our three hypothetical models of RV functional dependence on R and C. For all models, we assume that R and C depend on each other through the relation $\tau = 0.5$ s. In addition, we consider the same ranges of values of R (up to 2 mmHg s mL^{-1}) and C (up to 8 mL mmHg^{-1}) for all models, consistent with reference ranges for PAH.[6]

With the progression of PAH, we define three possible conditions: no PAH, mild PAH, and severe PAH. Transition from no PAH to mild PAH occurs at $R = 0.18$ mmHg s mL^{-1} (corresponding to the diagnostic threshold of 3.0 Woods units). In terms of RV function, we assume that this transition occurs at RVEF = 45%.[13] We further assume that transition from mild to severe PAH occurs at $R = 0.3$ mmHg s mL^{-1} (corresponding to 5.0 Woods units) and RVEF = 35%.[14] The ranges for RVEF are consistent with values obtained from magnetic resonance imaging.[10,15-17]

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RESULTS

For our first model, we hypothesize that RV function (i.e., RVEF) is equally sensitive to changes in R at any stage of PAH. This translates into a simple, linear negative relationship between R and RVEF (linear-R model; Fig. 1*a*, 1*b*). Because of the constant slope, the same change in R at either a mild stage or severe stage of disease causes the same decrease in RVEF. Combining this linear dependence with the constant τ, we then obtain a nonlinear relationship between C and RVEF (Fig. 1*b*). As a result, RVEF is clearly more sensitive to changes in C in severe PAH than mild or no PAH, which is supported by clinical evidence.[18]

For our second model, we alternatively hypothesize that RV function is equally sensitive to changes in C at any stage of PAH, resulting in a linear relationship between RVEF and C (linear-C model; Fig. 1*c*, 1*d*). As a result, we obtain a nonlinear relationship between R and RVEF: RVEF is more sensitive to R in mild or no PAH compared with the linear-R model, whereas in severe PAH large increases in R produce only modest decreases in RVEF. Because RV function is nearly independent of R at high values, this model suggests that C is a better predictor of outcome than R in severe PAH, which is supported by the clinical literature.[3] Note that this was not the case for the linear-R model: both R and C should predict outcomes well under those assumptions, albeit R linearly and C nonlinearly.

Lastly, given the dependence of arterial remodeling and stiffening on both acute[19] and chronic[20-23] increases in R and pulmonary artery pressure, for our third model, we assume that, in mild or no PAH, RV function depends mainly on R, whereas in severe PAH it depends mainly on C. That is, we assume that, in mild or no PAH, RVEF decreases linearly with increasing R, and in severe PAH, RVEF decreases linearly with decreasing C (mixed linear model; Fig. 1*e*, 1*f*). This model is able to account for both the limited sensitivity of RV function to C in mild or no PAH and the limited sensitivity to R in severe PAH. The linearity of the RVEF-R relationship for RVEF >35% is consistent with the linear relationship observed in mild and moderate PAH.[11] Similar to the linear-R model, the mixed linear model is consistent with the curvilinear RVEF-C relationship observed by Stevens et al.[18]

In Table 1, we summarize strengths and weaknesses of the three models on the basis of clinical evidence. In Figure 2, we directly compare the results from our models with the empirical correlations derived from the limited clinical data available.[11,18] The linear-R and mixed linear models show good overall agreement with the clinical data, with the linear-R model performing better in severe PAH. The linear-C model shows poor agreement with both the RVEF-R clinical data and the RVEF-C clinical data (Fig. 2).

Our analysis indicates that the linear-R model exhibits the best agreement with the clinical data available. On the other hand, the mixed linear model may be more consistent with reference ranges of R, C, and RVEF. The mixed linear model is also consistent with the hypothesis that a switch in RV function sensitivity to pulmonary vascular function occurs at the onset of severe PAH: changes in R become nearly irrelevant, whereas even modest decreases in C can have a large effect on RVEF.[4] We speculate that, because the efficacy of RV contraction depends strongly on LV contraction,[24] increases in the steady RV afterload can be accommodated well by RV hypertrophy. In contrast, when the timing of ejection is altered either by wave reflections or increases in the pulsatile RV afterload, the RV must contract in a nonsynchronized way with the septum and LV,[25] which leads to RV dysfunction and failure. Although there is evidence that a reduction in pulmonary arterial stiffness is associated with both an increased delay in wave reflection and an improvement in stroke volume,[26] additional data are needed to support this speculation.

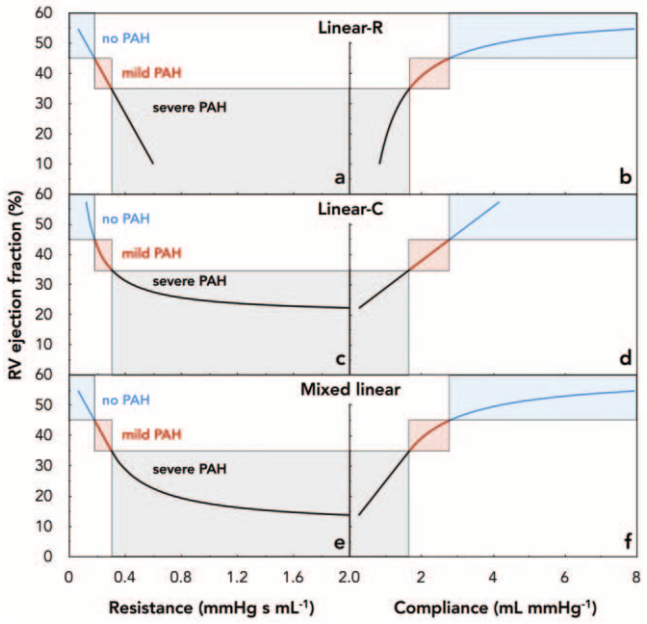

Figure 1. Schematization of the three models, showing plots of the right ventricular ejection fraction (RVEF) as a function of resistance (*a, c, e*) and compliance (*b, d, f*). Note that when plotting RVEF versus resistance, disease severity increases left to right, whereas when plotting RVEF versus compliance, disease severity increases from right to left. Shown are the linear resistance (linear-R) model, where RVEF decreases linearly with resistance (*a*, *b*); the linear compliance (linear-C) model, where RVEF increases linearly with compliance (*c, d*); and the mixed linear model, where RVEF decreases linearly with resistance in the range of mild or no disease (RVEF > 45%) and increases linearly with compliance in the range of severe disease (RVEF < 45%; *e, f*). Transition from no pulmonary arterial hypertension (PAH) to mild PAH is set to $R = 0.18$ mmHg s mL^{-1} and RVEF = 45%. Transition to severe PAH is set to $R = 0.3$ mmHg s mL^{-1} and RVEF = 35%; 1 mmHg s mL^{-1} = 16.7 Woods units.

DISCUSSION

Herein we developed three hypothetical dependencies of RV function (i.e., RVEF) on pulmonary vascular mechanical properties (i.e., R and C) to reflect on what we can learn from the RC con-

Table 1. Summary of the strength, weakness, and current clinical evidence in support of each of the three hypothetical models

Model	Strength	Weakness
Model 1 (linear-*R*)	In severe PAH, RVEF is more sensitive to changes in *C* than mild or no PAH[17]	*R* has a limited prognostic value[3,4]
Model 2 (linear-*C*)	In severe PAH, RV function is nearly independent of *R* at high values, whereas *C* is a better predictor of outcome[3,4]	The same sensitivity of RVEF to changes in *C*, independent of PAH severity[17,18]
Model 3 (mixed linear)	In mild or no PAH, RVEF decreases linearly with increasing *R*; in severe PAH, RVEF decreases linearly with decreasing *C*;[4,10,11,17,18] the transition point from the linear-*R* model to the linear-*C* model is defined by RVEF <35%[9,14-16]	In severe PAH, RVEF does not linearly correlate with *R*, as shown in García-Alvarez et al.[11]

Note: *R*: resistance; PAH: pulmonary arterial hypertension; RVEF: right ventricle ejection fraction; *C*: compliance.

stant about the progression of RV dysfunction in PAH. For all models, we assumed a constant characteristic time $\tau = 0.5$ s.[4,6] Recently, it has been found that the time constant may be lower ($\tau = 0.36$ s) in patients with normal mean pulmonary artery pressure (mPAP < 25 mmHg) and R ($R < 0.18$ mmHg s mL^{-1}).[27] The lower value of τ may reflect a lower R or a lower C (or a combination of both). In our models, the RVEF-R and RVEF-C curves for patients with normal mPAP would appear to be shifted to the left of the curves for the patients with PAH. Interestingly, if compared at the same C, patients with normal mPAP would exhibit equal or better RV performance (i.e., larger RVEF) compared with patients with PAH, as exemplified in Figure 3 (linear-R model).

A limitation of these hypothetical models of RV function dependence on R and C, which are tightly coupled in the pulmonary circulation, is that time dependence is absent. This is because there is a surprising lack of longitudinal studies aimed at investigating the time course of ventricular and vascular dysfunction in PAH. The functional dependencies proposed here, as well as the transition from mild to severe PAH, need to be put into the context of the time course of disease progression to provide guidance for clinical monitoring and treatment of PAH. Another limitation is that the models proposed here assume a fixed relationship between RVEF and R (or C, or both) independent of different τ values and RV properties. For instance, with progressive hypertrophy and fibrotic

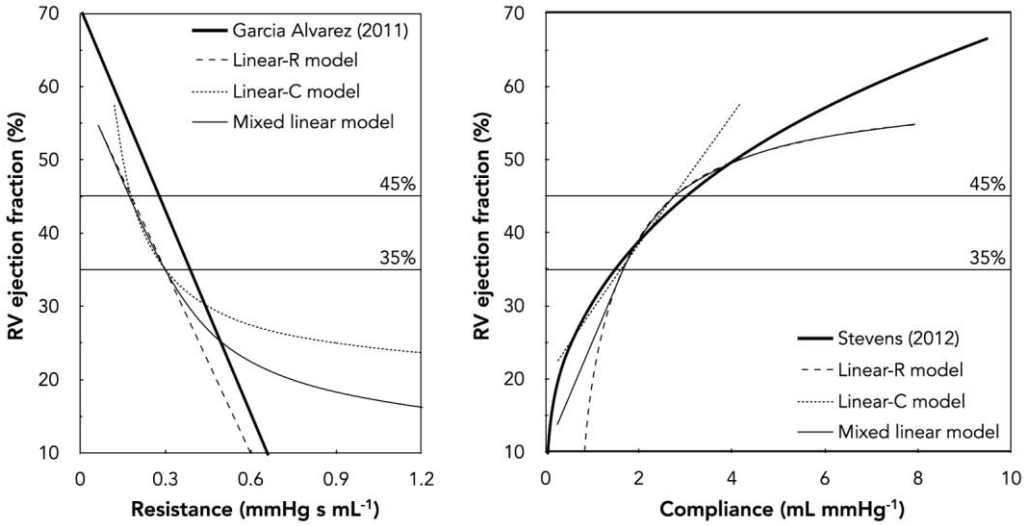

Figure 2. Comparison of the results from the linear resistance (linear-*R*; dashed line), linear compliance (linear-*C*; dotted line), and linear mixed model (solid line) with clinical data (thick solid line).[11,18] Right ventricle (RV) ejection fraction is plotted as a function of resistance (*left*) and compliance (*right*). Only data obtained for $\tau = 0.5$ s were included in this comparison. Note that the linear-*R* and mixed linear model are equivalent for RV ejection fraction >35% (mild or no pulmonary arterial hypertension). Also, as in Figure 1, note that disease severity increases from left to right when plotting RV ejection fraction versus resistance, whereas disease severity increases from right to left when plotting RV ejection fraction versus compliance.

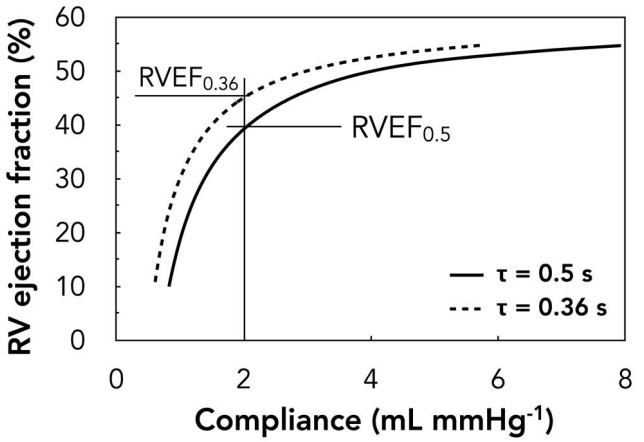

Figure 3. Effect of τ on the relationship between right ventricle (RV) ejection fraction (RVEF) and compliance as calculated using the linear resistance model. The time constant of the pulmonary circulation (τ) is assumed to be constantly equal to 0.5 s (solid line) or 0.36 s (dashed line). Individuals with comparable pulmonary arterial compliance but lower τ would exhibit higher RVEF, reflecting better cardiac performance.

remodeling of the RV, RVEF may decrease faster with increasing *R* or decreasing *C* than nonfibrotic RV. The lack of clinical data that quantify the impact of RV biological properties such as hypertrophy or fibrosis on RVEF independent of *R* and *C* prevented us from accounting for RV remodeling in the current models. Data from animal studies could help clarify the relationships.

Conclusions

In conclusion, we demonstrated that the linear-*R* model and the mixed linear model, which describe the dependence of RV function on metrics of pulmonary vascular function, are in good agreement with clinical evidence. A conclusive validation of these models will require more clinical data than are currently available in the literature. By presenting these models, we hope to stimulate the clinical research community to consider how predictive metrics of mortality in PAH might depend on disease stage and severity and to collect detailed longitudinal data on disease progression in different PAH subtypes. Identifying a relationship between measures of ventricular and vascular function, as well as the time course of progression in PAH subtypes, would be a significant advancement in the understanding of the mechanisms of RV failure, which could potentially lead to better strategies to manage RV dysfunction in PAH.

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