Diverse forms of pulmonary hypertension remodel the arterial tree to a high shear phenotype

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1Department of Pulmonary and Critical Care Medicine, University of California Davis Health System, Sacramento, California; 2Department of Anatomy, Physiology and Cell Biology, Veterinary Medicine, University of California, Davis, California; 3Respiratory Disease Unit, California National Primate Center, University of California, Davis, California

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Allen RP, Schelegle ES, Bennett SH. Diverse forms of pulmonary hypertension remodel the arterial tree to a high shear phenotype. Am J Physiol Heart Circ Physiol 307: H405–H417, 2014. First published May 23, 2014; doi:10.1152/ajpheart.00144.2014.—Pulmonary hypertension (PH) is associated with progressive changes in arterial network complexity. An allometric model is derived that integrates diameter branching complexity between pulmonary arterioles of generation n and the main pulmonary artery (MPA) via a power-law exponent (X) in \( n = 0.69 \times 2^{1-2/N} \) and the arterial area ratio \( B = 2^{1-2/N} \). Our hypothesis is that diverse forms of PH demonstrate early decrements in X independent of etiology and pathogenesis, which alters the arteriolar shear stress load from a low-shear stress (X > 2, B > 1) to a high-shear stress phenotype (X < 2, B < 1). Model assessment was accomplished by comparing theoretical predictions to retrospective morphometric and hemodynamic measurements made available from a total of 221 PH-free and PH subjects diagnosed with diverse forms (World Health Organization; WHO groups I-IV) of PH: mitral stenosis, congenital heart disease, chronic obstructive pulmonary lung disease, chronic thromboembolism, idiopathic pulmonary arterial hypertension (IPAH), familial (FPAH), collagen vascular disease, and methamphetamine exposure. X was calculated from pulmonary artery pressure (Pp,a), cardiac output (Q) and body weight (M), utilizing an allometric power-law prediction of X relative to a PH-free state. Comparisons of X between PAH-free and PAH subjects indicates a characteristic reduction in area that elevates arteriolar shear stress, which may contribute to mechanisms of endothelial dysfunction and injury before clinically defined thresholds of pulmonary vascular resistance and PH. We conclude that the evaluation of X may be of use in identifying reversible and irreversible phases of PH in the early course of the disease process.

Pulmonary hypertension (PH) is a “silent-killer” that can lead to irreversible changes in pulmonary vascular structure and function, increasing pulmonary vascular resistance (PVR), right ventricular failure, and death (30). The diagnosis of pulmonary arterial hypertension (PAH) is often difficult and confounded by clinical entities that also may express elevation of pulmonary artery pressure as part of their clinical phenotype. Much interest has focused on a World Health Organization (WHO)-developed nomenclature system that differentiates PH etiology into five clinical groups. This classification does little to elucidate PH etiology and pathogenesis because the mechanisms and diverse triggers that exist (30). It has been suggested that our continued lack of understanding of the early stages of PH may be perpetuated by limitations inherent in utilizing a reductionist approach to define a complex syndrome based on end-stage pathological observations of arteriolar vessel remodeling (5). Alternatively, for the purpose of early detection, treatment, and prevention, it may be beneficial to interpret the pulmonary arterial circulation globally as a complex adaptive system to identify a vascular branching phenotype evident in the early phases of the PH process that is, not only independent of inciting mechanism, but also susceptible to multiple triggers.

In the early 1900s, Richard Thoma theorized that pathological processes in organ systems produce characteristic changes in branching network complexity to maintain a hemodynamic-metabolic steady state that insures the appropriate blood flow for a given metabolic demand (44, 45). This hemodynamic-metabolic steady state is determined by the interaction between the mechanical power of the heart used to perfuse the organ system and the metabolic demands of the organ system. The mechanical power of the heart in this case is defined as the product of the fraction of cardiac output through the organ systemic perfusion pressure. The minimum hemodynamic power needed to meet the metabolic demand is adjusted by neural, humoral, and local mechanisms acting at precapillary arterioles. Consequently, organ-system flow in health and disease is distributed and adjusted via adaptations in arterial and capillary perfusion area. The same steady-state principles can be applied to the pulmonary circulation after birth, which is a low-pressure system that receives 100% of cardiac output. However, at rest, only a fraction of the pulmonary capillaries are recruited, and the pulmonary arterial vasculature cross-sectional area is considered to be nearly maximally vasodilated. In the case of maximal aerobic exercise, additional capillaries are recruited to meet increased gas exchange to meet metabolic demand. Moreover, because greater than 50% vascular obstruction is required for a healthy lung to produce an increase in pulmonary arterial pressure at rest (4), pulmonary arterial cross-sectional area adjustments to cardiac output demonstrate a reserve that acts to limit both arterial and capillary pressures. Thoma deduced that physiological dysfunction and disease introduce disturbing factors that chronically reduce the vascular cross-sectional area reserve to blood flow. These factors include a disruption of the regulatory aspects of arterial tone and the integrity of the vascular wall by altering its function and muscle thickness, which, not only encroaches on vessel cross-sectional area, but also disrupts diameter network complexity by reducing the area ratio between parent and daughter vessels. He advanced two basic hypotheses: I) under apparent steady-state conditions, pathological processes in mammalian organ systems demonstrate the emergence of a common phenotype of increasing network disorder between

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and/or inflammation in a positive-feedback fashion (16, 41). We next
arterioles during PH progression for the reason that area reduction
load in the main pulmonary artery and its amplification on terminal
epochs during PH progression (Fig. 1) (3), where MPA is the main
of delineating the trajectory of
MATERIALS AND METHODS

Our hypothesis is that PH of WHO groups I-IV are charac-
terized by alterations in arterial branching complexity along a
characteristic hemodynamic and morphometric trajectory,
from a non-PH state characterized by low arteriolar shear stress
to a PH state characterized by pathologically high shear stress.
Our objective was to develop an approach for the early detec-
tion of PH and the evaluation of PH progression by applying
Thoma’s hypotheses of changing arterial branching complexity
in disease. Using an allometric model of PH progression, we
derived a power-law scaling exponent that encompasses pul-
monary arterial cross-sectional area reduction and length prun-
ing. When applied to retrospective hemodynamic and morpho-
metric data, our model delineates early, mid, and late epochs of
PH progression. Although this approach purposely does not
address mechanisms, we demonstrated that the most aggressive
epoch is evident early, well before clinically defined thresholds
of PH and PAH are reached, and therefore may be instrumental
in helping to identify underlying mechanisms and their inter-
ventions.

MATERIALS AND METHODS

Methods summary. We formulate a predictive theoretical model
(see Model) based on Thoma’s descriptive principles and hypotheses
of physiological and pathological adaptation (44, 45). His principles
represent empirical scaling relationships, summarized as laws be-
 tween species. Our proposed allometric model of PH progression centers
on Thoma’s empirical diameter power-law for organ systems (Table 1),
where a monotonic decrease in \( X_{MPA} \) earmarks steady-state phases
of disease progression along with the degree of arterial area reduction.
Our model depends on a disease-free reference state that relies on
interspecies similarity and scaling relationships to predict common
conditions for pressure, flow, hemodynamic-metabolic steady state,
and arterial-capillary network organization as a function of body
weight (8–10) (Table 2). Here, the body-mass allometry exponents \( \alpha \)
represent theoretical approximations to empirically derived ones for
pulmonary capillaries, arterioles, and main pulmonary artery derived
by Dawson (8–10) utilizing similarity principles for the relationship
between blood volume, diameter, and length in conjunction with body
dimensions, which are subject to nonuniform scaling to achieve
maximum physiological vascular pressures independent of body
weight mass.

The model delineates PH progression as a paradoxical form of
hemodynamic afterload reduction constrained to a minimum-
power arterial network model of disease progression advancing via steady-state
energy-rate decrements in \( X_{MPA} \) and \( X_t \) from their reference condi-
tions, \( X = X_a = X = 2.25 \). The steady states for capillaries \( X \) and
the MPA comprise:

\[
I_C = \psi_{MPA-MPA} / \psi_{MPA} \times M^0 \tag{1}
\]

\[
I_{MPA} = \psi_{MPA-MPA} / \psi_{MPA} \times M^0 \tag{2}
\]

as defined in Table 1. PH progression is modeled by phases of X
reduction according to

\[
\frac{\psi_{MPA-MPA}}{\psi_{MPA-MPA}} \geq 1 \tag{3}
\]

where early phases of PH correspond to the ratio approximately equal
to 1.0. Equation 1 is assumed to be time invariant within an individual
and hold within and between species (8–10). Alternatively, later
phases of PH may demonstrate observed energy rates greater than the
reference for Eq. 2 but maintain a minimum-dissipation configuration
while maintaining Eq. 1. The minimum-power dissipation condition
reflects Murray’s law (32), implemented in an alternative manner by
determining the network value of \( X \) between the MPA and arterioles
generations \( n \) that minimizes the energetic metabolic rate associated
within arterial volume \( V_n \):

\[
Q = k_m \left( \frac{d_{MPA}}{2} \right)^{5MPA} 2^{(1-3X)^2} = \sqrt{\frac{\psi_{MPA}}{R_n}} \tag{4}
\]

where

\[
k_m = \pi \sqrt{m/8\mu} \tag{5}
\]

\[
m = \psi_{MPA}/V_n \times \psi_{O_2}/V_n \tag{6}
\]

Here, \( \mu \) denotes blood viscosity, considered independent of species
(10). The constant \( m \) reflects an interspecies, intraspecies time-invari-
antead state of energetic rates between the metabolic rate and
hemodynamic power delivered to an organ system. The ratio between
them \( \hat{I}_{MPA} = \psi_{MPA-MPA}/\psi_{O_2} \) is known as Li’s ratio (Table 1) (28)
and represents a size-scale invariant hemodynamic-metabolic steady state
between species. \( R_n \) is the resistance of a hemodynamic-equivalent
Table 1. Thoma’s laws of disease

<table>
<thead>
<tr>
<th>Steady-state</th>
<th>Law (citation) [pages]</th>
<th>Physiological Reference State</th>
<th>Power-Law Exponent/Area Ratio Trends</th>
<th>Disease Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hemodynamic-Metabolic</strong></td>
<td>$P \cdot Q = \psi_{PQ} \propto \psi_{QO2} \propto M^2$ = constant (44) [2, 269]</td>
<td></td>
<td>Law maintained in early stages</td>
<td></td>
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<tr>
<td><strong>Vascular Structure-Function</strong></td>
<td></td>
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<tr>
<td><strong>Organization Level</strong></td>
<td></td>
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<tr>
<td><strong>Vessel</strong></td>
<td>$Q \propto d^x$ (45) [357]</td>
<td>$2 \leq x \leq 4$</td>
<td>$x &lt; 2$</td>
<td></td>
</tr>
<tr>
<td><strong>Bifurcation</strong></td>
<td>$Q_p \propto d_p^x = d_1^x + d_2^x$ (44) [276-277] (45) [358] (19) [245-251]</td>
<td>$2 \leq x \leq 4$</td>
<td>$x &lt; 2$</td>
<td></td>
</tr>
<tr>
<td><strong>Flow-Condition: $Q_f = Q_1 + Q_2$</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>heteronomous: $Q_f &gt; Q_1 &gt; Q_2$</td>
<td>$d_p = d_1(1 + \gamma^x)^{1/2}$</td>
<td>$2 \leq x \leq 4$</td>
<td>$x &lt; 2$</td>
<td></td>
</tr>
<tr>
<td>homonomous: $Q_f &gt; Q_1 = Q_2$</td>
<td>$d_p = d_2^{1/2}$</td>
<td>$2 \leq x \leq 4$</td>
<td>$x &lt; 2$</td>
<td></td>
</tr>
<tr>
<td><strong>Organ System</strong></td>
<td></td>
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<tr>
<td><strong>Hemodynamic</strong></td>
<td>$d_p \propto Q_{organ}^{1/2}$</td>
<td>$x_{Qref} = f(X_{Mref})$</td>
<td>$x_Q &lt; x_{Qref} =$</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolic</strong></td>
<td>$d_p \propto M_{organ}^{1/2}$</td>
<td>$x_{Mref} = f(X_{Mref})$</td>
<td>$x_M &lt; x_{Mref} =$</td>
<td></td>
</tr>
<tr>
<td><strong>Flow-Network</strong></td>
<td>$Q_{organ} \propto d_p^x = \sum_{i=1}^n d_i^{x_i}$</td>
<td>$2 \leq x^i \leq 4$</td>
<td>$x^i &lt; 2$</td>
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<tr>
<td><strong>Morphometric Diameter-Flow Condition</strong></td>
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<tr>
<td>Asymmetric-heteronomous</td>
<td>$R_b = 1 + \gamma_{i}^{x_{i}} \neq 2$</td>
<td>$2 \leq X_d \leq 4$</td>
<td>$X_d &lt; 2$</td>
<td></td>
</tr>
<tr>
<td>Symmetric-homonomous</td>
<td>$R_b = 1 + \gamma_{i}^{x_{i}} = 2_{i=1}^{n}$</td>
<td>$2 \leq X_d \leq 4$</td>
<td>$X_d &lt; 2$</td>
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<tr>
<td><strong>Network Area Ratio</strong></td>
<td></td>
<td></td>
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<tr>
<td>Asymmetric-heteronomous</td>
<td>$\beta = (1 + \gamma_{i}^{x_{i}})/(1 + \gamma_{i}^{x_{i}})^{2_{i}}$</td>
<td>$\beta &gt; 1$</td>
<td>$\beta &lt; 1$</td>
<td></td>
</tr>
<tr>
<td>Symmetric-homonomous</td>
<td>$\beta = 2_{i=1}^{n} - x_{i}$</td>
<td>$\beta &gt; 1$</td>
<td>$\beta &lt; 1$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(19) [245-251]</td>
<td></td>
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</tbody>
</table>

Concept: a disease process over time is metabolically and hemodynamically “silent” in a steady state while vascular structure-function relationship complexity is progressively altered in a common direction of increasing dissipation disorder Thoma envisioned complexity change via unified scaling relationships/laws using the premise of hemodynamic-equivalent flows coupled to morphometric-equivalent networks; i.e., the same principles apply to cascading levels of branching (vessel, bifurcation, organ system), regardless of whether or not steady-state flow is “heteronomous,” coupled to heterogeneous/asymmetric diameters, or “homonomous” in a symmetric network. His translational disease concept predicts that unspecified metabolic hemodynamic work increases network complexity/disorder, by mechanisms unknown, but the process is empirically observable via $x_M$, or $x_Q$, coupled to an unknown relationship with arterial network complexity index $X_d$ ($x = f(X_Q)$). $\beta$, Bifurcation or network area ratio; $d$, vascular diameter; $d_P$, bifurcation or network parent diameter; $d_1$, bifurcation major diameter; $d_2$, bifurcation minor diameter; $d_M$, average diameter of arterial generation, or order, $n$; $\gamma$, daughter asymmetry ratio ($d_2/d_1$) of bifurcation or arterial network; $M$, body weight; Morgan, organ weight; $P$, arterial pressure; $Q$, blood flow; $\psi_{PQ}$, hemodynamic power as product $PQ$; $\psi_{QO2}$, metabolic rate; $Q_1$, entrance flow of bifurcation or organ; $Q_2$, bifurcation minor diameter flow; $Q_3$, bifurcation major diameter flow; $R_b$, branching ratio of a bifurcation $n = 1$, or arterial network ($n > 1$) that is symmetric with $n$ generations when $R_b = 2$, or asymmetric with order n if $R_b \neq 2$; $x$, vascular diameter exponent; $X_d$, vascular network diameter exponent; $x_Q$, entrance diameter blood-flow exponent; $X_M$, entrance diameter-mass exponent for organ, or body weight.

Arterial bifurcating network (22) with $n$ generations possessing diameter and length power laws with exponents $X = X_d = X_i$:

$$R_{MPA} = \frac{8\mu l_{MPA}}{\pi(d_{MPA}/2)^4}$$

(8)

where $R_{MPA}$ is the main pulmonary artery resistance

based on Poiseuille’s relationship where $l_{MPA}$ is the length of the MPA and $d_{MPA}$ is the entrance diameter of the MPA. The corresponding arterial volume is given by:

$V_{artery} = \frac{4}{3}\pi \left(\frac{d}{2}\right)^3$

where $d$ is the arterial diameter.
where $V_{\text{MPA}}$ is the entrance volume of the MPA

$$V_{\text{MPA}} = \pi \frac{d_{\text{MPA}}}{2} \quad (10)$$

Under Thoma’s schema, PH progression constitutes a disease of arterial network complexity that increases dissipation disorder via diameter and length pruning under apparent steady-state metabolic-hemodynamic conditions. Our assumed tree-pruning process (X decrements as via $X = X_0 = X_0$) represents one of many possible construed signature combinations of diameter and length, which impact arterial network complexity via a hemodynamic-morphometric scaling condition $Q \propto \psi_{Q,0}$, analogous to Thoma’s law $Q \propto d^n$ (45). Here, $x_P$ for a vessel, or $X_P$ for an organ, represents a monotonic index of dissipation intensity due to increasing network disorder as $X_I$ and $X_O$ regress from their control values. The functional consequences in a network are:

$$X_P = 1/(2 + (1/X_I) - (4/X_O)) \quad (11)$$

(Fig. 1). Although morphometric details of the pruning process are not clear (Fig. 1), this relationship and its graphic interpretation indicates that when $X_I$ and $X_O$ change, the state of power-dissipation disorder $X_P$ associated with flow either decreases or increases relative to the reference state $X_{P,\text{ref}} = 1.5$. Exercise in the disease-free state results
Fig. 1. Predictive model validation via forward-inverse modeling of diameter/length-power laws. By observation, pulmonary hypertension (PH) disease reduces diameter exponents and area ratios and also prunes their effective lengths, at the level of bifurcations, and as a population within subtrees and the arterial tree as a whole (6, 14, 36).

Thoma’s schema of maladaptive morphometric changes in branching complexity via metabolic-hemodynamic steady states leads to a simple predictive and integrative diameter/length power-law model of PH disease progression on the basis of phenotypic changes in arterial branching complexity that is, in principle, identifiable and validated by forward (morphometric) and inverse (hemodynamic) power-law data models (3). The basic element of topological organization common to the power laws are bifurcations. As the sources of information about structure and function are disparate, forward and inverse models purposely utilize limited available information at the level of bifurcations within their respective approaches, to ultimately lead to a common integrated diameter power-law relationship (arterial tree). For example, the forward-morphometric model (see Ref. 16) represents an asymmetric nonuniform model morphometric tree of a PH-free and PH state when viewed at all levels of organization. However, although the morphometric distribution is nonuniform and contains more detailed information, it possesses an average value consistent with the slope of the diameter power law, which changes in a direction of area reduction for the entire arterial tree in the course of PH progression. Conversely, the inverse hemodynamic model is devoid of morphometric information entirely. It is alternatively formulated on the basis of diameter/length adaptations subject to a principle of least work rate. The premise of $\beta_d = \beta_l$ delineates an energetic rate-favorable trajectory of maladaptation for both diameter and length pruning at the level of bifurcations, bifurcation distribution, and for the arterial tree as a whole that is coincident with Thoma’s hypothesis of disease progression and the forward model. PAH, pulmonary arterial hypertension.
degrees depending on the interrelationship between \( X_d \) and \( X_l \). Notably, the symmetric \( X_d \times X_l \) bifurcation relationship of Fig. 1 illustrates that, if \( X_l = 2.25 \) remains fixed at its reference value and \( X_d \) takes a progressive PH trajectory of \( X_d < 2.25 \), then greater dissipation intensities and states of disorder for \( X_d \) are experienced in its trajectory than compared with \( X_u = X_l \) decreasing concurrently. As the pulmonary circulation is a transducer and translator of hemodynamic force, the extra intensity reflects additional work delivered to remodel network complexity in a direction favorable to the organ system and organism. This suggests that the paradoxical maladaptive strategy associated with arterial diameter/length pruning during PH progression represents a trade-off balancing arterial afterload and arterial diameter/length reduction to maintain metabolic-hemodynamic homeostasis (Eq. 2) and increasing arterial dissipation to limit maximum capillary pressures from edema formation (Eq. 1) (8–10).

Thoma proposed that the steady-state blood flow delivered to an organ system is related to entrance diameter \( Q \propto d^n \) where, in turn, diameter is metabolically related to organ mass \( d \propto M^{1/3} \) (45). Intended to be empirical, the entrance exponents \( x_m \) and \( x_M \) become theoretically related to the arterial network organization, \( X \), if each phase of reduction in \( X = X_l = X_u \) associated with the pruning process is subject to the minimum work condition (Eqs. 4–6, Table 2-Eq. 14):

\[
x_M = 4 \left( 2 a_Q - 2a_{\phi_2} + 3a_{\phi_2}X^{-1} + \frac{1}{4} \right)
\]

For Thoma’s diameter-flow relationship the scaling exponent \( x_Q \) is

\[
x_Q = a_{\phi_2}X_{\text{MPA}}
\]

Here, the metabolic/hemodynamic steady state of \( a_{\phi_2} = 3/4 \) and \( a_Q = 7/8 \) represents an upper pressure-flow scaling limit independent of body weight that entails reference scaling laws in Table 1. Under these circumstances, \( X \) represents an arterial tree phenotype of the state of dissipation intensity and network complexity, predicting a unique trajectory of increasing disorder during PH progression under metabolic-hemodynamic steady-state conditions, independent of time, etiology, pathogenesis, individual, or species.

An adverse positive-feedback effect of PH progression is associated with increasing network disorder (\( X > 2, \beta > 1 \rightarrow X < 2, \beta < 1 \)), which acts to progressively amplify shear stress on arterioles to untoward levels (16)

\[
\tau_p = \tau_{\text{MPA}} = 2a_Q(3X^{-1} - 1)
\]

where

\[
\tau_{\text{MPA}} = \frac{4 \mu Q}{\pi (dp/2)^3}
\]

**Hemodynamic measurements:** \( X \) was calculated using the ratio

\[
\psi_{\text{MPA-ref}} = \frac{Q_{\text{MPA-ref}}}{Q_{\text{ref}}} = \frac{Q_{\text{obs}}d_{\text{MPA-ref}}^3}{Q_{\text{ref}}^3d_{\text{MPA-ref}}^3} = \frac{(k_Q)^{-2}(k_d)^{-4}k_G}{(k_Q)^{-2}(k_d)^{-4}k_G}
\]

which is based on Eq. 3, expressing it in terms of cardiac output, MPA diameter, and resistance-gain observed/reference ratios \( k_Q, k_d, k_G \), respectively. Observed values for \( \psi_{\text{MPA-ref}} \) and \( Q_{\text{obs}} \) were taken from retrospective clinical measurements of pulmonary pressure \( P_{\text{PA}} \), cardiac output \( Q \) in ml/min, and body weight \( M \) (kg) made in PH-free and PH subjects, assumed to be in a steady state of energetic rates. The observed diameter was calculated on the basis of a pressure-distensibility relationship:

\[
d_{\text{MPA-est}} = d_{\text{MPA-ref}}(1 + \alpha_{\text{ref}}(P_{\text{PA-obs}} - P_{\text{PA-ref}}))
\]

where \( d_{\text{MPA-ref}} \) is based on the human growth estimates made by Sluysmans and Colan (39) for the entrance to the pulmonary circulation.

The reference arterial distensibility, \( \alpha_{\text{ref}} = 0.02 \text{mmHg}^{-1} \) in the PH-free state, was considered a constant that is independent of mammalian species and animal size (21), whereas \( P_{\text{PA-ref}} = 8 \text{mmHg} \). The gain functions \( G_{\text{obs}} \) and \( G_{\text{ref}} \) are derived from the resistance state dictated by the condition of arterial network organization \( X_d = X_l \)

\[
G_{\text{obs}} = \frac{2n(3X^{-1} - 1)}{2(3X^{-1} - 1)}
\]

\[
G_{\text{ref}} = \frac{2n(3Xd_2 - 1)}{2(3Xd_2 - 1)} = 306.38n = 19
\]

Here, \( X \) is an unknown associated with \( G_{\text{obs}} \), whereas \( X_d = 2.25 \) is for \( G_{\text{ref}} \). The number of generations, \( n \), was evaluated from the morphometric data of Reeves and Noonan (34) (see Morphometric/steerometric measurements)

\[
X = \frac{(3X^{-1} - 1)}{(3X^{-1} - 1)} = 306.38n = 19
\]

and then solving for \( X \) by recursive iteration. Given \( X \), the area ratio was evaluated according to \( \beta = 2^{1-2\beta} \), and the shear stress in the MPA and amplification load on generation \( n = 19 \) arterioles was calculated via Eqs. 14 and 15, respectively, based on the \( Q_{\text{obs}} \). In effect, a subject’s profile values for \( \tau_d, \tau_{\phi_2}, \tau_{\phi_4} \) define an afterload-hemodynamic disease signature of the scaling distance from a hypertension-free reference state of \( (X = 2.25, \beta = 1.08, \phi_2 = \phi_4 = \phi_d = 1) \).

**Morphometric/steerometric measurements.** The number of generations \( (n = 19) \) in Eq. 20 was evaluated from the PH-free controls of Reeves and Noonan (34), which measured internal diameters down to 0.005 cm, along with a morphometric estimate of \( X_d \) in human PAH-free subjects and those diagnosed with idiopathic PAH. Their approach measured the vessel number-diameter volume density \( N \), of arterial diameters in two ranges (0.005–0.030 cm and 0.070–0.300 cm). However, due to the nonrandom manner in which Reeves and Noonan sampled thick lung sections, their estimates of \( N \) density are biased, and their number estimates based on \( N \) lead to nonsensical values for \( X_d \) (11). Alternatively, we substituted the ratio, \( N^\text{small}N^\text{large} = (\text{V}_\text{small}^\text{large})N^\text{large} \), whereas \( N^\text{large} = 2N^\text{large} \), which represents a size, shape, and distribution-free correction (11),

\[
X_d = \frac{\text{d}_{\text{small}}^\text{large}N^\text{large}^\text{large} - \text{d}_{\text{large}}^\text{large}N^\text{large}^\text{large}}{\text{d}_{\text{large}}^\text{large} - \text{d}_{\text{small}}^\text{large}}
\]

Using this correction the values of \( \text{d}_{\text{small}}^\text{large}, \text{d}_{\text{large}}^\text{large}, \text{N}^\text{large}, \text{N}^\text{small} \), we evaluated directly from Fig. 6 of Reeves and Noonan (34) and include three PH-free and three PH subjects.

**Patients.** Hemodynamic data of several patients with diagnoses of PH from WHO groups I-IV were considered from previously published data (Table 3), with additional data kindly supplied by investigators (25–27, 35, 43), which included pulmonary artery pressure \( P_{\text{PA}} \), cardiac output \( Q \), and body mass \( M \) or body surface area (BSA). The study of Lucas and coworkers (29) additionally supplied corresponding values of oxygen consumption that was used to evaluate the hemodynamic-metabolic ratio \( \text{HMPA} \) (Table 4).

In the case of reports reporting only BSA, body mass \( M \) was approximated by the Meeh formula \( M = 10 \times \text{BSA}^{1/2} \). The groups included controls free of PH (C); mitral stenosis (MS WHO group II); chronic obstructive pulmonary disease (COPD WHO group III); chronic thromboembolism (CTEPH WHO group IV); and congenital (CHD-PAH), idiopathic (IPAH), familial (FPAH), collagen vascular disease (CVD-PAH), and methamphetamine exposure (METH-PAH) (all from WHO group I).
Concurrent hemodynamic and metabolic measurements available from references to calculate $\psi_{O2}$ and $I_{\text{ara}}$, for Table 4. PH, pulmonary hypertension; CTEPH, chronic thromboembolism; CG, congenital; COPD, chronic obstructive pulmonary disease; CVD, collagen vascular disease; FPAH, familial pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; METH, methamphetamine exposure; MS, mitral stenosis.

Statistical analysis. For between-subjects analysis, ANOVA was used to evaluate trends of PH progression on the basis of average hemodynamic data analyzed including pulmonary artery pressure (PPA) [H9260/H9274], the external work-rate power ratio for the right ventricle, /H9260/H9274 (n in mmHg), the flow ratio $Q$, and the shear stress in the MPA $\tau_{\text{MPA}}$ (Eq. 14), along with its amplification factor in generation $n$ = 19 arteries as $\tau_{\text{amp}}$, and the change in phase for the study groups (placebo vs. treatment) that was dependent on the magnitude of treatment-placebo trend that was tested for significance if the overall covariance relationship was significant, then the adjusted treatment slope was tested for significance. If the overall covariance relationship was significant, then the adjusted treatment slope was tested for significance. If the overall covariance relationship was significant, then the adjusted treatment slope was tested for significance. If the overall covariance relationship was significant, then the adjusted treatment slope was tested for significance. If the overall covariance relationship was significant, then the adjusted treatment slope was tested for significance. If the overall covariance relationship was significant, then the adjusted treatment slope was tested for significance. If the overall covariance relationship was significant, then the adjusted treatment slope was tested for significance. If the overall covariance relationship was significant, then the adjusted treatment slope was tested for significance.

RESULTS

X-model morphometry. The values of $X_d$ evaluated in six cases from Reeves and Noonan (34) include the following:

Table 3. Hemodynamic data sources (P$_{PA}$, Q, M) | PH-Condition/Diagnosis | WHO Group | N | Source
<table>
<thead>
<tr>
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<th></th>
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</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td>44</td>
<td>(29)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>(25)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>(27)</td>
</tr>
<tr>
<td>CTEPH</td>
<td>IV</td>
<td>10</td>
<td>(25)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7</td>
<td>(25)</td>
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<td>2</td>
<td>(42)</td>
</tr>
<tr>
<td>CG</td>
<td>I</td>
<td>1</td>
<td>(25)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9</td>
<td>(43)</td>
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<tr>
<td></td>
<td></td>
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<td>18</td>
<td>(43)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8</td>
<td>(26)</td>
</tr>
<tr>
<td>METH</td>
<td>I</td>
<td>1</td>
<td>(25)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>(43)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35</td>
<td>(35)</td>
</tr>
</tbody>
</table>

Table 5. Phase categorizations of PH progression via X | Phase | X Range |
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>2.25 $\leq X &lt; 3.00$</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2.0 $\leq X &lt; 2.25$</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1.95 $\leq X &lt; 2.0$</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1.90 $\leq X &lt; 1.95$</td>
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<tr>
<td>5</td>
<td>1.85 $\leq X &lt; 1.90$</td>
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</tr>
<tr>
<td>6</td>
<td>1.80 $\leq X &lt; 1.85$</td>
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<tr>
<td>7</td>
<td>1.75 $\leq X &lt; 1.80$</td>
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<tr>
<td>8</td>
<td>1.725 $\leq X &lt; 1.75$</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>1.70 $\leq X &lt; 1.725$</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>1.675 $\leq X &lt; 1.70$</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>1.65 $\leq X &lt; 1.675$</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>1.50 $\leq X &lt; 1.65$</td>
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before. The change in phase for the study groups (placebo vs. treatment) was evaluated in conjunction with ANCOVA with reference to the baseline state variable (Var = X) that was adjusted for unspecified within-subject adaptations, categorized as either being worse defined by a phase increase Phase/16wk $> 0$, or designated better as defined by a phase decrease Phase/16wk $\leq 0$. The origins of the adaptations were not specified and were assumed either due to chance, previous treatments, the treatment itself, or an uncontrolled progression not responding to concurrent therapy.
case 1, control (male, 10 mo old) $X_d = 2.12$; case 2, control (female, 52 yr old) $X_d = 2.18$; case 3, control (male, 32 yr old) $X_d = 2.13$; case 4, PH-congenital defects (female, 11 mo old) $X_d = 1.65$; case 5, PH-IPAH (female, 29 yr old) $X_d = 1.58$; case 6, PH-CTEPH (female, 18 yr old) $X_d = 1.87$. Additional morphometric data include Horsfield and Woldenberg (19) estimate of a PH-free control derived from three sources $X_d = 2.3$. For vessel lengths in PH disease, Moledina and coworkers (31) evaluated $X_i$ within WHO functional classes I-IV as follows: class I, $X_i = 1.55$; class II, $X_i = 1.56$; class III, $X_i = 1.47$; class IV, $X_i = 1.3$; overall average $X_i = 1.46$. The morphometric-derived values $X > 1.55$ are plotted as white boxes in Fig. 2.

The number of generations for the bifurcating tree model in Eq. 20 was calculated as $n = 19$, evaluated according to $n = X_d \frac{\text{d}_{\text{MPA}}}{0.005}/\log(2)$. Here, $X_d = 2.14$ represents the average of the three case values of the Reeves-Noonan controls. The MPA diameter was assigned $d_{\text{MPA}} = 2.6$ cm, drawn from an allometric-derived value for a 75.4-kg adult via ($d_{\text{MPA-ref}} = 0.514MPA^{0.375}$) (39), consistent with the average mass of the adults of this study (75.4 ± 14.0 SD, $N = 178$).

X-model: between subjects. In the afterload shown in Fig. 2, ANOVA for $X$ was significant ($X: F = 592, R^2 = 0.96, P < 0.0001$), which demonstrated 12 statistically independent phases of progression. The frequency of diagnosis associated with each phase is summarized in Fig. 2E. Morphometric analyses of the Reeve’s-Noonan data from three control and three PH subjects demonstrated corresponding phases consistent with hemodynamic-derived values of $X_d$ and $\beta$.

There were significant changes in afterload with progressive phases in $X$ (Fig. 2, B–D). The diameter ratio (Fig. 2B) demonstrated monotonic increases from the baseline reference state, except during three epochs where $k_d$ was constant while $X$ was concomitantly decreasing (early: phases 3–4, mid: phases 5–6, and late: phases 9–10). The power ratio (Fig. 2C) demonstrated three epochs of constant power dissipation while $X$ was decreasing significantly, with the greatest decrement rate in $X$ observed early. The respective epochs (early, mid, and late) demonstrated statistically significant differences (http://aphp.org by October 15, 2017) between phases, which is statistically equivalent to the clinical definition of PH ($P_{PA} = 25$ mmHg, 95% CI (21, 28)). A mid epoch of elevated, but constant, pressure follows phases 5–6, where $P_{PA} = 35$ mmHg, 95% CI (32, 39), is characterized by a different statistically distinct slope of $\beta$ decrease than the early epoch, and is coincident with mid epoch power ratio (Fig. 3B). During the early epoch (phases 3–4), the slope of $\beta$ vs. phase (Fig. 3D) decreases in a constant fashion while pulmonary artery pressure $P_{PA}$ remains constant between phases, which is statistically equivalent to the clinical definition of PH ($P_{PA} = 25$ mmHg, 95% CI (21, 28)). A mid epoch of elevated, but constant, pressure follows phases 5–6, where $P_{PA} = 35$ mmHg, 95% CI (32, 39), is characterized by a different statistically distinct slope of $\beta$ decrease than the early epoch, and is coincident with mid epoch power ratio (Fig. 3B).
The late epoch of PH [phases 9–10, $P_{PA} = 56$ mmHg 95% CI (53, 59)] was also associated with concomitant significant decreases in $X$ and $\beta$ that were significantly different from the early and mid epochs. Figure 3C indicates that the progressive phases of $\beta$ are associated with a significant decrease in cardiac output but is earmarked by a cyclic pattern of alternating epochs of consistent flow as follows: a significant decrease, then subsequent increase in the next phase, followed by a reduction and sustained average covering more than one phase. This pattern is evident in phases 3–5, 5–7, and 8–12.

The shear stress calculated in the MPA and terminal generation arterioles demonstrates contrasting trends during area ratio regression (Fig. 3, A, D, and E). Significant attenuation in $\tau$-MPA during the early epoch is evident, based on concomitant increases in MPA diameter (Fig. 3B) and decreases in relative cardiac output (Fig. 3C). After phase 4, $\tau$-MPA was not significantly different between phases. In contrast, progressive amplification characterized the state of shear stress on generation in 19 terminal arterioles during PH progression (Fig. 3E) in conjunction with phases of area reduction (Fig. 3A). The amplitudes in the early epoch (phases 2–4) are associated with thresholds consistent with endothelial dysfunction, whereas the mid epoch (phases 5–6) is associated with thresholds and levels earmarking the transition from endothelial dysfunction to a broad range consistent with endothelial damage. The late epoch (phases 9–10) coincides with progressive decreases in $X$ and $\beta$ and a maximum peak-power ratio.

**DISCUSSION**

Our allometric model of pulmonary arterial branching complexity offers novel insight into the PH disease process. Unlike the interpretation of PVR, it utilizes a diameter/length power-law relationship to elucidate a common morphometric-hemodynamic phenotype that delineates PH progression in relationship to apparent hemodynamic steady-state conditions. This study demonstrates five important findings: 1) diverse forms of PH share a common phenotype progression characterized by phases of a monotonic reduction in $X$ ($X > 2 \rightarrow X < 2$) and arterial area ratio ($\beta \geq 1 \rightarrow \beta < 1$) that is independent of etiology and pathogenesis; 2) three epochs of progression are evident (early, mid, and late), each of which takes place under concomitant conditions of hemodynamic homeostasis between phases (pressure, flow, shear stress, and/or power dissipation); 3) the early epoch (phases 1–4 where $X > 1.90$) demonstrates the largest magnitude of reduction in $X$ and $\beta$ under steady-state conditions; 4) arterial area reduction to $\beta < 1$ constitutes a pathophysiological positive-feedback process to blood flow in which shear stress in arterioles is incrementally amplified to magnitudes that may initiate/exacerbate endothelial dysfunction and injury before the onset of PH; 5) Trepostinil intervention forestalls progression when administered at earlier phases ($X > 1.75$) compared with later ones ($X < 1.75$).

PH progression demonstrates a functional-morphometric afterload signature composed of advancing phases of $X$ reduction (Fig. 2A) that are associated with early, mid, and late epochs (Fig. 2D). Corresponding values of $X$ and MPA diameter ratio ($\kappa_d$) identifies an underlying normalized diameter power law $d_n = d_{MPA}^{2-nX}$ representing a hemodynamic-equivalent bi-
funiculating network of \( n = 19 \) generations (Fig. 2B). Each epoch is associated with a constant energy-rate ratio at the entrance to the pulmonary circulation (\( \kappa_{\phi} \)) (Fig. 2C) with the early epoch occurring before clinical definitions of PH and PAH are evident (Fig. 3). This process is not one of an increase in PVR but one of unspecified hemodynamic-metabolic work performed on arterial and arteriolar network organization under steadystate conditions (\( \kappa_{\phi} \approx \) constant), in accord with minimum work-rate/dissipation principles dictated by Eqs. 4 – 6 and 17. In this schema, PH progression decreases the negative diameter power-law slope \( X \) and increases \( d_{\text{MPA}} \), as inferred via a rising \( \kappa_{d} \) under an apparent constant hemodynamic energy rate \( \kappa_{\phi} \approx 1 \) (Fig. 2, B and C). This reduction in slope predicts that the larger arterial vessels will undergo chronic dilation (42) and a morphometric pattern of vascular pathology within smaller arterioles that will concomitantly diminish their diameter and branching topology via area reduction (Fig. 1). The predicted baseline and borderline PH values for \( d_{\text{MPA}} \) are consistent with observed values. In the disease-free state, the model MPA diameter power law adheres to a 3/8 power law (Table 1), which is consistent with the empirical 3/8 scaling law for MPA diameter in cm (\( d_{\text{MPA,ref}} = 0.514 M^{0.375} \)) evaluated during growth (39). For a 70-kg adult, the average value for MPA diameter in the disease-free state as observed in a large population (46) is \( d_{\text{MPA}} = 2.51 \) cm \( \pm 0.28 \) cm (\( N = 3,171 \)). The predicted early significant increases in MPA diameter (Fig. 2B, phases 2–4) are consistent with empirical findings of MPA dilation observed via CT in borderline (24) and progressive stages of PH (13). Lange and coworkers (24) demonstrated that significant MPA diameter dilatation is evident in borderline PH subjects, exhibiting an average diameter of 3.16 \( \pm 0.53 \) SD, which would correspond to a \( \kappa_{d} = 1.26 \) and phase 3 in Fig. 2, and their suggested cutoff to categorize borderline PH of \( d_{\text{MPA}} > 2.9 \) is consistent with a \( \kappa_{d} > 1.16 \) and phase 2. Thus our allometric-hemodynamic model (Eq. 16) is consistent with a spectrum of morphometric deviations of \( X \) in several epochs of PH (early, mid, and late) and consistent with the approach of Lange et al. (24) as a means for discriminating early phases of PH progression, which may be useful for purposes of early detection and therapeutic intervention (24, 31, 42).

The pruning process of PH, visually apparent in radiographs and CTs in various phases of PH (Fig. 1) (12, 31), is evident in our model as a functional reduction in \( X_{d} = X_{l} \) operating to minimize hemodynamic power dissipation to match the metabolic rate (Fig. 1). A question arises as to whether the pruning process we proposed represents a common morphometric-hemodynamic coupled modality universal to all diverse forms of PH over all phases. Our initial rationale for assuming \( X_{d} = X_{l} \) reduction in the hemodynamic model was that the theoretical predicted reference state identifies this condition as one for maximum pressures in a disease-free state independent of body weight and species (Table 2, Eqs. 10, 12 at rest). Under physiological conditions, the assumption \( X_{d} = X_{l} \) does not hold strictly for transient acute vasomotor changes, such as those induced by intense abnormal vasoconstriction via endothelin-1, where diameter is affected first, decreasing the bifurcation exponent to \( x < 2 \), whereas the exponent for length remains unchanged (18). However, as indicated by Fig. 1, if this condition remains imposed in a chronic way while \( X_{d} \) decreases, the overall work rate for a given flow at the entrance is elevated compared with an alternative adaption had the effective daughter lengths been compensated instead by obstruction. Alternatively, as this figure also illustrates, diameter-length obstruction together mitigates hydraulic power-dissipation intensity if daughter and lengths scale together to achieve minimum dissipation for the network \( x_{d} = x_{l} \) or \( x_{l} = (2/3)x_{d} \). This suggests that pruning of combined length/diameter network elements together represents a paradoxical afterload-adaptive strategy that diverts blood flow to low-resistance pathways in an effort to optimize ventilation/perfusion matching, while also minimizing the rate of energy dissipation while regulating capillary pressures (8–10). Unfortunately, morpho-
metric methods and necessary data to evaluate concomitant samples of \( X_d \) and \( X_l \) in humans are nonexistent to verify this premise at present. However, separate analysis of diameter and length power laws provides insight. Figure 2 summarizes the range of morphometric-derived \( X_d \) in the PH-free subjects, and alternative origins of PH morphometric-derived reductions in \( X_d \) are supported by Reeve and Nolan’s (22) diameter power law data measured in the lungs of patients who have died from PH. Recently, Moledina and coworkers (31) demonstrated reductions in the topological fractal dimension of CTS of pediatric patients with congenital heart diseases (31), which were skeletonized to vessel lengths. Their dimension, evaluated with respect to lengths distributed in the pulmonary vascular volume, is theoretically consistent to our \( X_l \). Although disease-free controls were not evaluated, they demonstrated that WHO class I-II patients exhibit similar dimensions, whereas class III-IV patients showed significant reductions to values comparatively smaller than those we observed for diameter morphometrically. Thus both diameter and length are reduced, consistent with the radiological appearance of vascular pruning during PH progression but likely at different rates in the tree remodeling process. Despite this limitation, our assumption of \( X_d \sim X_l \) represents an approximation that is an energetic rate-favorable one, applicable to early phases (Fig. 1).

Our results indicate that the most significant epoch of arterial area reduction appears early before the emergence of the clinical definition of PH (Fig. 3A). In this regard, changes in network topological organization and complexity represent a more sensitive functional index of PH progression. This resolution into phases of PH progression is based on arterial branching complexity and Thoma’s framework of a metabolic-hemodynamic steady state (Table 1), whose underlying power laws are likely more functionally sensitive to arteriolar area ratio changes, as opposed to arteriolar diameter changes when evaluated by pulmonary artery pressure or PVR. For example, PH is confirmed by right heart catheterization on the basis of a P/Q equal to three Wood units. Again in the PH state, and the value of \( X_d \) is significantly reduced relative to the control (shunt \( X_d \sim 1.73, \beta = 0.897, \) vs. control \( X_d \sim 2.02, \beta = 1.007 \)). The significance of the power law-based PH process revealed in their study was that the global reductions evident in \( X_d \) are due to the impact of regional local average ones occurring in arterioles via increased smooth muscle thickness encroaching on the corresponding area ratios \( \beta \) before PH was evident. Thus it is important to emphasize that the area ratio reductions by vascular remodeling appear before PH emergence.

PH progression by branching complexity and arterial network disorder, regardless of cause, exacerbates an unstable positive-feedback influence that likely contributes to endothelial dysfunction, disruption, and injury by concomitantly attenuating shear stress in large arteries and amplifying shear stress in small arterioles (Fig. 3, D and E). Vascular remodeling leading to PH is thought to result from a “multiple hit” model of cause, where a genetic susceptibility is first required, that is then followed by mechanistic pathways leading to arteriopathy that reduce diameter and increase PVR (30). Recently, epigenetic mechanisms that are responsive to shear stress and inflammation (47) have been implicated in the regulation of vascular tone and the pathogenesis of PH (20). Our results emphasize that the afterload changes we observed utilizing this model, as discussed earlier (large artery dilation and arteriolar area ratio reduction), represents a progressive positive-feedback disturbance to the endothelial-shear stress environment of the pulmonary circulation for which epigenetic mechanisms would be expected to exacerbate PH progression (Figs. 2–3) (47). For example, Fig. 3D indicates that the shear stress experienced in the MPA and large arteries is significantly reduced in the early phases of progression (phases 1–3) and reaches a steady state by phase 4. Tang and colleagues (42) recently inferred the same phenomena in the left and right pulmonary artery, with amplification to small artery vessels, utilizing their analysis of the branching geometry captured by the MRIs of controls and PH subjects. In essence, the large artery afterload reduction in PH subjects significantly reduced the average arterial shear stress to near stagnant levels, which when combined with endothelial dysfunction and damage, may contribute to a positive-feedback inflammation-injury process akin to atherosclerosis (37). In contrast, the arteriolar area ratio decrease with progressive PH transforms arterial network organization into a high-gain shear stress amplifier (1, 3, 16), in which the magnitude of arteriolar shear stress loaded onto arterioles demonstrates critical thresholds before dysfunction, followed by endothelial damage (33) (Fig. 3C). In the context of our analysis, shear stress does not represent an initiating
factor of PH (23); instead the amplitude of arteriolar shear stress should be interpreted as an index of the integrative positive feedback inherent in PH progression. For example, Dereddy and coworkers (28) recently found that the small arterioles in infants with PH arising from high-flow/low-flow congenital heart disease, bronchopulmonary dysplasia, or respiratory distress exhibit discriminatory patterns of endothelial dysfunction, injury, and smooth muscle proliferation and were dependent on the hemodynamic stimulus of elevated shear stress and/or inflammation. Consequently, increasing arterial network complexity/disorder chronically redistributes forces in large and small arteries, in which early transduction may translate into metabolic processes promoting proliferation and/or inflammation (40, 41).

The principal limitation of the power-law approach in its current form is that it is based on invasive hemodynamic measurements of pulmonary pressure and flow obtained via right heart catheterization in a limited number of PH-free and PH subjects (N = 221). Improved clinical discrimination and resolution between phases with greater statistical power would be facilitated by including data from registries composed of thousands of PH-free and PH subjects. However, invasive measurements are presently used to confirm PH diagnosis only and not intended for early screening. In this study, the intent of our method was to interpret the PH adaptive/maladaptive processes in terms of a simple allometric predictive model beyond PVR that could be applied to retrospective studies in which morphometric-hemodynamic data were already available. Despite these shortcomings, our model emphasizes and supports that global principles of steady-state physiology govern pathological processes masked in branching complexity and arterial scaling (8, 9, 44, 45), which apply to, not only humans, but also experimental mammalian models of the disease, independent of PH etiology and pathology. Alternatively, noninvasive inferences of diameter/length power-law behavior via impedance or flow waveform reflection measurement in the pulmonary artery, which enable values of X or arterial area ratio to be similarity calculated via inverse-scattering models, may fill this gap (2, 3). In this regard, retrospective and prospective studies utilizing a greater number of subjects that compare both invasive and noninvasive hemodynamic methods, in combination with morphometric/stereological approaches that delineate power-law relationships on the basis of vasculopathy populations earlier in the disease process (40) remain necessary to establish the discriminatory capability and resolution for early clinical detection (24).

The analysis of hemodynamic data from patients with PH obtained from the Trepostinil trial (Freedom-C trial) (43) suggests advantages of our model for early diagnosis and intervention (Fig. 4B). Our statistical analysis allowed us to determine whether an observed increase or decrease in \( X \) over the 16-wk trial period was present on the basis of prior therapy, the present therapy, or due to chance via \( \Delta bA_I \). This analysis indicates that patients characterized as having early phases of PH progression (phase 3: \( 1.90 < X \leq 1.95 \)) are the most responsive to treatment. Placebo-treated subjects demonstrated an aggressive progression by two to three phase increments over 16 wk, whereas Trepostinil-treated subjects from the same initial baseline did not change phase at all, indicating a protective-staving effect. However, both placebo and treatment group subjects starting the study at more advanced phases (phase 7: \( 1.75 < X \leq 1.80 \) or greater) demonstrated little or no change in phase. This apparently contradictory behavior is consistent with the PH phases delineated in Figs. 2A and 3A; earlier epochs of PH progression demonstrate phase changes of significantly greater area reductions than those demonstrated by later epochs. Thus, whereas the previous analysis of the Freedom-C study did not demonstrate a functional significant end point defined by an improvement of the 6-min walk (43), the reinterpretation of the clinical hemodynamic data suggests a significant drug action on arterial network organization whose effectiveness is enhanced in slowing disease progression by interventions at earlier phases of diagnosis. Figure 4B indicates that, despite the overall trend of subjects that were most likely to advance to progressive phases of the disease (Fig. 3A), there was a significant difference over the 16-wk time period when the treatment and placebo groups were classified into subgroups as either improving or becoming worse. Of those that became worse, the placebo group with the greatest increase in phase progression occurred in those subjects starting the study at earlier phases. In contrast, for those treatment and placebo subgroups that were classified as better, thereby increasing their area ratios, their response may represent a different baseline state of endothelial function and inflammation. This suggests a simple method to profile responders and nonresponders to therapy in PH progression in the early epochs; the direction of change in area ratio induced by a perturbation, such as exercise, associated with proliferation/inflammation biomarkers may be predictive of downstream positive-feedback mechanisms (12, 20, 40, 41).

In conclusion, our study suggests a common trajectory for arteriolar vascular remodeling in diverse forms of PH. This novel paradigm may alter our classification, intervention, and diagnostic approach with clinical populations that, to date, have not been thought of to share a common ground. The ability to diagnose at-risk populations at a stage of disease that is clinically silent offers the hope of preventing clinical deterioration, as suggested by the results of the early trial (15, 38). Last, our analysis of the data from the Trepostinil trial (Freedom-C trial) (43) offers a new understanding that interventions may have quite variable effects depending on the severity of disease of the study population that is not apparent through traditional hemodynamic techniques. This may serve as a valuable end point to guide future trial development.

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.

**AUTHOR CONTRIBUTIONS**

REFERENCES


