Conduit Arteries in Small and Large Mammals Express Different Material Property Changes in Response to Hypoxia-Induced Pulmonary Hypertension

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Hypothesis: *Rat conduit pulmonary arteries remodel and stiffen in pulmonary hypertension through a more collagen-dependent mechanism compared to calves or humans.*

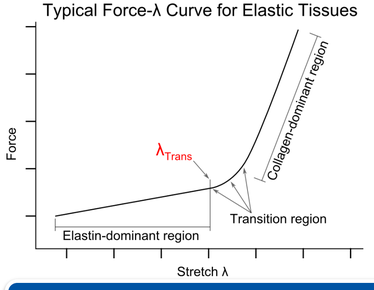
Objective

To determine how **inter-species differences** in vascular remodeling, due to pulmonary hypertension (PH), **affects the material properties** of the great pulmonary arteries (PAs).

- Artery morphology is more complex in large mammal PA tissue than in smaller rodents (rat, mouse)[1].
- Differences in PH vascular remodeling between small mammals (rat), large mammals (calf), and humans have not been investigated directly.
- Understanding these differences is important because:
  - Need to know the **limitations of the animal models** used in the study of PH vascular stiffening.
  - Inter-species differences **provide insight into how individual artery components influence the behavior of the composite tissue**.

Background

- Arteries have a non-linear Force-λ response to applied loads.
- Transition stretch (λ_{Trans}): stretch at which collagen begins to become engaged and able to carry load.
- $\lambda < \lambda_{Trans}$: Elastin mechanics responsible for low-stretch behavior.
- $\lambda > \lambda_{Trans}$: Collagen mechanics dominant at high-stretch.



$$\lambda = \frac{L_{Deformed}}{L_{Gage(original)}}$$

Fig. 1 Typical artery F-λ curve.

Methods

Animal models

- Rat: 10-Cont, 10-PH, ***hypobaric hypoxia***, 21d 430mmHg, age 10wks ±1wk
- Calf: 8-Cont, 11-PH, ***hypobaric hypoxia***, 14d 430mmHg , age 16d ±1d.
- Human: 3-Control, 7 PH, both **Idiopathic and Secondary PH grouped**, age < 19 yr, (not all tissues available for all patients).

Uniaxial force-stretch testing

- MTS Insight 2, materials testing system. Tested force-stretch response of circumferential tissues strip-sections under uniaxial load.

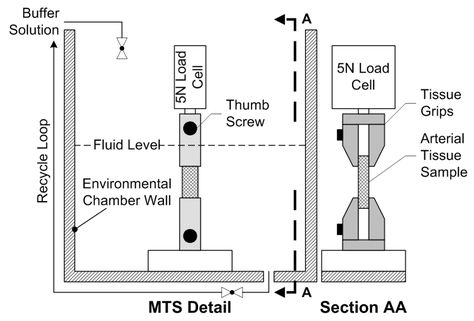


Fig. 2 Detail of material testing apparatus

Transition stretch calculation

- Calculated from the curvature (κ) of F-λ curve[2]

$$\kappa_{Trans} = \kappa_{PSS} + \frac{\kappa_{max} - \kappa_{PSS}}{100}$$

- κ_{PSS}: Avg. pre strain-stiffening $\kappa(\lambda_{PSS})$

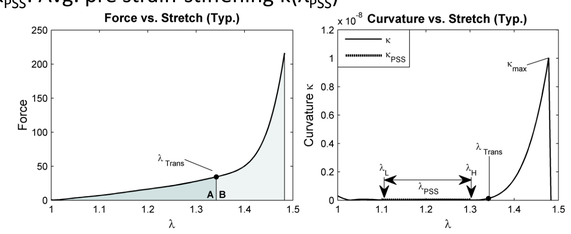


Fig. 3 Left: typical F-λ behavior of PA tissue, λ_{Trans} is the transition stretch which demarcates the elastin dominant (A) from the collagen dominant (B) region. Right: typical curvature plot of PA tissue

Results

- PH caused a **significant decrease in rat λ_{Trans}**
  - $\lambda_{Trans, RPA}$ = 1.80 ± 0.34 (Cont) → 1.48 ± 0.11 (PH)
  - $\lambda_{Trans, MPA}$ = 1.87 ± 0.25 (Cont) → 1.43 ± 0.16 (PH)
- **Calf and human PA tissues show no change in λ_{Trans}** due to PH remodeling.

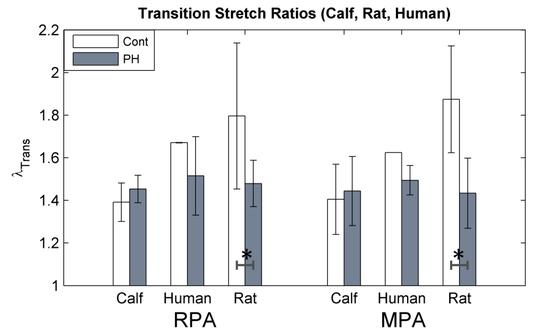


Fig. 4 λ_{Trans} in RPA, MPA of different species.
(*: Significant difference ANOVA-Tukey, p<=0.05, Error Bars ±SD)

- PH caused **consistent elevation of tissue stiffness** measured within the elastin dominant region.
  - Stiffness = slope(F-λ) within elastin-dominant region

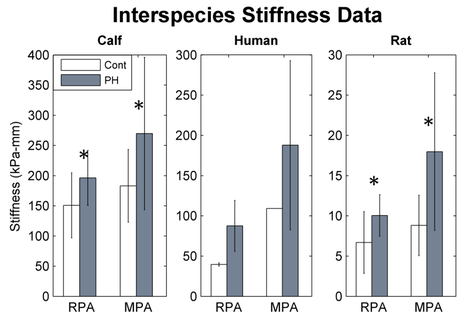


Fig. 5 Stiffness of RPA, MPA of different species. Calculated within elastin dominant region. (*: T-test p<= 0.05, Error Bars ±SD)

Discussion

- **Calves and humans** remodel through a more *elastin-dominant mechanism* in response to hypoxia-induced PH.
- **Rat** PA tissues remodel through a more *collagen-dependent mechanism*.
- **Leftward shift of λ_{Trans}** results in *increased collagen dependence* of physiologic hemodynamics in rat model and substantiates the claim that **rat** PH vascular remodeling is *dominated by collagen mechanics.*

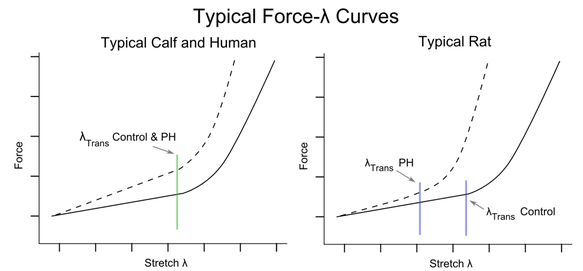


Fig. 6 Typical changes in PA F-λ curves due to PH remodeling in large and small mammals.

Conclusions

- PA vascular remodeling demonstrated **significant inter-species differences in λ_{Trans}**: measured as the deformation needed to initiate collagen engagement and load carrying.
- The lack of change in λ_{Trans} in the **large mammals** suggests that PA vascular remodeling occurs through more *elastin-dominant mechanisms.*
- PA **vascular remodeling in large mammals (calf, human) acts to better preserve cardiovascular windkessel function** than the remodeling of small mammal (rat) PA tissues.

References

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2. Lammers SR, et al. Am J Physiology-Heart and Circulatory Physiology 2008;295(4):H1451-H1459

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