IMPACT OF ELASTIN BIOMECHANICS ON PROXIMAL ARTERY STIFFNESS IN PULMONARY HYPERTENSION

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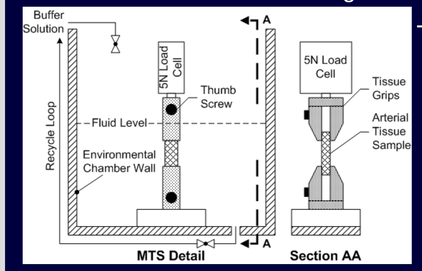
•**Problem**: Pulmonary vascular stiffness (PVS) is strongly correlated with the clinical outcomes of pulmonary arterial hypertension (PAH) and accounts for 30% to 40% of increased cardiac workload. [1]

•**Hypothesis**: Changes in the functional mechanical properties of elastin is one of the primary causes of the increased stiffness seen in proximal PAs due to hypoxia-induced PAH.

Methods:

•Animal model
- 3-Control, 6-Hypertensive male Holstein calves (2-wks)
- Hypertension induced by hypobaric hypoxia, 2-wks, 430 mmHg

•Uni-axial stress-strain testing



- MTS, Insight 2, material testing system used to test stress-strain response of circumferential tissue sections under uni-axial load

Fig. 1 Detail of material testing apparatus

•Elastin Purification
- Elastin was purified from pulmonary arteries using CNBr-formic acid digestion. [2]

•Morphology
- Artery thickness measured with digital calipers at 8 points for each tissue
- Elastin area fraction determined using image processing of VVG-elastin stained tissue sections (Matlab)

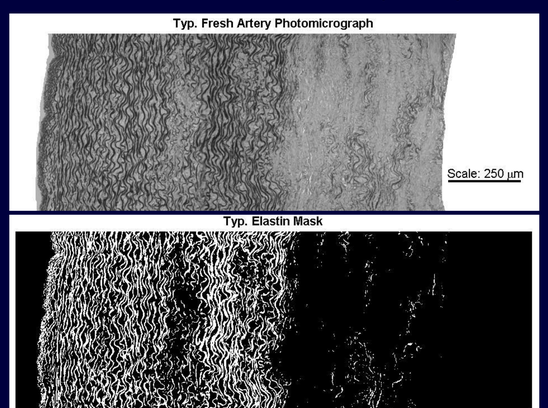
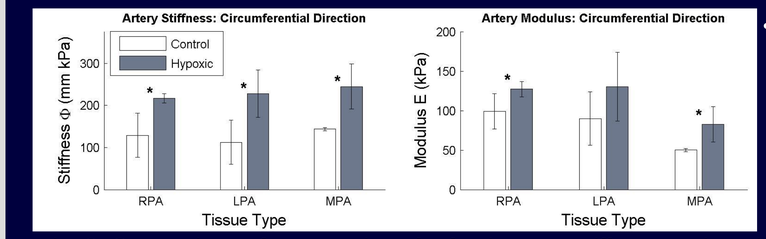


Fig. 2 Typical artery and elastin mask

Results:

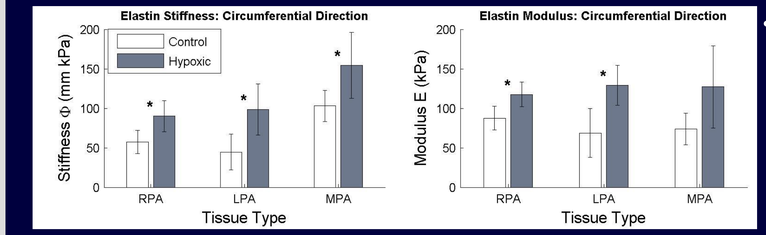
•Morphology
- 28% average increase in tissue thickness due to hypertension
- 16% average decrease in elastin area fraction due to hypertension
- 7% average increase in elastin content due to hypertension

• Material properties: Calculated at 35% strain



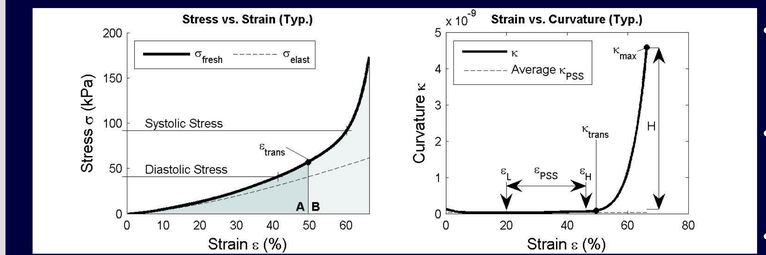
- Average results for arteries
  - 81% increase in stiffness (σ=23%, p << 0.05)
  - 46% increase in modulus (σ=13%, p = 0.02)

Fig. 3 Comparison of mean values for fresh artery stiffness and modulus



- Average results for elastin
  - 72% increase in stiffness (σ=33%, p = 0.01)
  - 65% increase in modulus (σ=28%, p << 0.05)
  - 48% of arterial load is carried by elastin, at a minimum

Fig. 4 Comparison of mean values for elastin stiffness and modulus

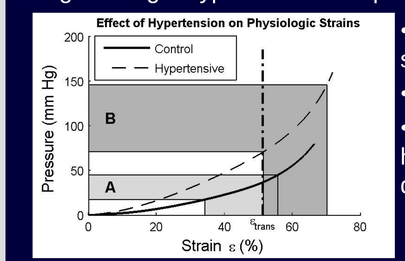


•Average diastolic strain
- 34% for control tissue
- 53% for hypertensive tissue

•Average systolic strain
- 59% for control tissue
- 72% for hypertensive tissue

•Average transition strain = 50%

Fig. 5 Left: typical behavior of fresh and elastin tissue, σ_{trans} is the strain of transition from the elastin dominant (A) to collagen dominant (B) region. Right: typical curvature plot of fresh tissue



- Increased pressures, due to hypertension, shifts physiologic strains to higher values
- The transition strain (ε_{trans}) is unaffected by hypertension
- Shift of the physiologic strain range to higher strains causes the hypertensive stress-strain response to operate outside the elastin dominant region
  - Increased strain stiffening leads to reduced physiologic strain range

Fig. 6 Physiologic region of the stress strain curve. Control stress-strain region labeled (A), hypertensive region (B) .

Results: Physiologic material properties

•PAH causes
- Significant elevation in both systolic and diastolic stiffness.
- Increased diastolic to systolic stiffness ratio.
- Decreased percent load-carrying capacity of elastin.

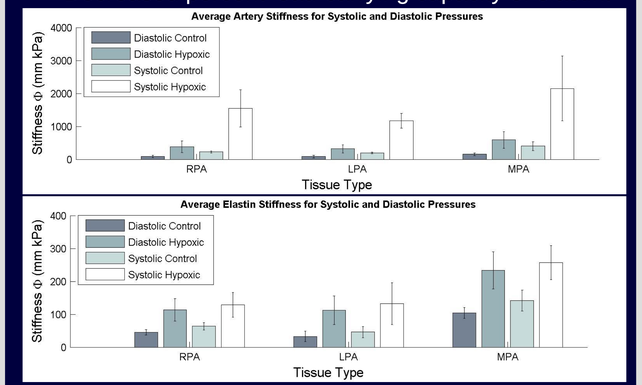


Fig. 7 Average systolic and diastolic stiffness for control and hypertensive tissues

Average physiologic stiffness change					Average elastin load	
Fresh Tissue	$\Phi_{Dias,\ Cont\ to\ PAH}$	293%	Elastin Tissue	173%	$\%Fn_{Dias,\ Cont}$	61%
	$\Phi_{Sys,\ Cont\ to\ PAH}$	510%		123%	$\%Fn_{Dias,\ PAH}$	48%
	$\Phi_{Cont,\ Dias\ to\ Sys}$	145%		39%	$\%Fn_{Sys,\ Cont}$	48%
	$\Phi_{PAH,\ Dias\ to\ Sys}$	278%		14%	$\%Fn_{Sys,\ PAH}$	32%

Table 1: Average values for physiologic stiffness change and percent elastin load-carrying capacity.

Conclusions:

•Mechanobiological adaptations of the continuum and geometric properties of elastin, in response to pulmonary hypertension, significantly elevate the circumferential stiffness of proximal pulmonary arterial tissue.

• Hypertension elevates the physiologic strain and causes the stress-strain response to operate outside the elastin-dominant stress-strain region. Although this results in increased collagen recruitment at systole, diastolic stress remains elastin-dependent.

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1.) Mahapatra S, et al. (2004). " Relationship of pulmonary arterial capacitance and mortality in idiopathic pulmonary arterial hypertension. J Am Coll Cardiol 47: 799-803.

2.) Lu Q., Ganesan K., et al. (2004). "Novel porous aortic elastin and collagen scaffolds for tissue engineering." Biomaterials 25: 5227-5237.