



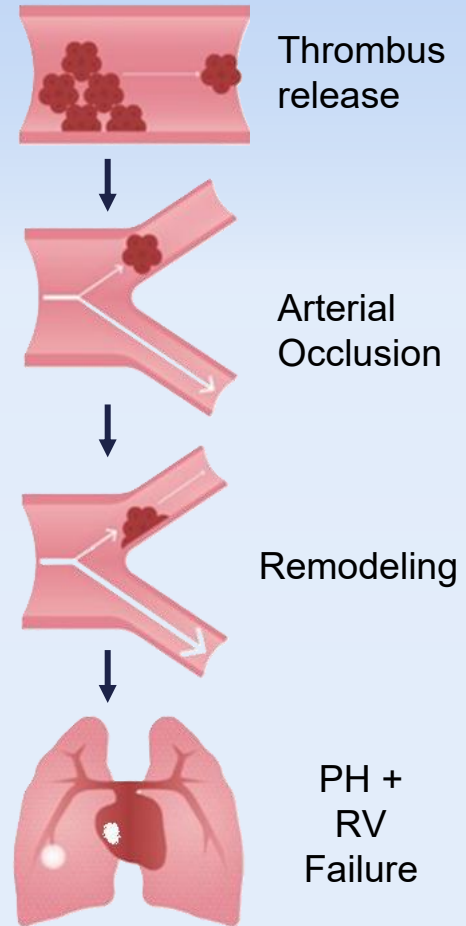
Angiogenesis May Compensate Vessel Occlusion to Mitigate CTEPH Severity

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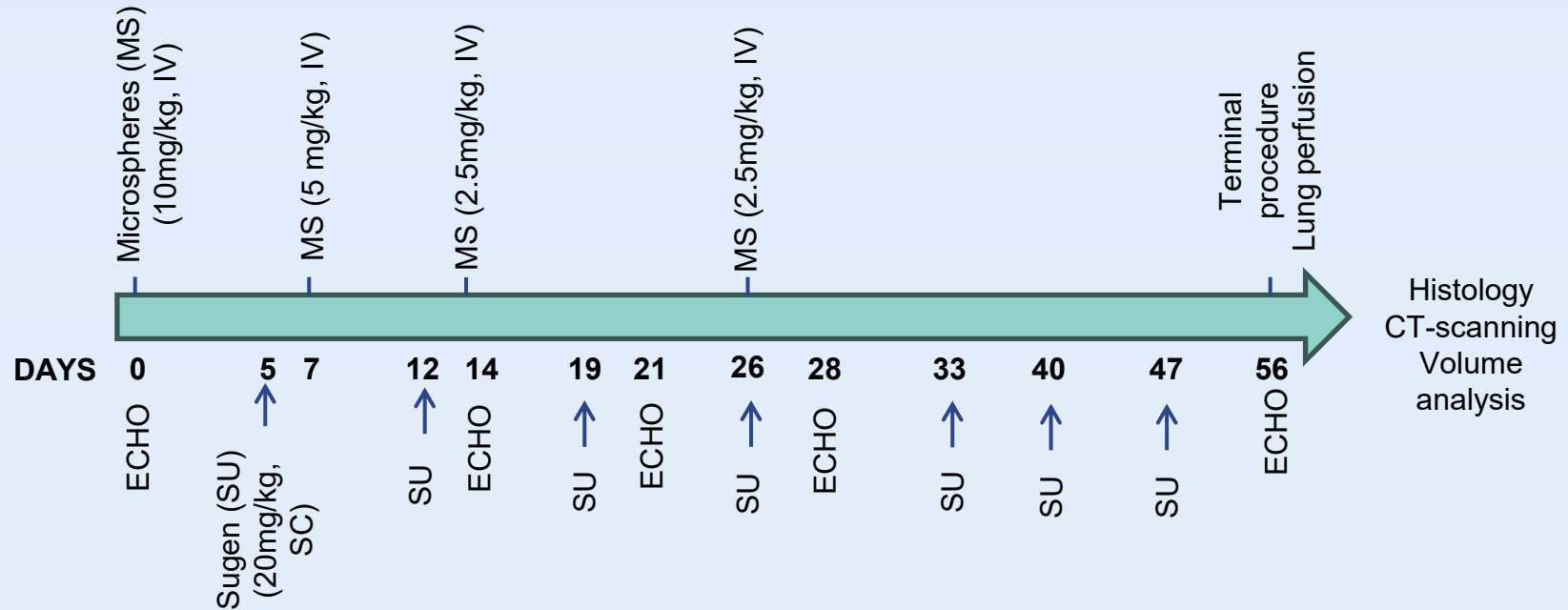
Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

- mPAP ≥ 25 mmHg (2018: 20 mmHg)
- Pulm. Vasc. Resis. (PVR) ≥ 3 WU (Wood units)
- Pulm. Artery Wedge Press. (PAWP) ≤ 15 mmHg
- May result from pulmonary embolism
- Persists despite 3 mo. of anticoagulants
- Non-resolved thrombus $\rightarrow$ remodeling + fibrosis
 $\rightarrow$ impairment of blood flow in the pulmonary arterial bed $\rightarrow$ PH.



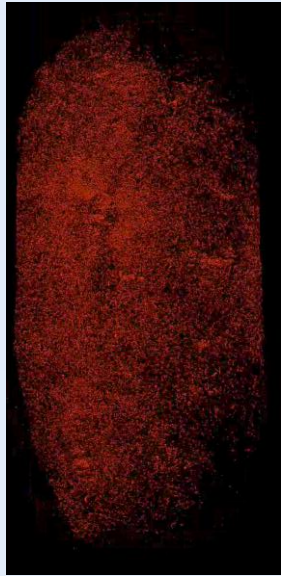
PAH Type IV induction

We validated the effect of 20-50 μm -microsphere injections combined with SU5416 in rats and used micro-CT to characterize the vascular remodeling.

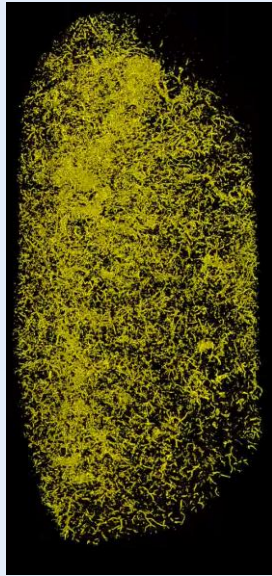


Micro-CT scans of the pulmonary pre-capillary vasculature

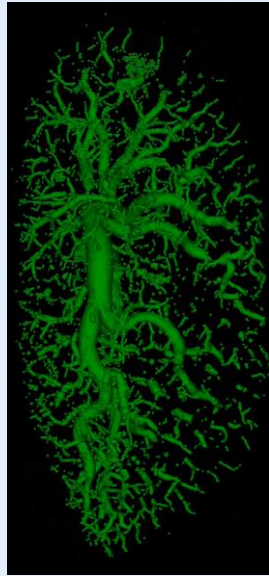
The left lobe of the lungs was perfused with MicroFil© and imaged by micro-CT. The vessels were separated in 3 groups based on size. Composite images are presented.



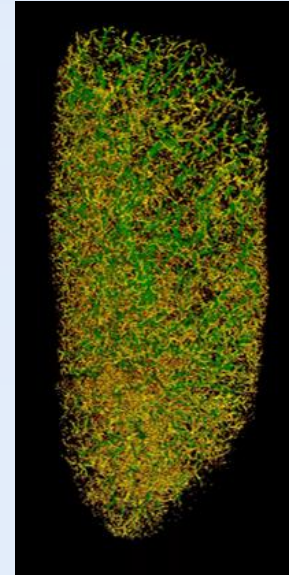
20 – 50 μm



50 – 100 μm



>100 μm

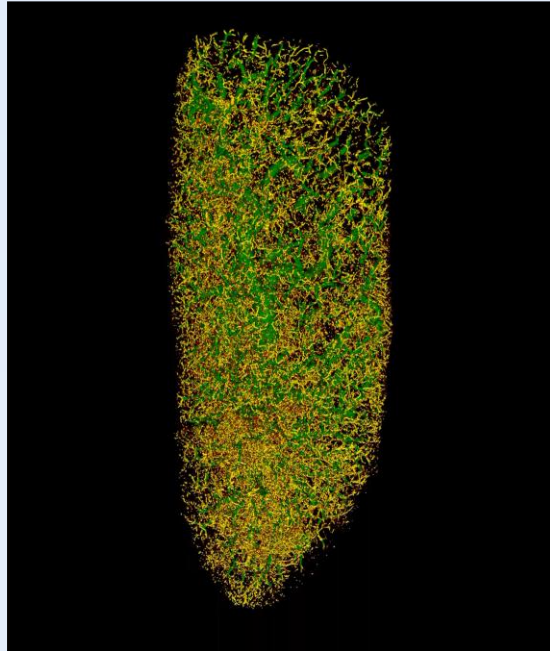


20-50 μm
51-100 μm
 ≥ 100 μm

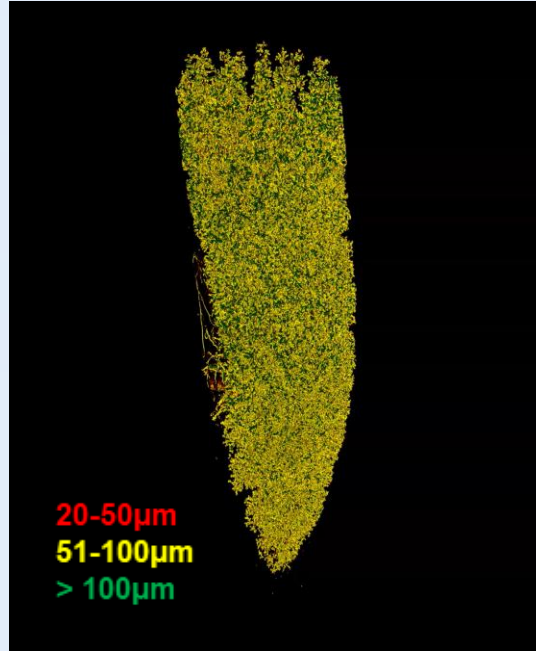
Pulmonary Arterial Remodeling

Composite images show greater vessel density in MS rat lungs, and significant pruning of vessels in MS+SU rat lungs compared to healthy animals.

Sham



MS



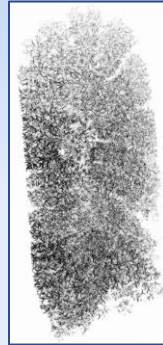
MS + SU



Microsphere Injections → Angiogenesis



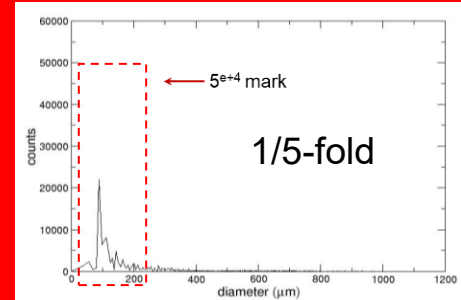
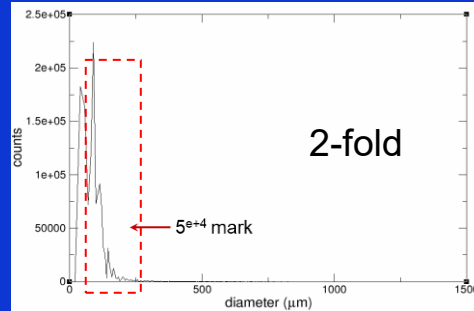
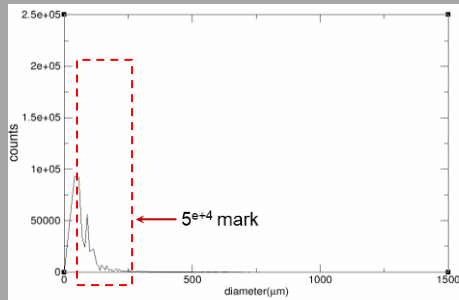
Sham



MS

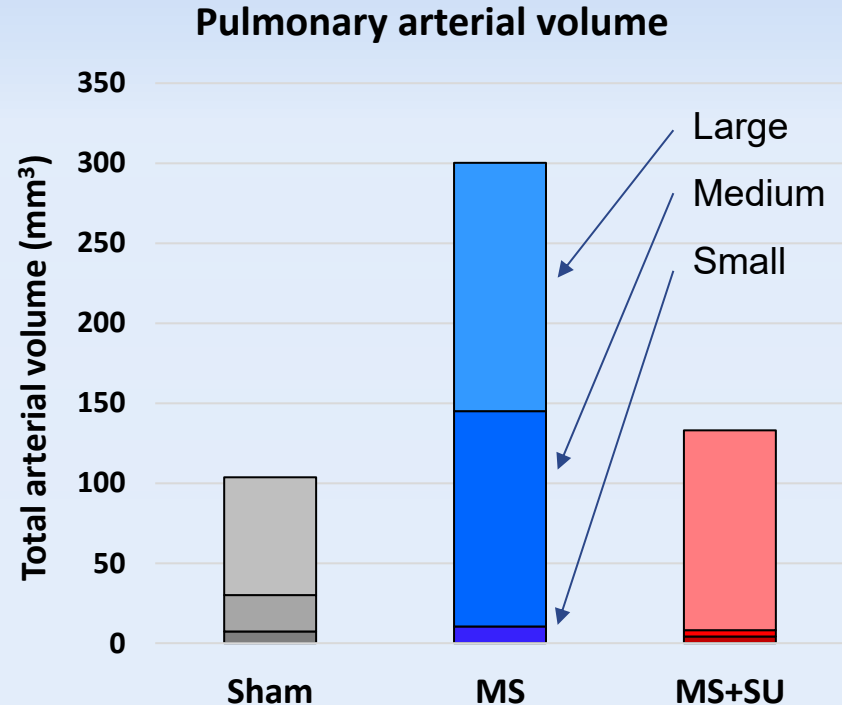


MS + SU



Angiogenesis Increases Pulmonary Arterial Luminal Volume in CETPH

Compiling pre-capillary, pulmonary volume density reveals a significant increase in medium- and large-size vessels in MS rat lungs, while only large vessels remain visible in MS+SU.



Day 56 Hemodynamics Assessment

The “pruning” of small vessels in MS+SU leads to significant RV afterload, with unchanged systemic pressure.

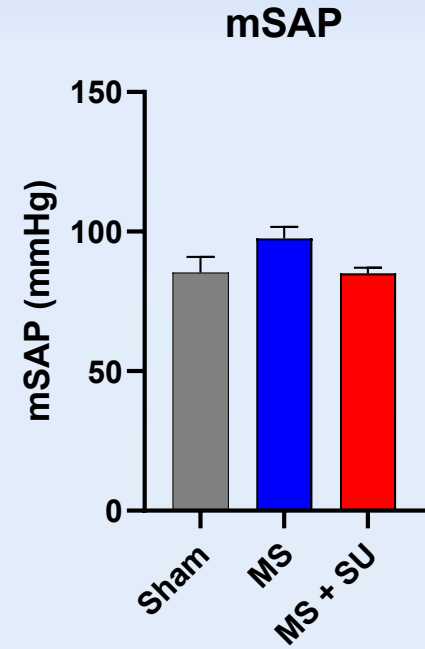
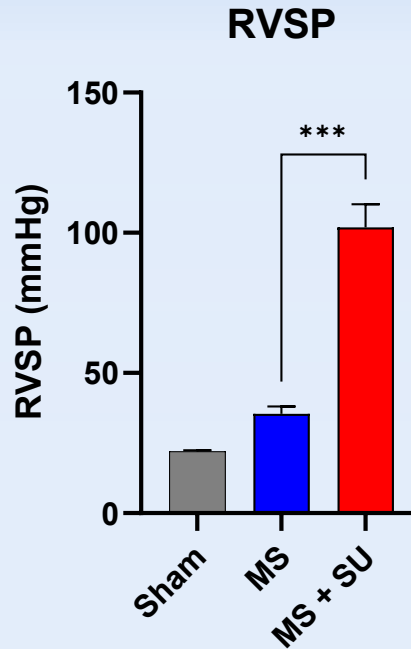
Adult Sprague Dawley male rats

n = 5 per group

Sham: Healthy 22 mmHg RVSP

MS: Microspheres 35.4 mmHg

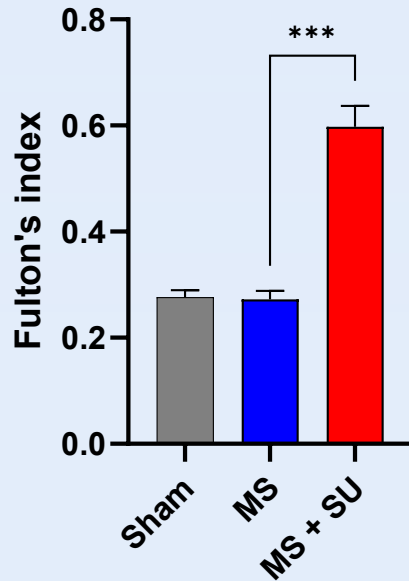
MS+SU: MS + Su5416 102 mmHg



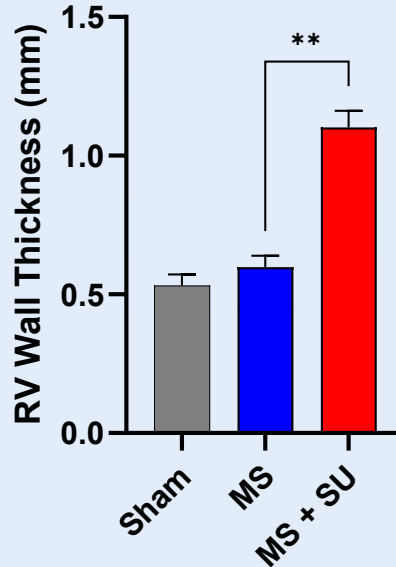
Cardiac Remodeling in CTEPH

Significant RV thickening and dilation result from pulmonary capillary pruning and hypertension.

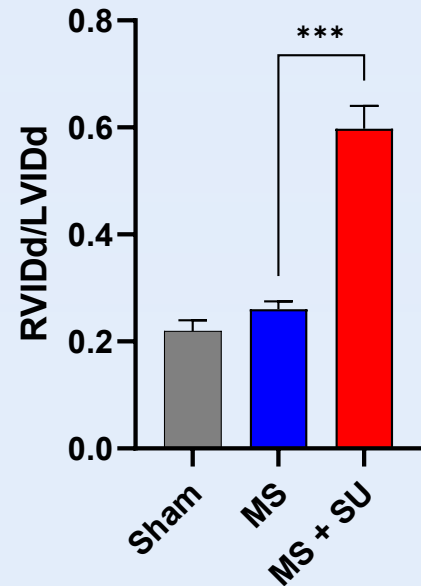
Fulton's Index



RV Wall thickness



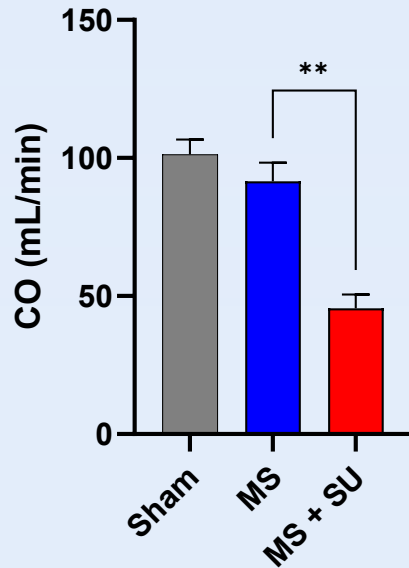
RV Dilation



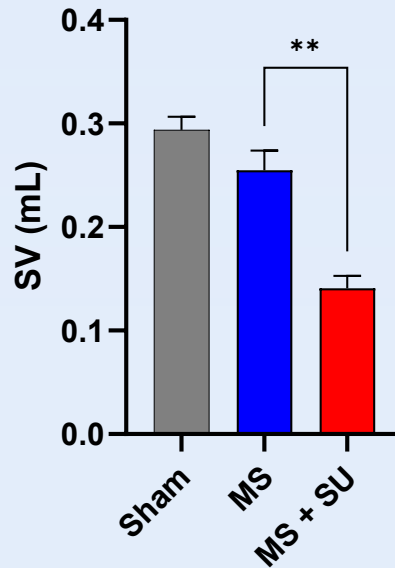
Reduced Cardiac Function

CTEPH leads to RV remodeling which is gradually progressing into early signs of RV failure.

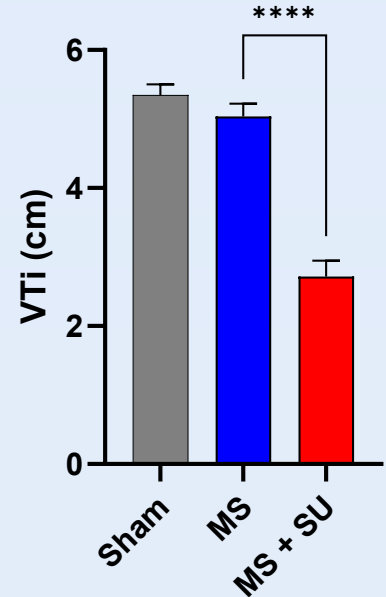
Cardiac Output



Stroke Volume

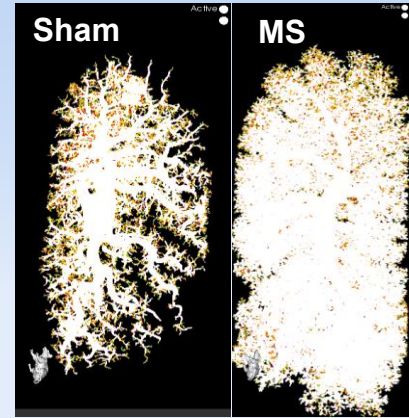


Velocity Time Integral



Key findings

- This robust animal model exhibited CTEPH-like features:
 - Capillary rarefaction (pruning)
 - Pulmonary hypertension (RVSP = 103 mmHg)
 - RV remodeling (Fulton: + 116%)
 - Early signs of heart failure
- Transient occlusion of vessels with microspheres triggers angiogenesis which **doubles** vessel numbers and vascular volume.
- Enhancing angiogenesis in pulmonary arteries smaller than 150 μm in diameter may represent a promising therapeutic strategy for CTEPH.
- Blocking VEGF-driven angiogenesis with Su5416 enhances the severity of the pulmonary microvascular occlusions leading to hypertension.



Thank you!



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Stéfan Daudelin
Judy Légaré
Charles-E. Laurent
Dany Salvail



Centre universitaire
de santé McGill
Institut de recherche



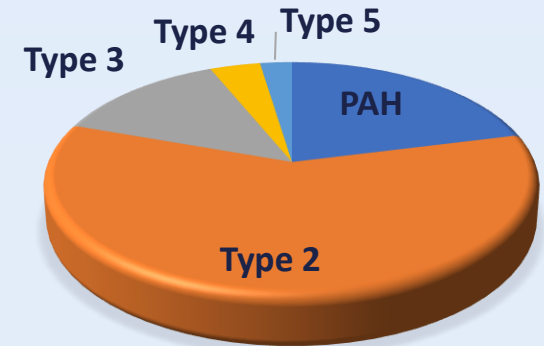
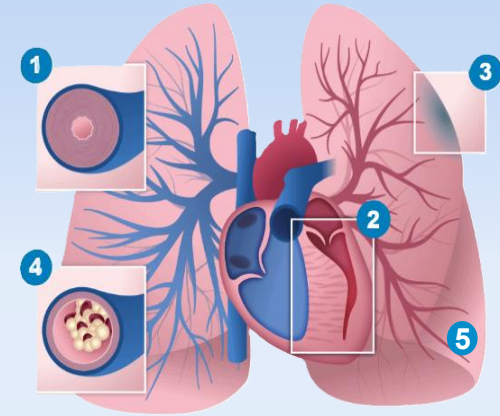
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Research Institute

Questions?

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Types of PAH and their animal models

1. PAH **MCT++** or **SuHx**,
2. PH due to left heart disease **TAC**
3. PH due to lung diseases and/or hypoxia **SuHx**, **CHx**, **CigSmoke**, **BLEO**
4. PH caused by pulmonary artery obstructions
5. PH with unclear and/or multifactorial mechanisms

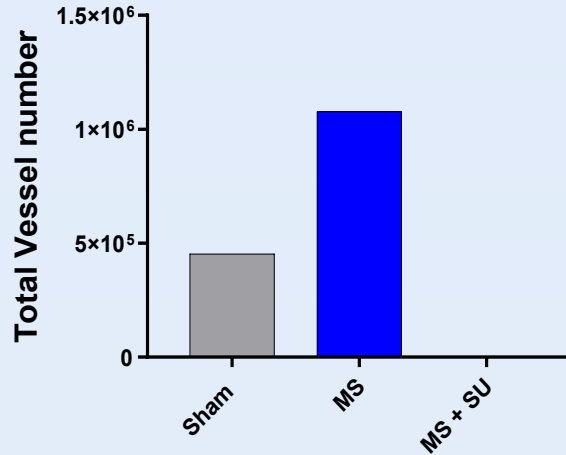


Harikrishnan S, et al. Int J Cardiol. 2018; 265: 212– 217.

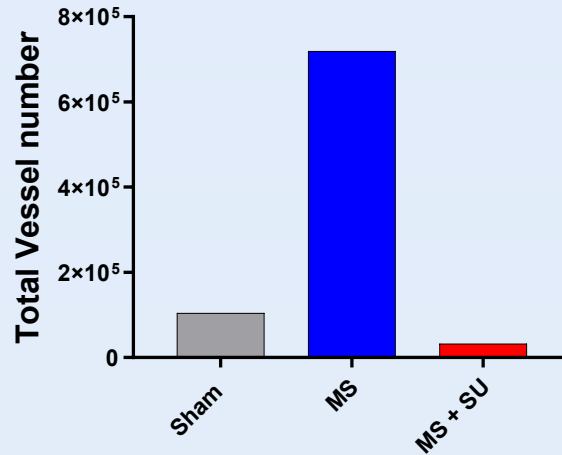
Microspheres + Su5416 → pruning of vessels

MS triggers a significant increase in vessel numbers while small vessels are either completely obstructed, or obliterated in MS+SU rat lungs.

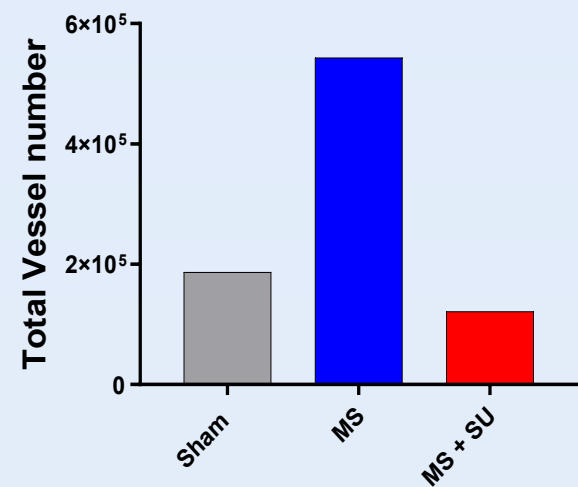
20-50 μm Lumen Diameter



50-100 μm Lumen Diameter



$\geq 100 \mu\text{m}$ Lumen Diameter



Normalized Vascular Lumen volume in CETPH

