Biology, form and function of the pulmonary vasculature

David B. Frank, MD, PhD
Assistant Professor of Pediatrics
Division of Pediatric Cardiology
Perelman School of Medicine at the University of Pennsylvania

CHOP-PennCVI
Cardiovascular Institute

Penn-CHOP
Lung Biology Institute

Pulmonary Vasculature: Aims

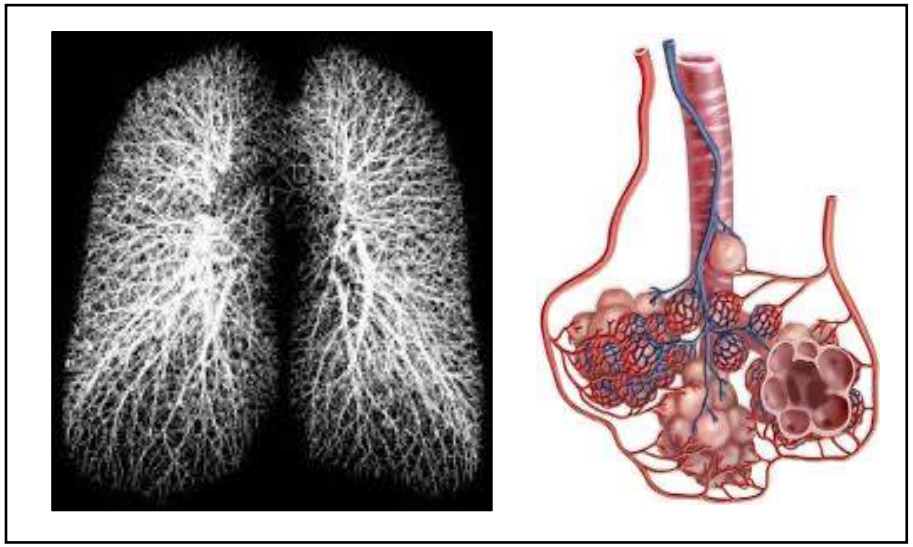
Form

Ontogeny

Function

Biology-Flow changes in the setting of CHD

Pulmonary Vasculature: Form



- Pulmonary veins and its branches are spatially separated from the PA and the airways.
- Large, fully formed muscularized pulmonary arteries closely following airways and its branches EXCEPT,
- Supernumerary or precapillary arterioles
- Smaller and branch at right angles to run within the interstitium of the lung

Pulmonary arteries and precapillary arterioles

- Pulmonary vessels, especially as they become arterioles and precapillary arterioles are thin-walled allowing for high compliance
  - Determine a majority of the resistance in the pulmonary circulation

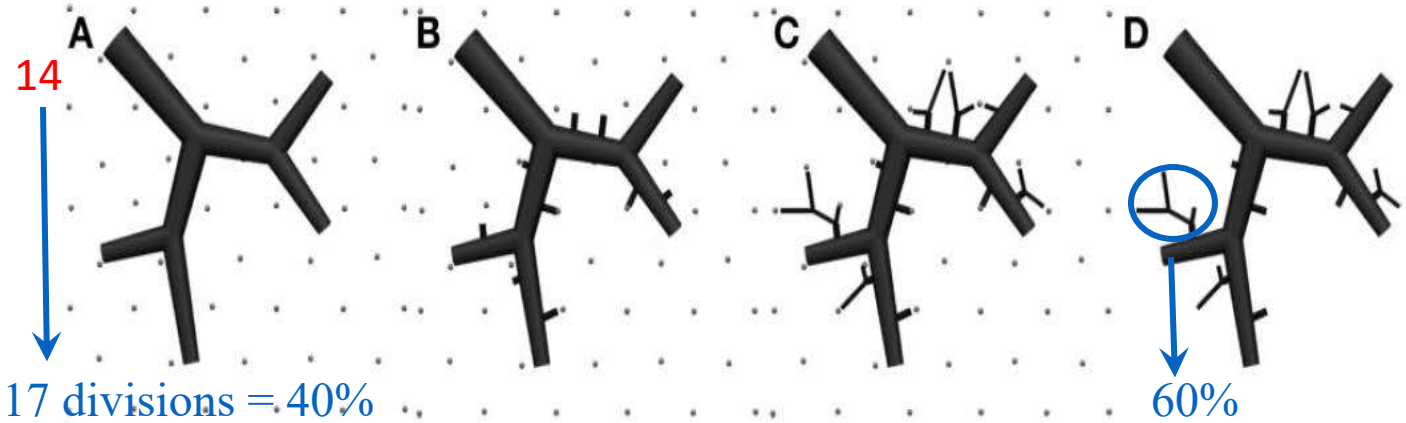


Fig. 3. Schematic illustration of the supernumerary algorithm. *A*: starting with the accompanying blood vessels and a uniformly distributed grid of points within the lung volume (each point representing an acinar unit). *B*: supernumerary branches emerge at right angles from the accompanying branch and grow toward the closest point. *C* and *D*: vessels branch and continue to grow toward the closest point, until the point is reached or an *order 6* (terminal order) vessel is obtained.

Burrowes KS *et al*. *J Appl Physiol* 2005

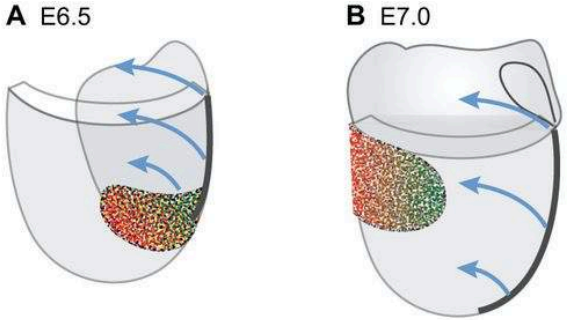
Pulmonary Vasculature Form

- Pulmonary veins are spatially separated from PAs and airways.
- PAs accompany the airway in the bronchovascular bundle EXCEPT,
- Supernumerary or precapillary arterioles are highly compliant and regulate resistance

Where and how do we form the pulmonary vasculature?

Ontogeny: Brief review of heart development

Primitive streak migration

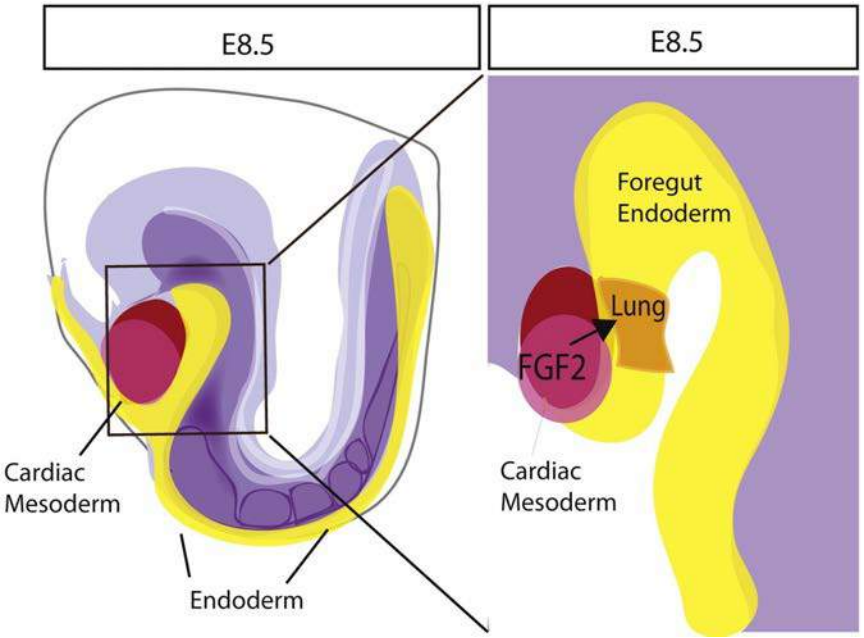


Secondary heart field patterns the RV, OT, and atria during development

Santini MP *et al*. *Development* 2016

Symbiotic relationships of the heart and lung

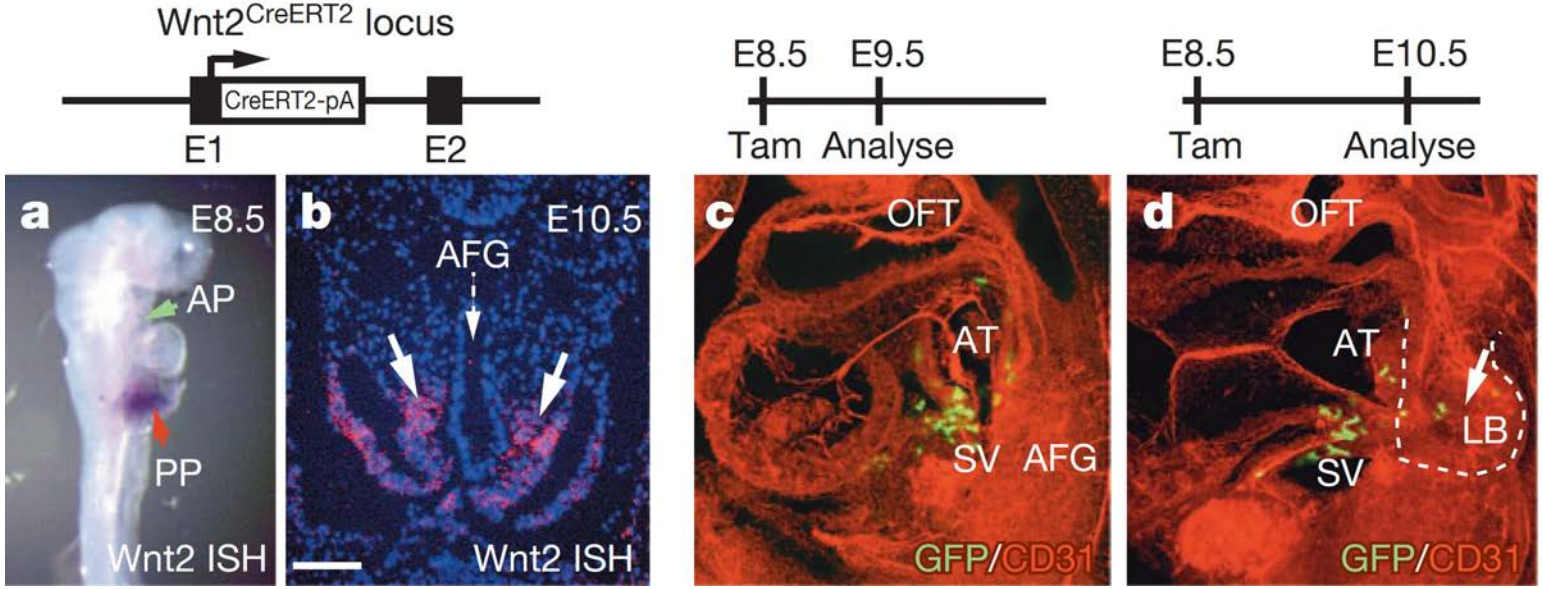
Lung epithelium is specified by cardiac (splanchnic) mesoderm



Kadzik R *et al*., *Cell Stem Cell* 2012

Symbiotic relationships of the heart and lung

Cardiac (splanchnic) mesoderm populates the lung mesodermal lineages including the vasculature



T Peng *et al. Nature* 2013

Pulmonary Vasculature Ontogeny

- Cardiac mesoderm instructs lung differentiation and populates the heart and lung mesoderm

How does the pulmonary circulation work?

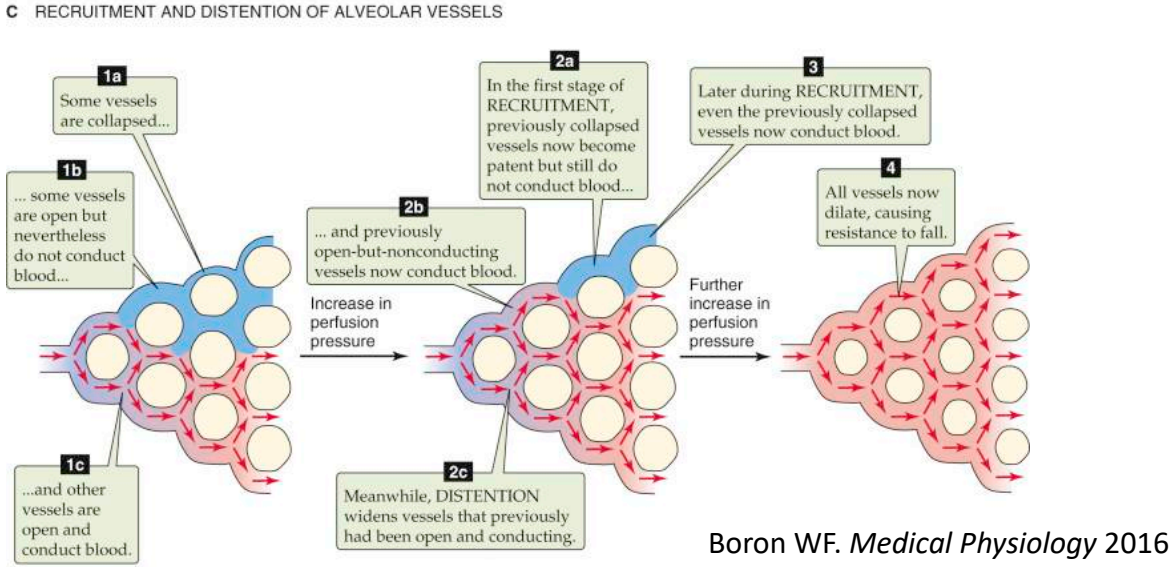
Pulmonary vasculature function: Perfusion

- Systemic circulation is high pressure and high resistance
  - High pressure to push blood to multiple organ vascular beds
  - High resistance to effectively regulate distribution of blood flow

- Pulmonary circulation is low pressure, low resistance and high compliance
  - Low pressure as it is only required to push blood blood throughout lung in addition to avoiding Starling forces (vessel leak/edema)
  - High compliance allowing distension, a large number of pre-capillary arterials, and a large capillary bed all lead to a low resistance circulation

Resistance and perfusion

- Although majority of resistance is regulated by arterioles (46%), the capillary bed (34%) also contributes significantly (Brody JS *et al*. *JCI* 1968)
- Recruitment a mechanism to lower capillary resistance and total resistance through increased pulmonary blood flow



Boron WF. *Medical Physiology* 2016

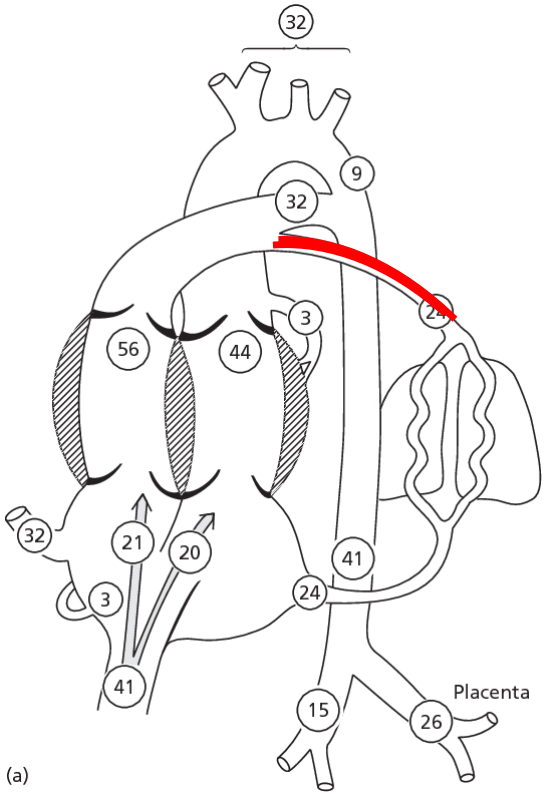
- In PH, there is an inability to increase perfusion in the setting of high precapillary arteriole resistance and thus recruitment is impaired and exercise tolerance is lower than normal

Pulmonary Vasculature Function

- Gas exchange
- Perfusion is a process of pulmonary blood flow dictated by a highly compliant precapillary arteriole network and the ability to recruit the capillary bed

How does perfusion and function change in CHD?

Pulmonary vasculature biology: Pulmonary blood flow

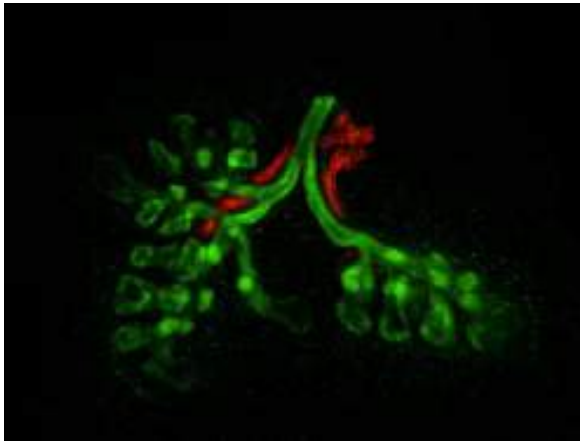


From Congenital Disease of the Heart: Clinical-Physiological Considerations, Abe Rudolph

Pulmonary blood flow

Too little

- PS/PA, TA, TGA, TOF

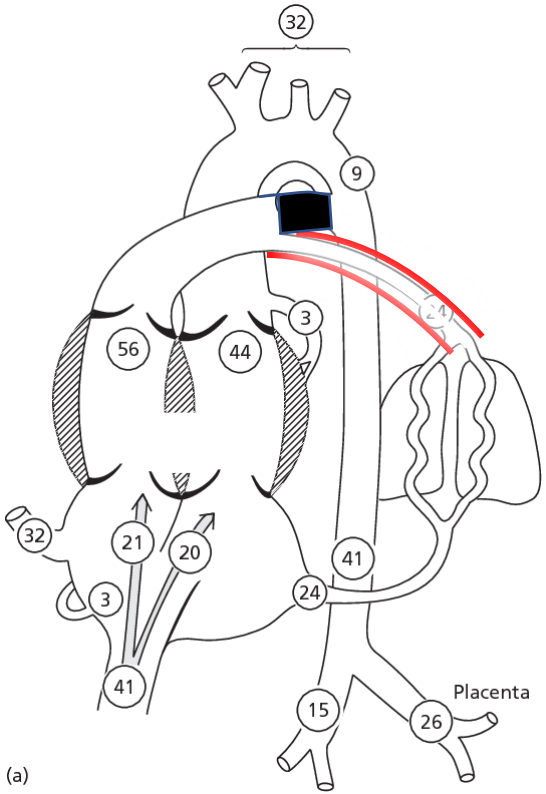


Arteries

Airways

- Compensatory vasodilation-> increased PBF-> shear stress-> vascular remodeling

Pulmonary vasculature biology: Pulmonary blood flow



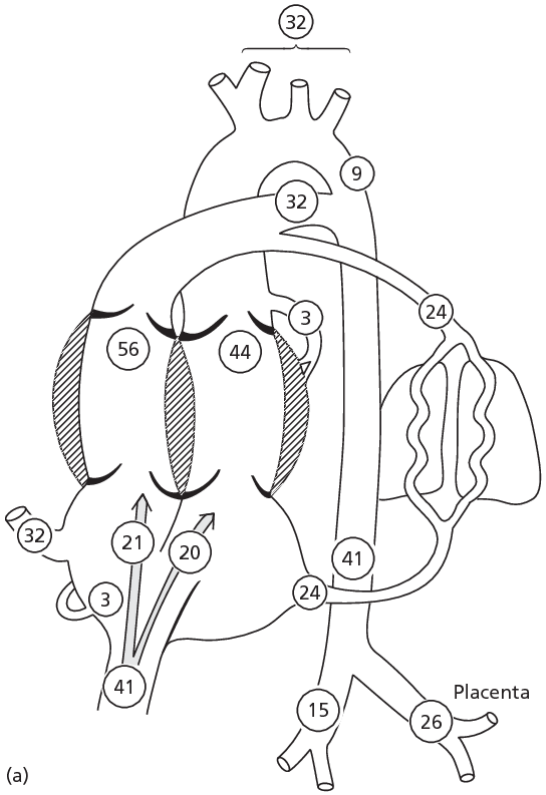
From Congenital Disease of the Heart: Clinical-Physiological Considerations, Abe Rudolph

Pulmonary blood flow

Too much

- Absent PDA, ASD, VSD, AVCD
- Compensatory vasoconstriction-> reduce PBF-> vascular remodeling

Pulmonary vasculature biology: Hypoxia

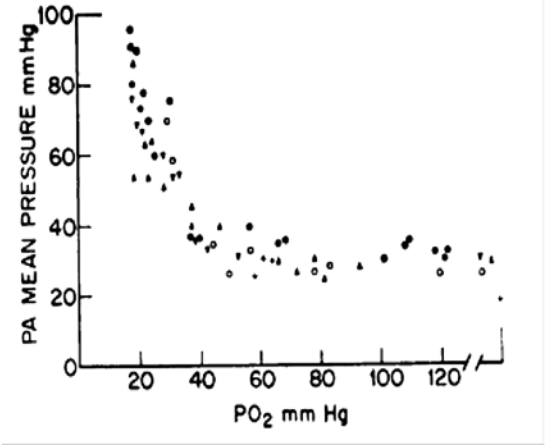


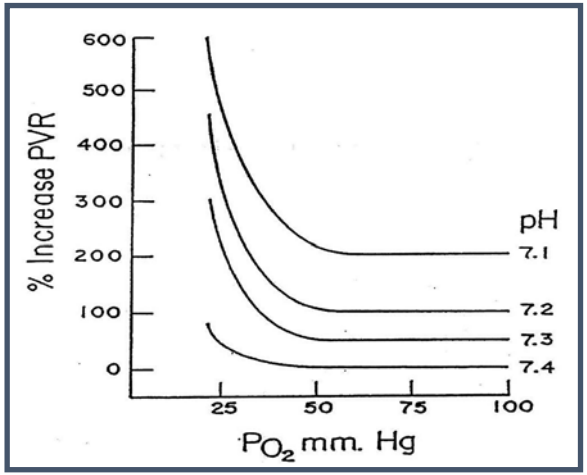
From Congenital Disease of the Heart: Clinical-Physiological Considerations, Abe Rudolph

Systemic vasculature ≠ Pulmonary vasculature in relation to hypoxia, pH, and P_{CO2}

- Age and context-dependent

Hypoxia > pH and P_{CO2}

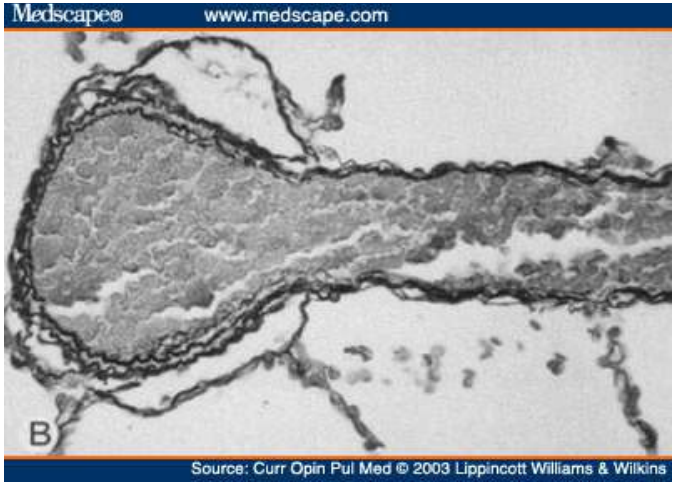


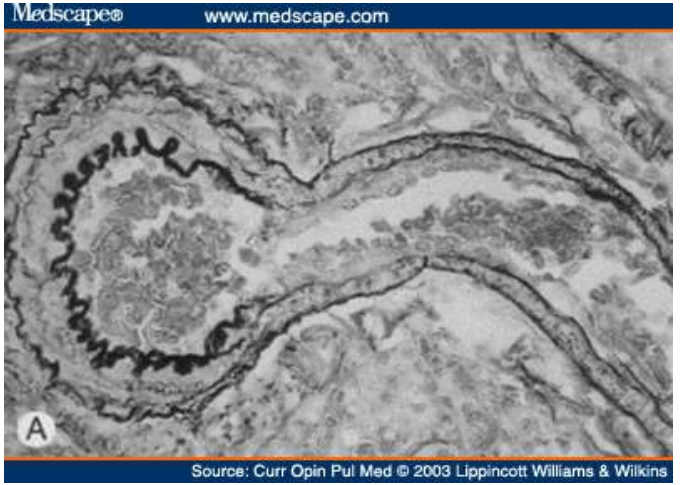


Rudolph & Yuan, J Clin Invest. 45:399-411, 1966

Pulmonary vasculature biology: Vascular remodeling

- Chronic hypoxia
- Increased pressure/shear stress
- Small precapillary arterioles become muscular
- Increase in resistance and reduction in flow-related distensibility





Summary

- Low pressure
- High compliance
- Low resistance
- Function is for gas exchange, perfusion determines this
- CHD resulting too little, too much, or hypoxia can lead to aberrant vascular remodeling