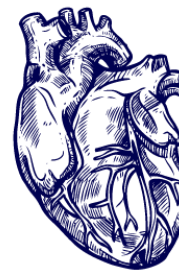


Primary Cast Episode 4 - Respiratory Physiology

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Primary Cast

1. Airway resistance & work of breathing

Describe factors affecting airway resistance in the lung

- Some of these factors are related to Poiseuille's (PWAH ZAY) law
 - Resistance is proportional to the length of the tube and the viscosity.
 - Resistance is inversely proportional to the radius to the 4th power
- Resistance is highest in medium sizes bronchi, low in very small airways
- It changes with different lung volumes, resistance decreases as the lung volume increases because the airways are pulled open by traction
- Resistance is also under the control of autonomic nervous system, where stimulation of beta adrenergic receptors causes bronchodilation. Stimulation of the parasympathetic system can cause bronchoconstriction. Reduced alveolar PCO₂ also causes increased resistance.

What factors determine the work of breathing?

- Elastic forces in the lung and chest wall
- Viscous resistance of the airways and tissues

What variables affect elastic workload?

- Large tidal volume increase workload
- Anything that reduces compliance of the lung
 - Lung volume
 - Increased tissue mass such as fibrosis
 - Loss of surfactant

What variables affect viscous resistance?

- Higher respiratory rates increasing flow rates
- Decreased airway radius i.e. bronchoconstriction
- Increased air density such as in scuba diving
- Increased air viscosity

2. Lung Volumes

What are the components of total lung volume and what are their typical volumes?

- Total lung capacity - approx 7L
- Vital capacity - the exhaled gas volume after a maximal inhale (5-6L)
- Residual volume - the amount of gas remaining after a maximal expiration (1.5-2L)
- Functional residual capacity - the volume of gas remaining in the lung after normal expiration (3L)
- Expiratory reserve volume 1.2L

- Inspiratory reserve volume 1.5L
- Tidal volume - the volume of gas moved in and out of the lung during normal breathing (500ml)

Which of these can be directly measured by spirometry?

Tidal volume and vital capacity

How can the residual volume be measured?

- Helium dilution
- Nitrogen washout measurement (both gas methods only measure ventilated residual volumes)
- Body plethysmography (measures total volume including trapped gas)

3. Dead Space

What is the anatomical dead space?

- Refers to the airway volume with ventilation but no blood flow
- The conducting airways do not participate in gas exchange
- Volume approx 150mls

How does this differ from physiological dead space?

- Anatomical dead space is determined by the morphology of the airways and the lungs
- Physiological dead space is the volume of airways and lung that does not eliminate CO₂
- These dead space volumes are almost identical in the normal lung
- Physiological dead space is increased in many disease states due to inequality of blood flow and ventilation in the lung i.e. V/Q mismatch

How are the different dead spaces measured?

- Fowler's method for anatomical dead space
- Bohr's method for physiological dead space - calculated fraction of tidal volume by measurement of mixed expired CO₂ and arterial CO₂

What will lead to increased physiological dead space?

- V/Q mismatch

4. Compliance

What is pulmonary compliance?

- Compliance = volume change per unit of pressure change
- It is a measure of elastic recoil of the lungs and chest wall
- Compliance is maximal in mid inspiration and lower at extremes
- Normally 200ml/cm H₂O

How does compliance vary throughout the upright lung?

- At the apex the intrapleural pressure is higher to keep lung expanded against its own weight (10cm H₂O, compared to 2.5cm H₂O at base)
- The apex of the lung is already distended so there is less compliance
- Greater compliance at the base means it has better ability to ventilate

What are the main determinants of compliance?

- Surface tension of the alveoli (2/3rds) - which depends on alveolar pressure, radius and surfactant (as described by the Law of Laplace where $P = 2 \times \text{Tension}/\text{Radius}$)
- Elastin and collagen fibres (1/3rd)

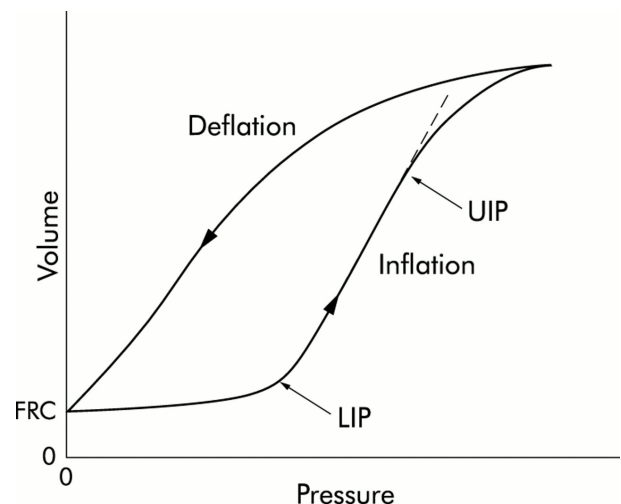
What factors increase or decrease pulmonary compliance?

- Decrease - alveolar oedema, pulmonary fibrosis, pulmonary venous hypertension, unventilated lung
- Increase - age, emphysema, surfactant

Note: Additional questions can ask you to draw a pressure volume curve of the normal lung.

Needs to show:

- Hysteresis (means the compliance of the lung is different in inspiration and expiration. Lung volume is higher for any given pressure during deflation. You need to show 2 curves)
- Closing volume (does not reach 0% lung volume, lung contains air at 0 pressure)
- Lung becomes stiffer at higher lung volumes i.e. compliance decreases at limits of elasticity



5. Surfactant

What are the physiological effects of surfactant of the lung?

- Increased lung compliance
- Reduced work of breathing
- Improved stability of alveoli
- Keeps alveoli dry via reduced transudation of fluid

What is surfactant and how does it work?

- Surfactant is a phospholipid
- Produced by type 2 pneumocytes in the alveoli
- Fast synthesis with rapid turnover
- Formed relatively late in foetal life
- With surfactant present, the surface tension changes greatly with the surface area
- Molecules of DPPC (which make up surfactant) are hydrophobic at one end and hydrophilic at the other, When aligned on the surface, their repulsive forces oppose the normal attractive forces between the liquid surface molecules.

6. Pulmonary blood flow

Describe the normal distribution of pulmonary blood flow.

- Influenced by gravity
- Decreases from the base to the apex
- Under normal conditions, flow almost ceases at the apex
- Distribution is more uniform with exercise
- 3 main zones (There is also zone 4 which occurs at very low lung volumes)

What are the main determinants of flow in these 3 zones?

- Zone 1 at the apex = alveolar pressure greater than arterial and venous pressure. Usually does not occur under normal conditions and is essentially alveolar dead space)
- Zone 2 at the mid lung = arterial pressure greater than alveolar pressure, both greater than venous. (represents recruitment)
- Zone 3 at the base = Arterial pressure is the highest - allowing most blood flow (represents distension and recruitment)
- There is also zone 4 which occurs at very low lung volumes

How is distribution of pulmonary blood flow actively controlled?

- Hypoxic pulmonary vasoconstriction - alveolar hypoxia directly constricts pulmonary arteries, directs blood away from poorly ventilated diseased lung areas.
- Important at birth.
- Mechanism - NO, endothelin-1, TXA2, low pH, autonomic system.

What extra-pulmonary factors influence pulmonary blood flow?

- Blood volume
- Cardiac output
- Atmospheric pressure
- Temperature
- Pathology e.g anaemia, cancer, infection
- Exercise
- Posture

Please describe the relationship between pulmonary vascular resistance and pulmonary vascular pressure.

- Respiratory circulation is a low resistance system
- There is capacity for the resistance to decrease with increased pressure
- Mechanism: vascular recruitment with low level pressure increase and vascular distension with higher level pressure rise.

How does lung volume influence pulmonary vascular resistance?

- Vascular resistance initially decreases as lung volume increases, then begins to rise again.
- At very low lung volumes, the pressure must reach a critical opening level to enable any flow
- At very high lung volumes, when alveolar pressure exceeds pulmonary capillary pressure, pulmonary vascular resistance will increase because the pulmonary capillaries become squashed.

Please explain how cardiogenic pulmonary oedema occurs.

- Starling's law
- Difference in capillary and interstitial hydrostatic and colloid osmosis pressures. Significant increases in net outward pressure result in interstitial oedema, especially at perivascular and peribronchial spaces. Further increases of outward pressure result in fluid entering the alveolar spaces.

7. Gas Exchange

Explain Fick's Law of diffusion

- Gases diffuse across a surface by passive diffusion
- Fick's Law states the rate of diffusion across a membrane is directly proportional to the area of the membrane, the pressure gradient across the membrane and the diffusion constant.
- It is inversely proportional to the thickness of the membrane

What is the difference between a diffusion limited and a perfusion limited gas?

- Blood traveling through the alveolar capillary has 0.75 seconds for gas exchange
- The ability of a gas to reach partial pressure equilibrium depends on its reaction with substances in the blood

Perfusion limited gas (Nitrous)

- Partial pressure on both sides of the membrane equilibrates so rapidly that no further diffusion into the blood can occur from the alveoli unless the blood flow rate through the capillary increases

Diffusion limited gas (Carbon monoxide)

- Partial pressure of the gas does not achieve equilibrium in the time that blood spends in the pulmonary capillaries.
- Transfer of gas is limited by how much gas can get across the membrane

Explain how oxygen exchange is limited across the pulmonary capillary.

- Perfusion limited under most circumstances
- Oxygen combines with Hb and equilibrium is achieved after 0.3 seconds

What would you expect would be the effect of heavy exercise on oxygen uptake in the pulmonary capillary?

- Increased pulmonary blood flow, so reduced time for combination of O₂ with Hb (0.25secs)
- Possible reduced O₂Hb saturation
- Effects also influenced by the altitude

How is diffusion capacity measured?

Carbon monoxide is used because its uptake is diffusion limited - single breath test is used.

8. Oxygen

How is oxygen transported in the blood?

- Dissolved; where the amount dissolved is proportional to the partial pressure (Henry's Law) → 0.3ml per 100ml blood per 100 mmHg
- Most is combined with Hb. 20.8ml O₂/100ml blood (at Hb level of 15g/dl)

Draw and label (or describe) the O₂/Hb dissociation curve

- X axis = PaO₂
- Y axis = SpO₂
- Sigmoid shaped curve
- 4 main points
 - SpO₂ 98% and PaO₂ 90mmHg
 - SpO₂ 90% and PaO₂ 60mmHg
 - SpO₂ 75% and pAO₂ 40mmHg (venous blood)
 - SpO₂ 50% and PaO₂ 27.5mHg (P50)

What are the implications of the shape of this curve?

- Flat upper portion means that if the PO₂ in alveolar gas fails, the loading of O₂ is little affected
- Steep lower part means peripheral tissues can draw a large amount of O₂ for only a small drop in capillary pO₂

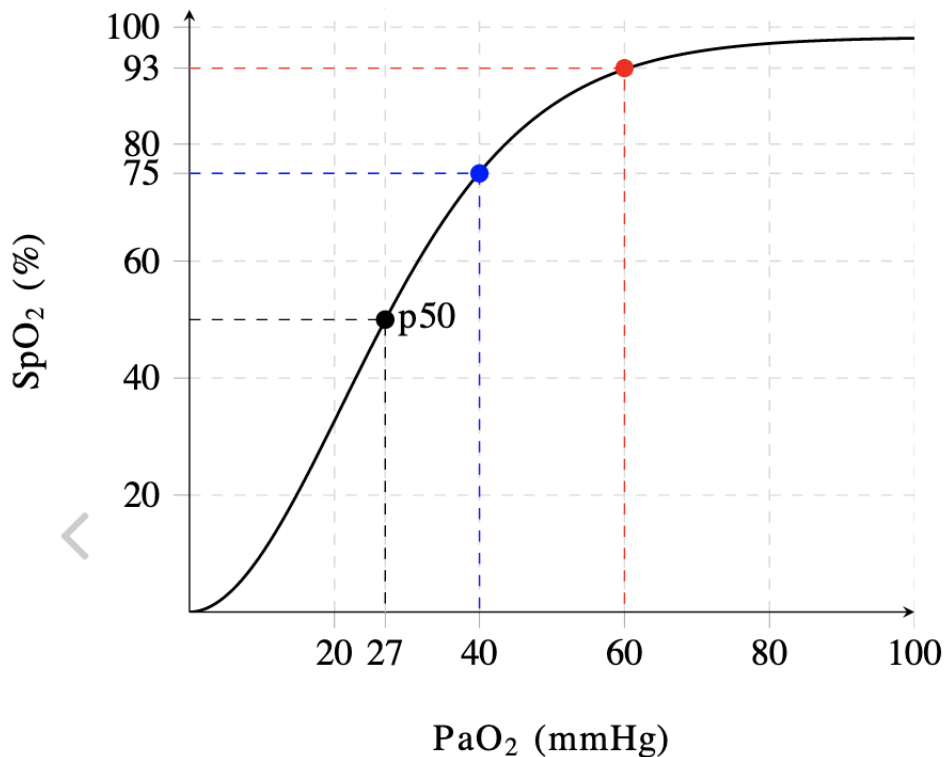
What factors shift the curve?

- Things that shift to the right
 - Increased temperature
 - Increased pCO₂
 - Increased H⁺ or decreased pH
 - Increased 2-3 DPG
- Left shift is via the reverse of those things and also carbon monoxide

What are the effects of carbon monoxide on the haemoglobin oxygen transport capacity?

CO has 240 times the affinity of O₂ for Hb, hence oxygen saturation is greatly reduced and Hb oxygen carrying capacity is reduced. CO also shifts the dissociation curve to the left, interfering with unloading of O₂.

The curve! Borrowed from https://partone.litfl.com/oxygen_storage.html#id



Note: you should also be able to draw the curve to demonstrate the relationship between oxygen concentration and pO₂. I had so much trouble learning this that I just memorised the graph from here: <https://litfl.com/oxygen-concentration-curves/>

9. Carbon Dioxide

How is carbon dioxide transported in the blood?

Three forms (percentages for arterial blood)

- Dissolved (5-10%)
- Bicarbonate (90%) formed via the equation $\text{CO}_2 + \text{H}_2\text{O} = \text{H}_2\text{CO}_3 = \text{H}^+ + \text{HCO}_3^-$. The first reaction is slow in plasma but fast in red cells due to the presence of carbonic anhydrase. The second reaction (ionic dissociation) is fast without an enzyme.
- Carbamino compounds (5%) haemoglobin is the most important. Reduced Hb binds more CO₂.

What is the chloride shift?

- The ionic dissociation of carbonic acid results in bicarb and H⁺ formation within the red cell.

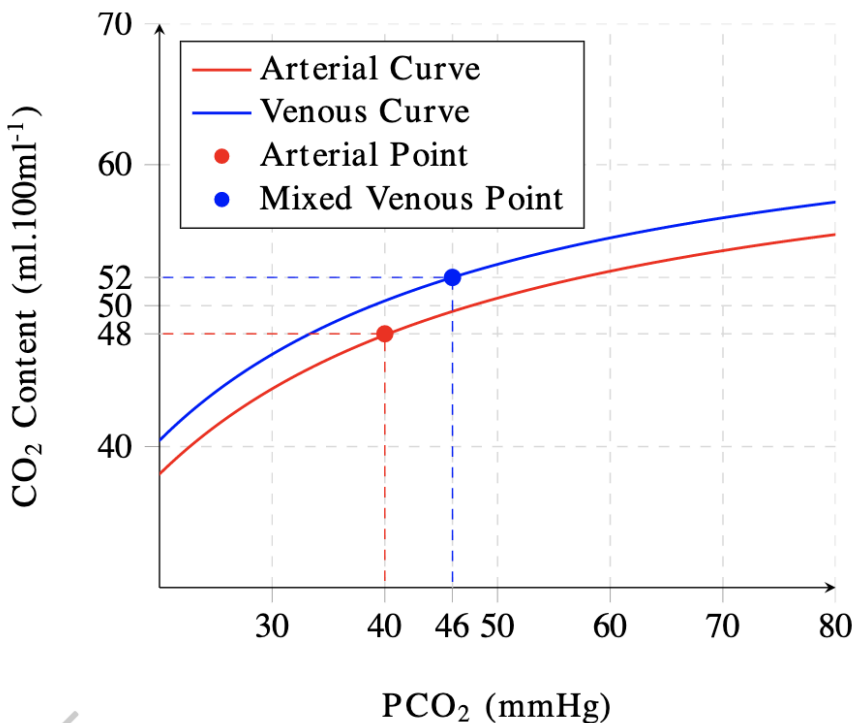
- The bicarb diffuses out of the cell but H^+ cannot because the cell membrane is relatively impermeable to cations.
- To maintain electrical neutrality Cl^- ions move into the cell from the plasma.

What is the haldane effect?

- The fact that de-oxygenation of Hb increases its ability to carry carbon dioxide.
- It enhances the removal of CO_2 from tissues
- Promotes the dissociation of CO_2 from Hb in the presence of O_2 i.e. in the lungs, which is vital for alveolar gas exchange.

Note: Some questions ask for you to draw and explain the CO_2 dissociation curve from the resp physiology book. This includes stating that doxyHb binds more H^+ ions and forms more carbamino compounds, so venous blood carries more CO_2 than arterial blood, therefore the curve for venous blood lies above that for arterial blood on the graph. Worth knowing how to draw the shape and label the x and y axis.

From: https://partone.litfl.com/carbon_dioxide_transport.html



10. The Alveolar Gas Equation

What is the alveolar gas equation?

$$PAO_2 = PiO_2 - PaCO_2/R$$

PAO₂ - alveolar oxygen partial pressure

PiO₂ - the oxygen partial pressure of inspired air

PaCO₂ - alveolar partial pressure of CO₂

R - respiratory quotient

How is the Alveolar arterial gradient calculated?

- The difference between the PAO₂ and the measured PaO₂ from ABG

What is the physiological significance of an A/a gradient?

- Represents a V/Q mismatch

Can you explain the difference between the alveolar and arterial oxygen concentrations in the healthy adult.

- Physiological shunting of the lung
- Blood enters the arterial system without passing through a ventilated area of lung
- Bronchial arterial blood flows to pulmonary veins
- Coronary artery blood flows to coronary veins and then to the left ventricle
- Lung atelectasis

11. Hypoxaemia

What are the causes of hypoxaemia in general?

Hypoventilation

- Drugs - morphine, barbiturates
- Chest wall damage
- Respiratory muscle paralysis
- Asthma

Diffusion limitation

- Impaired diffusion process across the pulmonary capillary i.e. exercise, thickened blood/gas barrier, low O₂ mixture inhaled
- Conditions include APO, pulmonary fibrosis, LVF

Shunt

- Refers to blood entering the arterial system without having passed through ventilated areas of the lung
- Abnormal vascular connection i.e. AV fistula, congenital cardiac defect

V/Q mismatch

- The most common reason
- Regional variances exist or pathological such as PE

- Hypoxaemia cannot be corrected by increasing ventilation

Describe the clinical effects of acute hypoxia

- Disorientation
- Confusion
- Headache
- LOC
- Tachycardia
- Hypertension or hypotension
- Diaphoresis
- Tachypnoea
- AMI
- Arrest

Describe the different types of TISSUE hypoxia

- Hypoxaemic hypoxia - arterial PO₂ is reduced
- Anaemic hypoxia - PO₂ is normal but the Hb is reduced so O₂ carrying capacity is reduced
- Ischaemic or stagnant hypoxia - blood flow and O₂ delivery is decreased
- Histotoxic hypoxia - because of toxins, tissues cannot use the delivered oxygen

12. V/Q

What happens to the V/Q ratio from the top to bottom of an upright lung?

- Both ventilation and perfusion increase as you go down the lung
- Perfusion increases more than ventilation
- This results in the V/Q ratio decreasing down the lung

Explain why V/Q mismatch causes a reduction in PO₂ whilst arterial CO₂ remains relatively normal.

- Due to the differences in their dissociation curves
- VQ mismatch impacts on gas exchange, causing hypoxaemia and hypercapnia.
- Chemoreceptors respond to this and increase ventilation.
- The CO₂ dissociation curve is linear in working range. So, increased ventilation is able to correct the high pCO₂ by increasing the output of CO₂ from the lungs.
- The O₂ dissociation curve is not linear.
- So, high V/Q areas (ventilated but not perfused) can only boost the PO₂ slightly with increased ventilation.
- Low V/Q areas (Perfused, but not ventilated) have proportionally low PO₂ (close to venous blood).
- Regardless of the inequality, the PO₂ remains low.

What test can be done in clinical practice to demonstrate a VQ mismatch?

- Calculating the A-a gradient
- V/Q scan
- CTPA

13. Control of Ventilation

What parts of the brain control respiration?

Automatic control

- Medulla. Pacemaker cells in the pre-Botzinger complex
- Pons. Pneumotactic centre modifies the medullary activity
- Voluntary control from the cerebral cortex

What other sensors are involved in the control of ventilation?

- Peripheral and central chemoreceptors
- Pulmonary stretch receptors in lungs, muscles, joints
- Irritant receptors in airways
- J receptors - respond to engorged capillaries
- Baroreceptors - arterial, atrial, ventricular and pulmonary.
- Pain/temperature receptors
- Proprioceptors from intercostals, diaphragm, muscles, joints, tendons

How are chemoreceptors involved in the control of ventilation?

Central

- Located on the ventral surface of the medulla
- Sensitive to changes in H⁺
- CO₂ readily penetrates the BBB and enters CSF and brain interstitial fluid
- The increase in CO₂ causes increased H⁺ in the CSF, stimulating ventilation
- This increases both the rate and depth of breathing
- If there is a decrease in H⁺ concentration in the CSF, this inhibits ventilation and causes cerebral vasodilation leading to enhanced diffusion of CO₂ into the CSF
- The CSF pH is 7.32, has less buffering capacity than blood so the pH changes more for any given change in pCO₂
- Prolonged pH changes can be compensated for by HCO₃⁻ transport across the BBB meaning that chronic CO₂ retainers can have a near normal CSF pH

Peripheral

- Located in carotid and aortic bodies
- Contain glomus cells with high blood flow and high dopamine concentration
- Fast response to decreasing O₂, which stimulates them.
- Responsible for all the increased ventilation in hypoxia - maximal response occurs when PaO₂ is < 50mmHg but can be stimulated below 10mmHg
- Impulses transmitted to respiratory centre to increase ventilation

- Decreased pH can cause a response from carotid receptors
- They have a minor but rapid response to changes in PaCO₂

14. Exercise

What are the effects of exercise on the respiratory system?

Gas exchange

- ↑Respiratory uptake and consumption of O₂ and production of CO₂
- ↑Lung diffusing capacity due to ↑diffusing capacity of the membrane and increased pulmonary blood volume
- ↓ V/Q mismatch

Ventilation

- ↑Respiratory rate
- ↓ FRC
- ↑Tidal volume
- ↑Minute ventilation

Pulmonary Blood flow

- Distension and recruitment of pulmonary blood vessels increases the total cross sectional area of the pulmonary vasculature
- ↑Total pulmonary blood volume
- ↑Cardiac output and pulmonary blood flow
- ↑Pulmonary vascular pressure
- ↓pulmonary vascular resistance

Other respiratory effects

- ↑respiratory exchange ratio due to increased carbohydrate metabolism
- O₂Hb dissociation curve shifts to the right in the tissues and to the left in the lungs
- Additional capillaries open up in peripheral tissues,

What changes occur in blood gases during exercise?

- ABG little affected at moderate exercise but at high workloads can be significant
- pH falls due to lactic acidosis
- PaCO₂ falls to compensate for the acidosis
- PaO₂ rises
- Arterio-venous pH, PaO₂ and PaCO₂ differences increase

15. Altitude

What are the initial physiological responses at high altitude?

- Hyperventilation due to hypoxic stimulation of peripheral chemoreceptors, increased ventilation causes loss of CO₂
- Respiratory alkalosis - inhibits a higher resp rate
- Renal excretion of bicarbonate and bicarb shift out of CSF normalises the pH, allowing the resp rate to increase again
- Increased 2-3 DPG with initial rightward shift of the o₂Hb dissociation curve, then a left shift due to the alkalosis
- Alveolar hypoxia causes pulmonary vasoconstriction then pulmonary HTN

What are the longer term physiological effects of altitude exposure

- Polycythaemia from increased EPO
- Increased blood viscosity
- Increased carriage of O₂
- Pulmonary HTN → leads to RVH
- Increased number of capillaries in peripheral tissue
- Increased cellular oxidative enzymes
- Increased mitochondria

What are the symptoms of acute mountain sickness?

- Headache
- Fatigue
- Dizziness
- Palpitations
- Nausea
- Loss of appetite
- Insomnia

16. Metabolic

Outline the metabolic functions of the lung

- Synthetic function
 - Synthesis of phospholipids including surfactant
 - Collagen and elastin synthesis
 - Carbohydrates including mucopolysaccharides
- Activation of angiotensin I to Angiotensin II via Angiotensin Converting Enzyme in the capillary endothelium
- Inactivation of circulating factors
 - Bradykinin
 - Serotonin
 - PGE₁ and 2

- Noradrenaline
 - Removal of leukotrienes
 - Immune function via secretion of IgA

Study that measured the pH and lactate in Olympic rowers:

http://bionics.seas.ucla.edu/education/Rowing/Physiology_1999_01.pdf