

# Non-respiratory functions of the lung

Deepak Joseph MBBS, MD, FRCA

Raju K Puttaswamy MBBS, FRCA

Hari Krowidi MBBS, MD, FRCA



## Key points

The lung, with its unique ability to distend and recruit pulmonary vasculature, acts as a reservoir of blood, fine tuning preload to the left heart to optimize cardiac output.

The lung acts as a filter against endogenous and exogenous emboli, preventing them from accessing systemic circulation.

Pulmonary epithelium forms the first line of defence against inhaled particles.

Pulmonary endothelial cells are responsible for uptake, metabolism, and biotransformation of several exogenous and endogenous substances.

Pulmonary metabolic capacity is easily saturated, but pulmonary endothelial binding of some drugs alters their pharmacokinetics.

The primary function of the lungs is gas exchange. However, the lungs perform several important non-respiratory functions that are vital for normal physiology.

## Vascular reservoir

The volume of the blood passing through the pulmonary vessels is equal to the right ventricular output, of which 70–100 ml is within the pulmonary capillaries<sup>1</sup> and takes part in gas exchange. The remaining blood volume is held within the pulmonary vasculature.

## Recruitment and distension

The lung has an extremely distensible vasculature, which enables it to cope with large variations in venous return, especially during postural changes, exercise, and increased intravascular volume. The two mechanisms involved are recruitment and distension of the pulmonary vasculature.<sup>2</sup> At resting cardiac output, the pulmonary vascular bed is not fully perfused. In the face of an increased cardiac output, underperfused areas of the pulmonary vasculature are 'recruited' to accommodate an increase in blood flow and to prevent an increase in pulmonary arterial pressures. The walls of the pulmonary vasculature are thin and contain relatively little smooth muscle, which make it compliant to increased blood volume. The pressure in the pulmonary circulation is approximately six times less than that of the systemic circulation and both arteries and veins increase in calibre with lung expansion. This 'distension' along with 'recruitment' helps in altering the lung blood volume by 500–1000 ml.

## Postural and ventilatory changes

A change in posture from supine to erect in normal individuals results in ~400 ml of pulmonary blood volume being redistributed to the systemic circulation. During forced expiration against a closed glottis (e.g. valsalva

manoeuvre), the pulmonary blood volume decreases by 50%. On the other hand, the pulmonary blood volume doubles with forced inspiration. Changes in pulmonary vascular volume are also influenced by the activity of the sympathetic nervous system.<sup>1</sup>

## Filter for blood borne substances

The lung is ideally positioned to filter out particulate matter such as clots, fibrin clumps, and other endogenous and exogenous materials from entering the systemic circulation. This plays an important role in preventing ischaemia or even infarction to vital organs.

## Physical filtration

The lung acts as a physical barrier to various blood borne substances, but is not completely efficient in protecting the systemic circulation. Pulmonary capillaries have a diameter of 7 µm. But it has been shown in animal studies that glass beads of up to 500 µm can pass through a perfused lung.<sup>3</sup> Post-mortem studies have shown that almost 25% (15–40%) of the population have a probe patent foramen ovale. Increased pressure in the right atrium secondary to events such as coughing or valsalva manoeuvre produces demonstrable blood flow between the right and left atria. Therefore, emboli, particularly fat and gas emboli, can still pass through the pulmonary capillary filter, or bypass the lung entirely via the foramen ovale. The pulmonary microcirculation is designed to maintain alveolar perfusion in the face of substantial embolization. However, emboli blocking major vessels or extensive micro-embolization can result in life-threatening ventilation–perfusion mismatch. Pulmonary micro-embolism also initiates neutrophil activation leading to increased permeability and alveolar oedema in the affected area and has been implicated in the aetiology of acute lung injury.

## Deepak Joseph MBBS, MD, FRCA

Consultant Anaesthetist  
Birmingham Heartlands Hospital  
Birmingham B9 5SS  
UK  
Tel: +44 (0)121 424 2000  
Fax: +44 (0)121 507 4349  
E-mail: drdeepakjoseph@gmail.com  
(for correspondence)

## Raju K Puttaswamy MBBS, FRCA

Specialist Registrar  
Department of Anaesthesia and Intensive Care  
Queen Elizabeth Hospital  
Birmingham  
UK

## Hari Krowidi MBBS, MD, FRCA

Consultant Anaesthetist  
Department of Anaesthesia and Intensive Care  
Queen Elizabeth Hospital  
Birmingham  
UK

### Chemical filtration

Pulmonary capillaries also produce substances that break down blood clots. Pulmonary endothelium is a rich source of fibrinolysin activator, which converts plasminogen present in plasma to fibrinolysin, which subsequently breaks down fibrin-to-fibrin degradation products. The lung thus has an efficient fibrinolytic system, which lyses clots in the pulmonary circulation.<sup>2</sup> In addition, the lung is the richest source of heparin (which inhibits coagulation) and thromboplastin (which by converting prothrombin to thrombin, promotes coagulation).<sup>1</sup> Hence the lung may play a role in the overall coagulability of blood to promote or delay coagulation and fibrinolysis.

### Defence against inhaled substances

Every day, about 10 000 litres of air comes in to contact with 50–100 m<sup>2</sup> of alveolar epithelium. There are various mechanisms along the respiratory tract that are involved in providing protection against inhaled physical and chemical substances.

### Defence against inhaled particles

A pseudo-stratified ciliated columnar epithelium lines the upper airway from the posterior two-thirds of the nose to the respiratory bronchioles. This is covered with a 'mucous blanket' that is composed of a highly viscous mucopolysaccharide gel secreted by goblet cells in the epithelium and mucous cells of the submucosal glands, floating on a low-viscosity serous fluid layer secreted by the bronchial glands. This 'mucous blanket' forms the first line of defence against inhaled physical substances.

### Muco-ciliary escalator

The cilia beat within the serous layer of the airway lining fluid in a co-ordinated fashion at a frequency of 10–15 Hz. In healthy individuals, this action moves the overlying mucus towards the pharynx at a rate of about 1 mm min<sup>-1</sup> in the small peripheral airways, but can be as quick as 20 mm min<sup>-1</sup> in the trachea. This is known as the 'muco-ciliary escalator'. Inspired particles >5 µm are deposited by impaction on the mucus covering the nose and larger airways. Particles between 2 and 5 µm in diameter are deposited by sedimentation in smaller airways, where the airflow rates are extremely low. The cilia propel this outer 'blanket' of mucus with the entrapped particles and microorganisms over the serous layer. They act together to move the mucus from peripheral airways to central airways, from which the mucus is expectorated or swallowed. Smaller particles (<2 µm) reach the alveoli as aerosols and about 80% is exhaled.<sup>4</sup> The rest may be deposited in the alveoli as a result of Brownian motion. Random movement of microscopic particles suspended in a liquid or gas is caused by collisions with molecules of the surrounding medium is termed

Brownian motion after its identifier, Scottish botanist Robert Brown (1773–1858).

### Factors affecting muco-ciliary function

Impaired muco-ciliary function may be because of abnormal mucus production or defective ciliary motility. The secretions of goblet cells are stimulated by inhaled irritant gases and inflammatory mediators. Neural control of bronchial gland secretions is mediated by the parasympathetic nervous system via the vagus nerve, increasing secretions with vagal stimulation, and vice versa. Secretions are also reduced by administration of opioids. Ciliary motility is impaired by dehydration, smoking, anaesthesia, dry inspired gases, extremes of temperature, and ciliary dysmotility syndromes,<sup>5</sup> for example Kartagener syndrome. Drugs that depress ciliary motility include inhaled anaesthetic agents, local anaesthetics, opioids, atropine, and alcohol.<sup>5</sup> *In vitro* studies have shown that midazolam, propofol, thiopental, and dexmedetomidine do not directly impair ciliary motility, whereas high doses of ketamine and fentanyl stimulate ciliary motility.<sup>6</sup>

### Effects of impaired muco-ciliary function

A defective muco-ciliary escalator can lead to chronic sinusitis, recurrent chest infections, and bronchiectasis. When muco-ciliary clearance is decreased, cough becomes increasingly important for the removal of secretions from the airways. In intensive care, the disruption of this function by critical illness, intubation, ventilation, and prolonged high-inspired oxygen concentrations predisposes the patient to atelectasis, hypoxia, and infection.

### Immune function

Optimal lung defences require coordinated action of multiple cell types. Immune function within the lung is mediated by pulmonary alveolar macrophages (PAMs) and a variety of immune mediators.

### Pulmonary alveolar macrophages

Amoeboid PAMs engulf the particles that reach the alveoli and deposit them on the muco-ciliary escalator or remove them via blood or lymph. The macrophages are particularly effective against bacteria and ensure that the alveolar region of the lung is effectively sterile.<sup>1</sup> PAMs also have a role in antigen presentation, T-cell activation, and immunomodulation. When PAMs ingest large amounts of inhaled particles, especially cigarette smoke, silica, and asbestos, they release lysosomal products into the extracellular space causing inflammation and eventually fibrosis. Neutrophil activation within the lung also leads to release of proteases such as trypsin and elastase. These chemicals, while very effective at destroying pathogens, can also damage normal lung tissue. This is prevented by the proteases being swept away by the mucus coating the respiratory tree, and by conjugation with alpha<sub>1</sub>-antitrypsin, which renders them inactive.<sup>4</sup> Hence, in alpha<sub>1</sub>-antitrypsin

deficiency, surplus trypsin and elastase leads to tissue destruction that in turn leads to pulmonary emphysema.

### Immune mediators in the lung

The airway epithelial cells secrete a variety of substances such as mucins, defensins, lysozyme, lactoferrin, and nitric oxide, which non-specifically shield the lung from microbial attack.<sup>7</sup> They also produce a number of mediators of inflammation such as reactive oxygen species, cytokines [tumour necrosis factor (TNF $\alpha$ ), interleukins (IL-1 $\beta$ ), granulocyte/macrophage colony stimulating factor (GM-CSF)], and platelet activating factor to recruit inflammatory cells to the site of inflammation. Immunoglobulins, mainly IgA, present in the bronchial secretions resist infections and help maintain the integrity of the respiratory mucosa.<sup>8</sup>

### Immunomodulation therapies in lung disease

New therapies using immunomodulating agents to prevent or minimize non-specific inflammation within the lungs are being developed. Broncho-Vaxom® (OM-85 BV; OM Laboratories, Geneva, Switzerland), a lyophilized bacterial extract from eight species of bacteria (*Haemophilus influenzae*, *Neisseria catarrhalis*, *Klebsiella pneumoniae*, *Streptococcus pyogenes*, *Streptococcus viridans*, *Staphylococcus aureus*, *Klebsiella ozaenae*, *Diplococcus pneumoniae*), has been found to enhance antibody synthesis together with better resistance to bacterial infection resulting in a well-balanced, non-inflammatory immune response against invading pathogens. This results in a reduction in the number and duration of chest infections in chronic obstructive pulmonary disease (COPD) patients.<sup>9</sup> Recombinant interferon- $\gamma$ 1b administered as an adjuvant along with anti-tuberculosis therapy has been shown to reduce the inflammatory response in the lung, improve clearance of pathogenic tuberculosis bacteria, and improve constitutional symptoms in patients suffering from pulmonary tuberculosis.<sup>10</sup>

### Defence against inhaled chemicals

The large surface area of the alveoli is perfectly suited for gas exchange, but can also serve as a portal of entry for inhaled toxic agents. The fate of these inhaled chemical substances depends on their size, water solubility, inspired concentration, and their metabolism within the lung.<sup>4</sup> Akin to hepatic metabolism, both phase I and II metabolism takes place within the lungs. Metabolism of inhaled chemicals is detailed in a separate section of this article.

### Endocrine and metabolic functions

Isolated pulmonary neuroendocrine cells (PNECs) and innervated cell clusters called neuroepithelial bodies (NEBs) are widely distributed in the airway mucosa and are together referred to as the 'pulmonary neuroendocrine system'. The role played by these cells in health and disease is becoming clearer.<sup>11</sup> They secrete a wide variety of amines (e.g. serotonin) and peptides (e.g. bombesin). PNEC play a significant role in cell growth, differentiation, and

**Table 1** Summary of metabolic changes to hormones on passing through the pulmonary circulation. 5-HT, 5-hydroxytryptamine; ANP, atrial natriuretic peptide; PG, prostaglandin; ATP, adenosine triphosphate; ADP, adenosine diphosphate; AMP, adenosine monophosphate. Reproduced with permission from Lumb.

Group	Effect of passing through pulmonary circulation		
	Activated	No change	Inactivated
Amines		Dopamine Epinephrine Histamine	5-HT Norepinephrine
Peptides	Angiotensin I	Angiotensin II Oxytocin Vasopressin	Bradykinin ANP Endothelins
Arachidonic acid derivatives	Arachidonic acid	PGI <sub>2</sub> PGA <sub>2</sub>	PGD <sub>2</sub> PGE <sub>2</sub> PGF <sub>2</sub> alfa Leukotrienes
Purine derivatives			Adenosine ATP ADP AMP

branching morphogenesis in the developing lung. NEBs are located at airway bifurcations and degranulate in the presence of hypoxia. It is postulated that they act as hypoxia-sensitive chemoreceptors linked to the central nervous system by their vagal afferent sensory fibres.

While some of the endocrine and metabolic functions of the lung are ill defined and poorly understood, others are well established and summarized in Table 1.

### Amines

The pulmonary endothelium selectively takes up norepinephrine and serotonin (5HT) from blood while sparing histamine, dopamine, and epinephrine. This results in the removal of 30% of norepinephrine and 98% of 5HT in a single pass through the lungs.<sup>4</sup> Norepinephrine is metabolized by intracellular monoamine oxidase (MAO) and catechol-O-methyl transferase, while MAO breaks down 5HT. There are no effects on histamine, dopamine, or epinephrine because these compounds cannot be transported into the pulmonary endothelial cells due to the lack of an active transport mechanism.

### Peptides

Angiotensin-converting enzyme (ACE) is found in plasma and systemic vascular endothelium, but is present in much larger quantities on the endothelium of pulmonary vessels. On passage through the lung, the inert decapeptide angiotensin I is converted into the vasoactive octapeptide angiotensin II by ACE. Although the circulation time within the pulmonary capillaries is <1 s, 70% of the angiotensin I reaching the lung is converted to angiotensin II.<sup>2</sup> The latter is 50 times more active than its precursor and is unaffected on passing through the lung. Similarly, the vasoactive nonapeptide bradykinin is also broken down by ACE in the lung. Atrial natriuretic peptide and endothelins are also removed by the lung.

### Arachidonic acid derivatives

Arachidonic acid metabolites PGE, PGE<sub>2</sub>, PGF<sub>2α</sub>, and leukotrienes are metabolized extensively in the lung by specific enzymes, while PGA<sub>2</sub> and PGI<sub>2</sub> pass through unchanged. As with catecholamines, the selectivity for specific prostaglandins is attributed to selectivity in uptake pathways and not to intracellular enzymes.

### Purine derivatives

The purines adenosine monophosphate (AMP), adenosine diphosphate, and adenosine triphosphate are metabolized to adenosine by specific enzymes on the surface of the pulmonary endothelial cells. Adenosine is taken up rapidly into the endothelial cells where it is phosphorylated to AMP or deaminated to inosine and ultimately to uric acid.

This selectivity of the lung seems to imply that it acts as a metabolic filter removing certain locally important vasoactive substances, while substances important to systemic regulation pass unaffected. It also implies that vasoactive substances normally removed by the lung may have profound systemic effects if they were to bypass the lung.

### Pulmonary drug metabolism

The lung is an important extra-hepatic site for mixed function oxidation by the cytochrome P450 system but unlike hepatocytes, their activity cannot be induced. Their metabolic capacity is small and easily saturated. An important role of lungs may therefore be to act as a buffer by binding i.v. drugs, preventing an acute increase in systemic concentrations. The same metabolic systems also play a role in the biotransformation and detoxification of inhaled substances.

### Pulmonary extraction

Pulmonary extraction refers to the transfer of a drug from the blood into the lung. The drug may then be metabolized or released unchanged back into the blood. Several drugs, including some used during anaesthesia, are taken up, metabolized, or released slowly from the lungs.<sup>12</sup> Pulmonary endothelial cells are the primary site for binding or metabolism of i.v. drugs. They have high metabolic activity and an important role in breaking down endogenous substrates, but their metabolic capacity is low and easily saturated.

#### Effects of pulmonary drug extraction

In most patients, i.v. drugs are retained in the lungs by binding to specific sites on pulmonary endothelium. Pulmonary extraction buffers the rate of rise in drug concentration within the systemic circulation. Pulmonary extraction may also help maintain a steady-state concentration by releasing 'excess' bound drug as the plasma concentration decreases. In the presence of moderate-to-severe right-to-left shunts, loss of buffering from lungs could result

in a dangerous rise in the plasma concentration for certain drugs, for example, lidocaine. Co-administration of drugs such as antidepressants and beta-blockers, which compete for similar binding sites, or the presence of significant lung disease has also been shown to decrease pulmonary uptake of drugs resulting in potentially toxic systemic concentrations.<sup>12</sup> Conversely, some drugs tend to accumulate within the lung causing dangerous local toxicity, for example paraquat, nitrofurantoin, bleomycin, and amiodarone.

#### Pulmonary extraction of anaesthetic drugs

While most drugs used in anaesthesia are taken up by the lung to some extent, only prilocaine is metabolized within the lung.<sup>12</sup> Drugs with a significant pulmonary uptake are basic amines with a pKa of >8. Other factors known to influence the pulmonary uptake are molecular weight, lipophilicity, protein binding, ventilation, perfusion, oxygenation, co-administration of other drugs, cardio-pulmonary bypass, ageing, lung pathology, and anaesthesia.<sup>10</sup> None of the drugs with high pulmonary extraction undergo significant metabolism within the lung. As the systemic levels decrease, drug is released from the lung. The extent of pulmonary extraction for anaesthetic agents is shown in Table 2.

#### Pulmonary metabolism of inhaled drugs

There are three major benefits that may be attained by delivering medication to the lungs via the inhaled route: rapid onset of action, high local concentration by delivery directly to the airways (and hence high therapeutic ratio and increased selectivity), and needle-free systemic delivery of drugs with poor oral bioavailability.<sup>13</sup> As a consequence of rapid absorption and low metabolic activity, many inhaled drugs have near-complete bioavailability via the

**Table 2** Pulmonary extraction, metabolism or both of drugs used in anaesthesia

Drugs	Extraction
Local anaesthetics	
Lidocaine	41–51%
Prilocaine	40%
Mepivacaine	20%
Bupivacaine	12%
I.V. anaesthetic agents	
Diazepam	30%
Propofol	28%
Thiopental	14%
Opioids	
Fentanyl	75%
Meperidine	65%
Alfentanil	10%
Morphine	4–7%
Neuromuscular blocking agents	
Vecuronium	No significant pulmonary uptake
Atracurium	No significant pulmonary uptake
D-Tubocurarine	No significant pulmonary uptake
Rocuronium	No significant pulmonary uptake
Catecholamines	
Norepinephrine	16%
Dopamine	20%

lung. However, some isoforms of the cytochrome P450 enzymes are present in higher quantities in the lung in comparison with the liver. This may explain why some inhaled drugs such as theophylline, salmeterol, isoprenaline, budesonide, and ciclesonide undergo significant metabolism in the lung, while others do not. Metabolism of inhaled chemicals is not always beneficial. For example, some innocuous chemicals in cigarette smoke are metabolized into potential carcinogens by the lung. In an attempt to improve airway selectivity and minimize systemic side-effects; several drugs, particularly inhaled steroids, have been designed to take advantage of bio-transformation within the lungs as prodrugs or soft drugs.

### Prodrugs

An inactive drug that is metabolized to its active form before or at its biological target within the lung is called a 'prodrug'. The prodrug beclomethasone dipropionate is metabolized to the more potent 17-beclomethasone monopropionate by esterases in the lungs. This reduces the risks of side-effects within the oropharyngeal tract from this steroid.<sup>13</sup> Another steroid, ciclesonide, is metabolized into its active form by esterases in the lungs and further reversibly conjugated to fatty acids. Similarly, reversible conjugation of budesonide with fatty acids within the lung helps to retain it within the larger airways. Budesonide conjugates are gradually hydrolyzed and free budesonide is regenerated. This results in prolonged lung retention, increased duration of action, and a lower elimination time.

### Soft drugs

An active drug molecule that is readily inactivated by hydrolysis at its target site within the lung or blood is called a 'soft drug'. Several soft drug steroids (itrocinonide,  $\gamma$ -butyrolactone steroids, flucortin butyl-ester, and butixocort propionate) have been in clinical development as inhaled drugs with the purpose of maintaining a high local intrinsic activity, but are readily inactivated in the lung or blood avoiding systemic spillover and side-effects.<sup>13</sup>

### Platelet formation in the lung

The abundance of megakaryocytes in the pulmonary circulation coupled with a higher platelet count within the pulmonary vein when compared with the pulmonary artery suggests that megakaryocytes undergo fragmentation within the lungs to produce platelets. However, the precise role and extent to which lungs contribute towards the production of platelets remains unclear.<sup>14</sup>

Megakaryocytes bypassing the lung may have a role in the aetiology of clubbing and hypertrophic osteoarthropathy. One theory suggests that megakaryocytes bypassing the pulmonary vascular bed in the presence of pulmonary pathology or a right-to-left shunt lodge in nail bed capillaries. Their interaction with the vascular endothelial cells leads to the release of a variety of factors, including platelet-derived growth factor and vascular endothelial growth factor. This causes vascular hyperplasia and proliferation of periosteal layers, resulting in clubbing and hypertrophic osteoarthropathy.<sup>15</sup>

### Conclusion

The lung is responsible for several important non-respiratory functions, vital for maintenance of normal physiology. Evolving research has not only contributed to improved understanding of these roles, but also opened new diagnostic and therapeutic avenues for a variety of medical conditions.

### Declaration of Interest

None declared.

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Please see multiple choice questions 21–24.