

CHAPTER 1

HISTORICAL INTRODUCTION

1.1 BEFORE THE TWENTIETH CENTURY

Michael Servetus (1511–1553) born in Aragon, Spain, is credited with the discovery of the pulmonary circulation, although a 14th century Arabic physician Ibn-an-Nafis, unknown to Servetus, had reached similar conclusions. A Spanish physician and theologian, Servetus was burnt at the stake in Geneva for his religious beliefs about the nature of the Trinity, published in his book “The Restoration of Christianity” (Figure 1.1.1). In an obscure part of this treatise, after arguing that the soul of man lies in the blood itself, he says of the lung *“the communication is not through the middle wall of the heart as is commonly thought; but, by a very ingenious arrangement, the subtle blood is urged forward by a long course through the lungs; and is poured from the pulmonary artery into the pulmonary vein, where the blood is mixed with inspired air”*. His chief reason for predicting that blood must circulate from the right to the left side of the heart through the lungs (after all he had no microscope) was *“the notable size of the pulmonary artery; it was not made of such sort or such size, nor does it emit so great a force of pure blood from the heart into the lungs, merely for their nourishment”*.



Figure 1.1.1. Michael Servetus (1511–1553), Spanish physician and theologian, discoverer of the pulmonary circulation.

4 Pulmonary Circulation

One of the pioneering microscopists, Marcello Malpighi (1628–1694), physician to Pope Innocent XII, corresponded with his friend, the mathematician, Giovanni Borelli. His first letter contains the first description of the lung alveoli, and his second the first observations of the pulmonary capillaries! The alveoli were “*an almost infinite number of orbicular sinused vesicles, just as in a honeycomb we see alveoli formed by wax spread out into walls*”, and of the pulmonary capillaries “*I could clearly see that the blood is divided and flows through tortuous vessels, and that it is not poured out into spaces but is always driven through tubules and distributed by the manifold bendings of the vessels*”.

At about this time (1667), Robert Hooke (1635–1703), assistant to Robert Boyle (1627–1691), by “*pricking all the outer coat of the lungs with the slender point of a very sharp pen-knife*” was able to maintain life in a dog at constant lung volume by passing air through the lungs with two pairs of bellows in series. This proved that it was a supply of fresh air rather than respiratory movement which was essential to life. The eighteenth century saw the isolation of the respiratory gases and an appreciation of their different roles. Joseph Black (1728–1799), Professor of Medicine in Glasgow, showed the presence of carbon dioxide in expired air by exhaling through lime water. Oxygen was isolated independently by Joseph Priestley (1733–1804), a Unitarian minister in Leeds, and Carl Wilhelm Scheele (1742–1786) from Sweden. Antoine Laurent Lavoisier (1743–1794) from Paris, the most distinguished chemist of his generation and a high-ranking civil servant, was the first to formulate the complete process of pulmonary gas exchange in a memoir (1777): “*Eminently respirable air (“oxygine”) that enters the lung, leaves it in the form of chalky aeriform acids (CO₂) in almost equal volumeRespiration acts only on the portion of pure air that is eminently respirablethe excess, its mephitic portion (nitrogen) is a purely passive medium which enters and leaves the lung without alteration*”. Tragically, he was condemned to death by a French Revolutionary Tribunal, and guillotined in Paris; his body was thrown into a common grave.

In the nineteenth century, Carl Ludwig (1816–1895), Professor of Physiology in Leipzig, coupled mercury manometers to recording kymographs to measure systemic blood pressure. Beutner, one of his students, in 1852 measured the pulmonary artery pressure in cats, finding an average value of 17.5 mmHg, about 13% of the systemic level. The Fick Principle (the gold standard for the measurement of total pulmonary blood flow) appeared as a brief note in the proceedings of the Würzburg Physicalische-Medizinsche Gesellschaft in 1870. Adolph Fick (1829–1901) was actually more famous for his law of Diffusion in Fluids, published at the age of 26 years!

J.B. West’s collection of historical essays (1999a) is an excellent source of reference to pre-20th century respiratory physiology.

1.2 THE TWENTIETH CENTURY

1.2.1 Cardiac catheterisation

The first sampling of blood from the pulmonary artery (so-called ‘mixed venous’ blood) for the application of the Fick Principle in humans was done by Werner Forssmann (1904–1979) in Germany in which he courageously introduced a ureteric catheter into his antecubital vein and guided it himself with the aid of fluoroscopy, into his right atrium. Clinical cardiac catheterization, including measurement of pressures in the right atrium, right ventricle, pulmonary artery (Figure 1.2.1), and left atrium (directly by trans-septal puncture, or indirectly by pulmonary arterial wedging) was developed by André Cournand (1895–1988) and Dickinson Richards (1895–1973) and their colleagues at the Bellevue Hospital in New York in the 1940s.

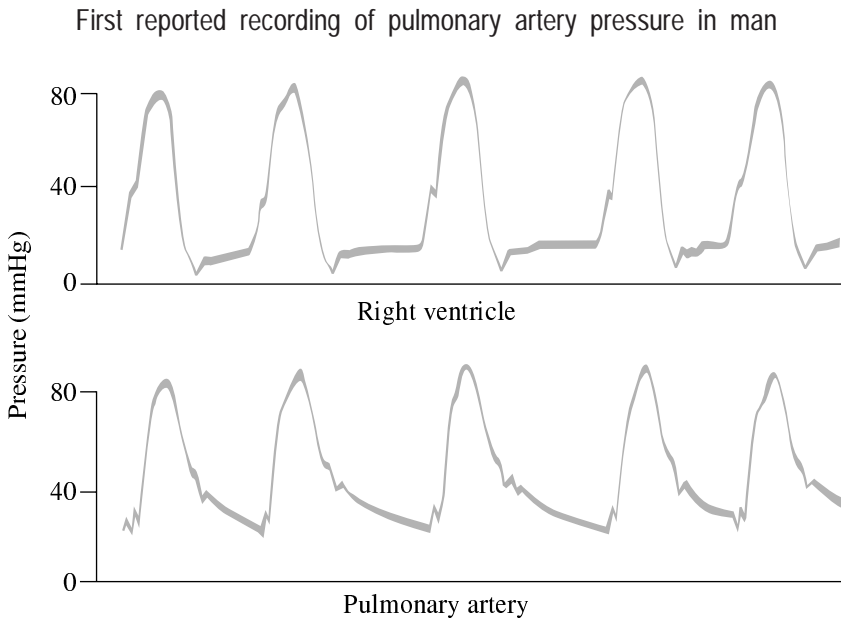


Figure 1.2.1. Simultaneous tracings in right ventricle and pulmonary artery in a patient with severe pulmonary hypertension (redrawn from Cournand, A., Bloomfield, R.A. and Lauson, H.D. (1945) *Proc Soc Exptl Biol Med* **60**, 73).

Forssmann, Cournand and Richards received the Nobel Prize in 1956. With right heart catheterisation, pulmonary arterial and left atrial pressures and, using the Fick principle, cardiac output could be measured at rest and on exercise in healthy volunteers, and pulmonary vascular resistance (PVR) derived for the first time. Their Nobel Laureate acceptance speeches make inspiring reading (Cournand, 1957; Richards, 1957). Both expressed debts of gratitude to their mentors, William F. Hamilton (of dye dilution curve fame) in the case of Cournand, and Lawrence J. Henderson (of the Henderson-Hasselbach equation) in the case of Richards. In his Nobel lecture (1957), Richards gives an excellent survey of existing knowledge about pulmonary heart disease and cor pulmonale. Cournand (1957) warns us to “*beware of the danger of seeking security for our concepts in the accumulation of facts*”.

1.2.2 Hypoxic vasoconstriction

von Euler and Liljestrand’s demonstration of hypoxic pulmonary vasoconstriction (HPV) was published in 1946 (Figure 1.2.2). They worked at the Karolinska Institutet in Stockholm, and made the inspired guess, foreshadowing the \dot{V}_A/\dot{Q} era, that “*oxygen want and carbon dioxide accumulation call forth a contraction of the lung vessels, thereby increasing the blood flow to better aerated lung areas, which leads to improved conditions for the utilization of the alveolar air*”.

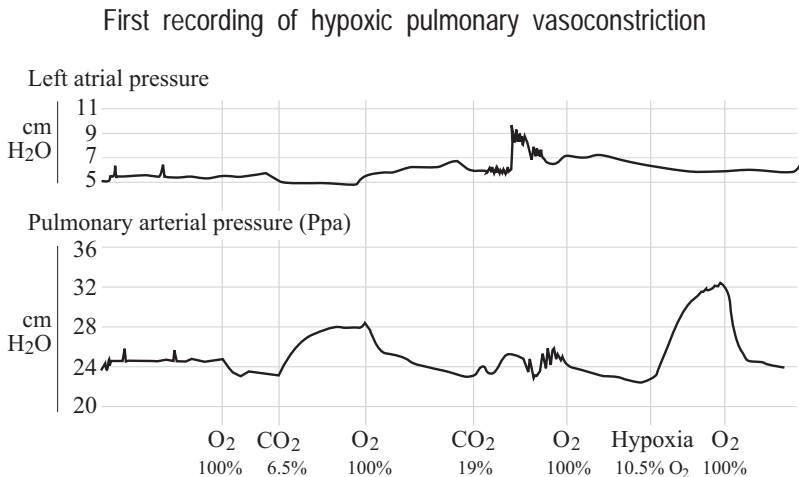


Figure 1.2.2. Cat anaesthetized with chloralose, open thorax with mechanical ventilation. 6.5% CO₂ in pure oxygen caused a moderate rise and hypoxia (10.5% O₂) a larger rise in Ppa. Acidosis caused by 19% CO₂ inhalation caused a rise in systemic blood pressure only (redrawn from von Euler and Liljestrand, 1946).

1.2.3 Distribution of blood flow

Dock (1947), a physician at the Long Island College of Medicine, Brooklyn, NY, noted that in work published from Cournand and Richards' laboratory in 1946 systolic pulmonary arterial pressure in recumbency was 18–30 mmHg. In the upright position, he reasoned that the upper quarter of the lung would be relatively ischaemic (Figure 1.2.3). He then said: “*Alveoli which are aerated through the bronchi, but deprived of the flow of pulmonary arterial blood, with its low oxygen saturation, will have the highest oxygen and lowest carbon dioxide content. This favours the growth of tubercle bacilli.*” Dock also noted that in mitral stenosis, the pulmonary arterial pressure is 2–6 times as high as in normal subjects, that apical ischaemia does not occur, and that apical tuberculosis is rare (though common in congenital pulmonary stenosis). Writing when anti-tuberculous chemotherapy was just being introduced, he stated that the beneficial effect of sanatorium treatment for pulmonary TB was that patients were *lying down in bed*, and not because they were breathing mountain air!

Dock (1947) reasons that apex of upright lung is ischaemic

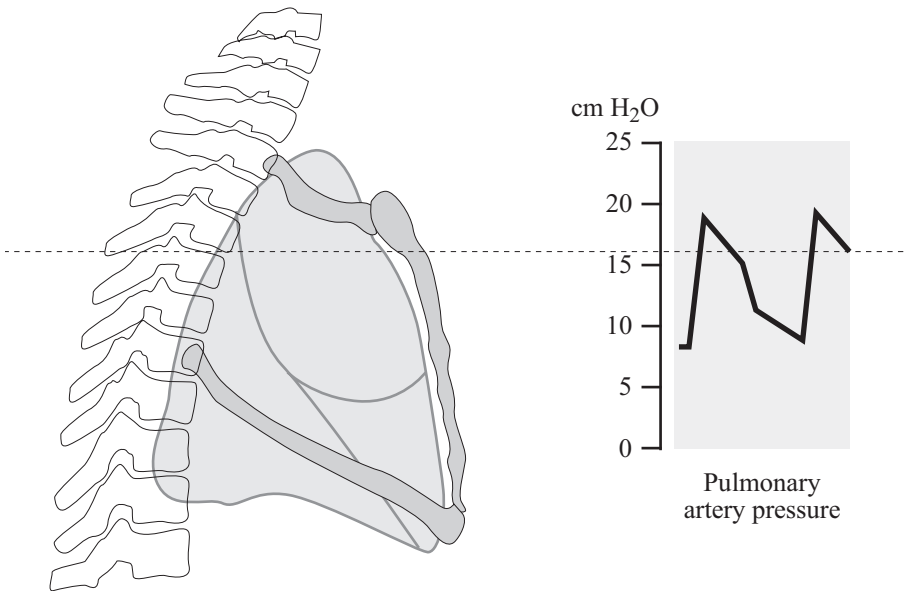


Figure 1.2.3. Relationship between pulmonary arterial pressure and the height of the upright lung, from which Dock (1947) deduced the reason for the apical location of pulmonary tuberculosis.

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Nevertheless, the discovery of a *systematic* gradient of blood flow from cranial to caudal in the upright position was entirely fortuitous (see West (1999b))! The Medical Research Council had commissioned a cyclotron at Hammersmith Hospital to produce neutrons for radiotherapy. A spin-off from deuteron bombardment was the production of the positron-emitting radionuclide of oxygen (^{15}O). When inhaled in the form of carbon dioxide (C^{15}O_2), remarkable and unexpected results were seen.

First demonstration of vertical blood flow gradient

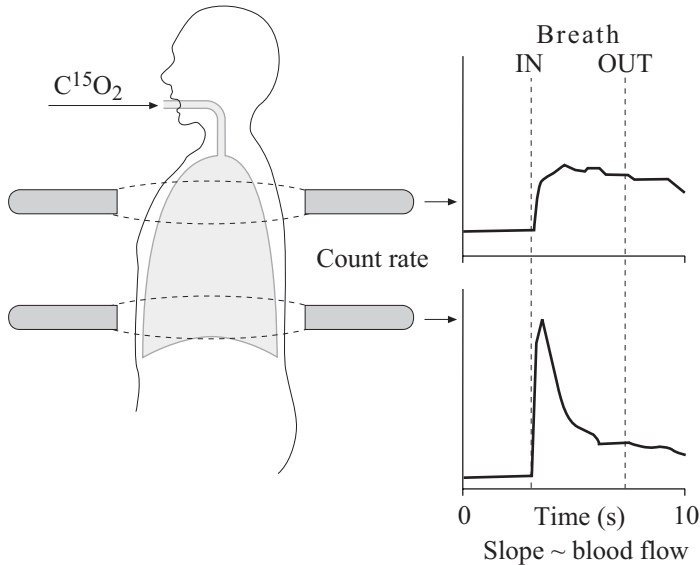


Figure 1.2.4. C^{15}O_2 , when inhaled, is rapidly converted in alveolar tissue to H_2^{15}O by carbonic anhydrase, and then removed from the counting field by local blood flow whose rate is proportional to the downslope of the radioactivity curve (redrawn from West and Dollery, 1960).

1.2.4 Pulmonary haemodynamics

The different effect of inflation of the lung on the extra-alveolar versus the alveolar vessels was first shown by CC Macklin (1946), who worked in Montreal. He called the two vascular compartments *expanded* and *compressed*. Another important concept, in view of the low pulmonary artery pressure, was that of the “vascular sluice” or “waterfall” or “Zone II effect”. Banister and Torrance (1960) in Oxford, S. Permutt and colleagues (1962) from the Johns Hopkins Hospital and J.B. West et al. (1964) from the Hammersmith Hospital developed the notion.

1.2.5 Diffusion

A famous controversy, lasting from about 1870 to 1923, concerned the secretion of oxygen by the lungs. Christian Bohr (1855–1911) from Copenhagen (the ‘Bohr’ effect describes the effect of CO₂ on the position of the oxygen blood dissociation curve), and JS Haldane (1860–1936) from Oxford (the ‘Haldane’ effect is the effect of oxygenation on the CO₂ dissociation curve) were the distinguished proponents of the oxygen secretion theory; both claimed to have shown that arterial PO₂ was higher than alveolar PO₂. This theory was eventually discredited by Bohr’s most famous pupil, August Krogh (Nobel prize winner in 1920 for his work on capillaries) in a series of papers published, with his wife, Marie, in the *Skandinavisches Archiv für Physiologie* in 1910. August Krogh began by apologising to his mentor “*I wish here not only to acknowledge the debt of gratitude which I, personally, owe to him (Bohr) but also to emphasize the fact, patent to everybody who is familiar with the problems here discussed, that the real progress made during the last twenty years in the knowledge of the processes in the lungs, is mainly due to his labours*”.

Later (in 1915), Marie Krogh published an elegant paper describing the clinical measurement of the diffusion constant (now called the diffusing capacity [DLCO], or transfer factor [TLCO]) for carbon monoxide). Her method was “rediscovered” 40 years later, and updated in a “classic” paper by Ogilvie et al. (1957) which described and validated the single breath measurement of DLCO [TLCO], a test which is still one of the most widely used and useful pulmonary function tests, because it is a “window on the pulmonary circulation”. The physiological basis of the DLCO was brilliantly expounded by FJW Roughton (who had earlier discovered the enzyme carbonic anhydrase) from Cambridge and RE Forster from Philadelphia in their *DM–Vc* paper (1957) whose title (38 words and 203 characters in length) would not be acceptable to any journal today!

1.2.6 Ventilation–perfusion (\dot{V}_A/\dot{Q}) ratios

The modern approach to oxygen and carbon dioxide exchange (the \dot{V}_A/\dot{Q} story) stems from “contract” research sponsored by the United States Navy and Air Force during the Second World War. In Rochester, New York, Wallace Fenn (1893–1971), Hermann Rahn (1912–1990) and Arthur Otis exploited the oxygen–carbon dioxide diagram and developed the unique \dot{V}_A/\dot{Q} line which contained every possible combination of alveolar PO₂ and PCO₂ for a given mixed venous blood and inspired air composition (Rahn, 1949) (see Chapter 4.3, Blood flow and pulmonary gas exchange, Figure 4.3.4). At the same time, but working independently, RL Riley

(1911–), first with JE Lilienthal (1911–1955) and then with A Cournand (Riley and Cournand, 1949) put forward the notion of “ideal” alveolar air and the three compartment model of gas exchange in terms of “ideal”, physiological shunt (*mixed venous-like*) and dead space (*inspired air-like*) compartments. The work of these two groups, which is as intellectually satisfying as anything else in physiological science, laid the foundation for the modern approach to pulmonary gas exchange.

1.2.7 Lung liquid

René Laënnec (1781–1826), who worked in Paris but was a Breton by birth, was the inventor of the stethoscope and gave the first clear description of *cor pulmonale*. In his “Traité de l’Auscultation Médiante”, he described clearly the clinical and pathological features of pulmonary oedema, which he defined as “*an infiltration of serum into the pulmonary tissue, carried to a degree such that it significantly diminishes its permeability to air*”. Ernest Starling (1866–1927), Professor of Physiology at University College, London, in 1896 put forward his famous Filtration–Absorption hypothesis “*...although the osmotic pressure of the proteids of the plasma is so insignificant, it is of an order of magnitude comparable to that of the capillary pressures; and whereas capillary pressure determines transudation, the osmotic pressure of the proteids of the serum determine absorptionso that, at any given time, there must be a balance between the hydrostatic pressure of the blood in the capillaries and the osmotic attraction of the blood for the surrounding fluids*”. Starling published a paper in 1894 (with AH Tubby) on liquid clearance from the pleural space.

In relation to lung lymphatics, Staub’s chapter (1997) mentions the pioneering work of William Miller (1858–1939) from the University of Wisconsin, Heinrich von Hayek (1900–1969), from Würzburg and Vienna, Cecil Drinker (1887–1956), from Harvard University, and Frederick Courtice (1911–1992), from the Australian National University. NC Staub made major contributions to our understanding of the pathophysiology of pulmonary oedema between 1970 and 1990.

A simple but influential paper was published by Guyton and Lindsey (1959) (Figure 1.2.5) which established the threshold for oedema accumulation in the lung in relation to Starling’s hydrostatic and osmotic balance of forces.

Pulmonary oedema is related to hydrostatic and osmotic pressures

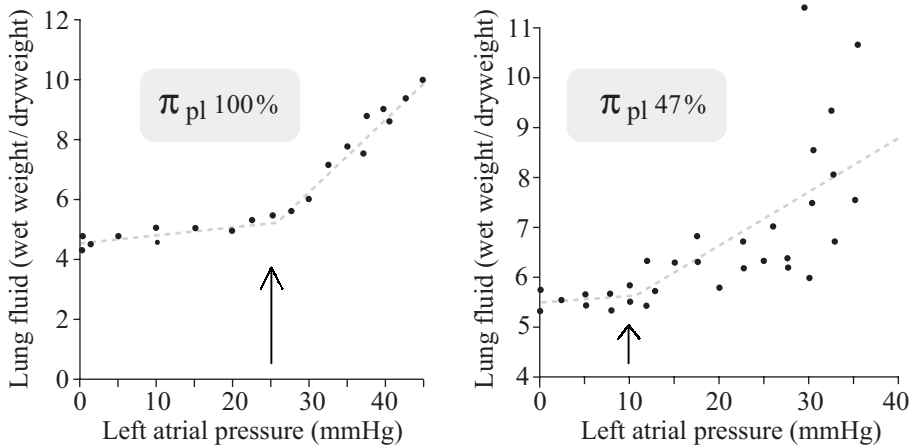


Figure 1.2.5. Fluid accumulation in lungs of anaesthetized dogs after raising left atrial pressure to varying levels for 30 minutes. Threshold for oedema formation is 25 mmHg at normal plasma protein oncotic pressure (π_{pl}), falling to 10 mmHg when oncotic pressure is reduced by half (redrawn from Guyton and Lindsey, 1959).

1.3 1970 TO THE PRESENT DAY

In the last 30 years much more has been discovered about the pulmonary circulation than in the preceding 400 years! The major advances have been in the basic sciences. The mechanism of hypoxic pulmonary vasoconstriction (HPV) is now more understandable in terms of the physiology of potassium and calcium ion channels. Cellular movement from blood to tissue, and within the extracellular matrix, is dependent on cell adhesion molecules (integrins and selectins) and chemokines. Genetic influences upon pulmonary vascular disease are being unravelled.

The walls of pulmonary blood vessels and the extravascular matrix are part of a dynamic equilibrium — cellular, structural and metabolic. Arteries and capillaries respond to high pressure and damage in stereotyped ways; arterial remodelling, in response to pulmonary hypertension, involves synthesis and secretion of an array of proteins which strengthen the vessel wall. At an organ level, there is a better appreciation of major sites of vascular resistance, and of the reasons for non-uniform blood flow distribution.

We hope the essence of this “new science” will stimulate the senses of the reader as she or he browses through the twelve other chapters of this *Introduction to “the largest circulation in the mammalian body”*.

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