

Evolution and the pulmonary circulation

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We were sitting, I recall, in the canteen of the Medical School at Birmingham. It must have been 1958. I had just returned from a year and a half at the Bellevue Hospital, New York, my mind still reeling from the experience of working in the cardiopulmonary laboratory of Andre Cournand. Donald Heath had returned from the Mayo Clinic where he had coolly reshaped the face of pulmonary vascular pathology. And it was there, in the canteen, that we planned to write a book on the pulmonary circulation. It was the beginning of a collaboration and friendship which was to last to this day and through which I came to appreciate, among many other things, those imaginative intellectual processes whereby static anatomical images of dead tissue under the microscope can be transfigured into dynamic concepts of living pathological processes.

During the succeeding 30 years our mutual interests led us on a series of expeditions to high altitudes which, in unexpected ways, added a depth of understanding and insight into common diseases back home. We were concerned, not with the short term problems of acclimatisation encountered by the occasional visitor to the mountains, but with the evidence for genetic adaptation in populations of humans and animals that have, for generations, been fated to spend their entire lives there.

Such studies have, inevitably, prompted wider considerations of the way in which genetic influences have fashioned the lungs and, in the following review, I shall try to give a more general background of the evolution of the lungs and to show how important evolutionary influences may be in understanding the pulmonary circulation.

Pollution of the atmosphere with oxygen

Life on our planet began in an atmosphere devoid of oxygen. The first organisms derived their energy from the breakdown of complex molecules which had been formed in the immense heat of the creation of the world. Some of the primitive pathways of anaerobic metabolism persist to this day in every cell of our bodies.

It may be that the supply of such complex molecules became used up. Perhaps for this reason, or more probably out of random discovery, about a billion and a half years ago a group of microorganisms discovered a way of producing biologically useful energy from the sunlight which fell unfiltered on the earth. These were the blue-green algae. The essential substance through which the conversion of energy could be effected, and which gave them

their characteristic colour, was chlorophyll.

The problem for the rest of the inhabitants of the planet was that the new process of energy transformation had a highly toxic waste product. This was oxygen. Its toxicity is not due to the diatom of the molecule of oxygen, but to other forms of oxygen known as oxygen free radicals. The free radicals are highly reactive chemically and attack many organic molecules.¹ They inactivate enzyme proteins by oxidising their sulphhydryl groups, and they destroy cell membranes by forming lipid peroxides.

The new photosynthetic process was highly successful to the extent that the earth's atmosphere gradually accumulated oxygen. Such pollution spelt death to most of the forms of life then existing, and the threat to the world community must have been immense.

Doubtless, through genetic processes they responded by developing mechanisms of chemical defence. Some were simple intracellular compounds such as glutathione which could scavenge the free radicals. Others, such as superoxide dismutase, were enzymes. Even today these defences are still protecting the cells in our bodies, preventing – for example – our adipose tissue from going rancid inside us.

Oxygen as fuel

The force of life is always opportunistic and, at a certain point, some organisms learned how to use the properties of oxygen as an electron donor and proton acceptor and to harness its reduction to the formation of ATP. An even more astonishing step was the takeover by nucleated organisms of these oxygen utilising forms, which became incorporated in their cytoplasm as mitochondria where they have remained ever since. In this extraordinary way oxygen changed from being a lethal pollutant of the atmosphere to become the element most generally essential to life on the planet.

Diffusion and convection

Life had its origin in water, and the first cells floated freely in that medium which is essential to all living organisms. The cell wall was a subtle compromise between the necessity to maintain a barrier which would protect an identity and the necessity to import and export materials. Because of their minute size the unicellular organisms were able to exchange food and excrement directly across their surface. The movement of such materials to and from the cell was primarily by diffusion, although the random currents of the watery environment must also have provided a fortuitous

help. As multicellular organisms developed and grew larger, however, simple diffusion became inadequate and they needed to impose their own convective streams on the surrounding water in order to maintain an adequate exchange. Many simple organisms, such as the coelenterates and sponges, use the surrounding water as their sole means of convective transport, which serves the combined functions of ingestion, respiration, and excretion.

As animals grew ever larger and more complex, an internal convective transport system also became essential. The external convective system was retained and, in primitive chordates such as amphioxus or the tunicates, provides a means for filtering food at the same time as for respiratory exchange. Even in such an advanced form of life as the fishes the function of the external convective system is still mixed. The passage of water through the mouth is used for ingestion, while its movement across the gills serves to exchange, not only respiratory gases, but also water and salts and ammonia, the chief end product of nitrogenous metabolism.

The migration of the animals on to dry land imposed great restrictions on the external convective system. In amphibia considerable exchange of water, salt, urea, and respiratory gases could still take place across the moist skin. Exploration far from the water's edge required an impervious skin and so those functions of the skin largely became discarded. Instead the skin took over the function of regulation of temperature which was required by the evolution of warm blood. By now the exchange of respiratory gases was restricted to the newly evolved lungs where a certain obligatory loss of water and heat also took place, while the excretion of nitrogenous waste was restricted to the kidneys.

Motion of the body as a whole is also a form of external convection. The ambivalence of the function of movement is expressed at its simplest in the *Paramecium*. Does it swim? Or is it simply renewing the water around it? Many fish use swimming to force water across the gills and to trap food in the pharynx. The movement of any predator is only an extension of the same principle. And we all walk away from our own excrement. In these ways movement of the body takes its place alongside the other convective systems.

Oxygen requirements

The development of the warm blooded mammals and birds was accompanied by a tenfold increase in oxygen consumption. Such an increase was made possible by the new external convective medium. Oxygen is relatively insoluble in water (about 0.3 ml/100 ml/100 mm Hg), and its abundance in air permitted an impressive decrease in the volume of ventilation.² On the other hand, the internal convective medium was not so substantially changed, so that the internal distribution of the increased consumption of oxygen could be met only by an increased cardiac output. The cardiac output of most mammals is in the region

of 90–150 ml/min/kg, while that of fishes³ is about 10–40 ml/min/kg.

A visit to the local butchers and fishmongers will illustrate the reason for the increase in oxygen consumption. Mammalian and avian flesh is mostly red, while fish flesh is white. The white skeletal muscle of the fish derives its energy mainly from an anaerobic glycolytic breakdown, while the red skeletal muscle of the mammals and birds is rich in mitochondria and the carrier pigment myoglobin which permits an increased use of oxygen. Glycolysis can provide energy only for short intense periods of activity. The great advantage of oxidative metabolism is that it permits the prolonged activity that has made the warm blooded animals so dominating a force on the planet.

The cardiovascular system

In the crustaceans and molluscs the internal convective system is an open one. The cardiac pump moves blood through the arteries directly into the intercellular spaces, whence it returns to the heart through ostia. In the vertebrates the cardiovascular system has become – for the most part – a closed one, the blood being separated from the interstitial liquid by capillaries. There are points in the circulation, however, where this separation is not complete – in the liver, spleen, marrow, and renal glomeruli. In addition the lymphatic system provides a direct communication between the blood and the interstitial liquid.

The fish heart⁴ comprises a single atrium and ventricle. The blood is expelled from the ventricle into the ventral aorta, then passes through the gills before reaching the dorsal aorta. The supply of blood to the tissues is from the dorsal aorta through a second capillary bed in series with the exchange capillaries of the gills.

The amphibian heart is composed of two atria and one ventricle. Systemic venous blood returns to the right atrium, while blood from the primitive lungs passes to the left atrium. The presence of a spiral valve in the conus arteriosus and the positions of the atrio-ventricular orifices are believed to direct most of the systemic return to the lungs, and most of the pulmonary venous blood to the rest of the body.

In mammals and birds the systemic and pulmonary circulations have become completely separated, apart from a minute communication through the bronchial circulation.

Pulmonary and systemic perfusion pressures

The separation of the circulatory system into two parts was accompanied by a striking difference in the two arterial pressures. The reason for a high systemic arterial pressure is usually ascribed to the necessity of perfusing the head in the upright posture. Guyton,⁵ for instance, states: "One of the obvious purposes of pressure control is to keep the pressure high enough so that blood can flow to all tissues of the body even when some of the tissues are far above

the level of the heart. For instance, in giraffes the mean arterial pressure is regulated to a level between 200 and 300 mm Hg; this much pressure is required to assure blood flow to the top of the head. At the other extreme the regulated level of the arterial pressure in primitive fishes may be as low as 30 mm Hg; because there are no hydrostatic gradients in fishes this is an adequate pressure to assure blood flow to all tissues."

However, the arterial pressure of the turkey is as high as that of the giraffe,⁶ and aortic rupture in turkeys is a common problem for breeders. And why is the blood pressure of the mouse as high as ours, or that of the sparrow even higher? Or why does the seal need a blood pressure four times as high as the dogfish?

A survey of the arterial pressure throughout the vertebrates⁷ reveals that a high blood pressure is a feature of the warm blooded animals. It arrived together with the separation of the circulation into two parts, and with the vastly increased capacity for physical exercise which accompanied the use of oxygen by red muscle. The explanation for the high arterial pressure of the warm blooded animals⁸ lies in the capacity of the heart to increase its output during exercise. During maximal exercise there is a massive vasodilatation of the vessels supplying the muscles, so that the total systemic resistance is near the lowest anatomically possible. The perfusing pressure during exercise is thus what it has to be in order to supply the muscles with blood. Even if the system had been set at a low resting pressure, the arterial pressure during exercise would have to increase to approximately this level. In that case, at the moment when the left ventricle had to increase its output it would be subjected to a substantial increase in afterload. Experience from the isolated heart shows how unadapted to this is the myocardium.⁹ It seems that it proved most effective for the body to maintain a stable high arterial pressure and to modulate the local supply of blood by variations in regional peripheral resistance.

Evolution of the lung

The lung was the organ which evolved to meet the greatly increased requirements for oxygen derived from a new external convective medium. It required the redesigning of both internal and external convective systems. Internally the circulation was divided into two parts, which maintained the primitive low perfusion pressure in the lungs while increasing greatly the perfusion pressure in the rest of the body. Externally an elaborate system of branching airways emerged from a single out-pouching of the pharyngeal ectoderm. The lightness of the air permitted a to-and-fro convective motion instead of the continuous one-way flow across the gills. Separating the two systems was a vast and delicate exchange membrane less than 1 μm thick. It was as big as a squash court, and yet had been organised in a space the size of a football, small enough not to be an encumbrance.

The efficiency of the design is staggering, yet

it suffered from two weaknesses – a susceptibility to obstruction of the airways and a susceptibility to flooding. The first was inherent in the to-and-fro convective system. Powerful reflex glossopharyngeal systems evolved to protect the trachea from inhaling obstructing material, while in the terminal airways an ingenious feedback system controlled the perfusion according to the alveolar partial pressure of oxygen and thus maintained ventilation:perfusion ratios and the systemic arterial oxygen saturation. The implications of this in the adaptation of humans and animals to high altitude are discussed by David Williams (pages S9–S13). The second defect, a susceptibility to flooding, was inherent in the new interface between air and water. Pulmonary oedema could never occur in the fish. It is one of the prices of evolution.

Pulmonary oedema

I shall not discuss here the forms of pulmonary oedema resulting from chemical attack of the alveolar capillary wall except to note that, in many of these, free radicals of various origins have been implicated.

Oedema of haemodynamic origin depends on the pulmonary capillary pressure. The low arterial pressure in the pulmonary circulation, together with the low arterial resistance and relatively high venous pressure, allow a total drop in pressure across the lungs of only about 5 mm Hg. Undoubtedly this contributes to the constancy of the capillary pressure. The chief threats to the pulmonary capillary pressure come from a displacement of blood from the systemic to the pulmonary compartments, and an increase in total plasma volume.

The pulmonary blood volume is only about one tenth of the systemic blood volume. This makes the pulmonary capillary pressure particularly sensitive to any disability of the left ventricle. When the output of a ventricle is reduced blood is transferred from the compartment upstream to the compartment downstream. It is therefore easy to see how a small reduction in output of a damaged left ventricle could lead to sufficient blood being transferred from the systemic to the pulmonary compartment to cause a substantial increase in pulmonary capillary pressure. (The same is not true of the right ventricle since the maximal quantity of blood that could be shifted from the lungs into the systemic circuit is somewhat less than a pint, and the effect should not be different from that of giving a person a "unit" of blood.) It is a matter of evolutionary misfortune, therefore, that the left ventricle has to support an afterload much greater than does the right, and that the coronary arteries, subjected to an evolutionally imposed high pressure, are susceptible to atheroma.

To these possible effects of a damaged left ventricle are almost always added the effects of an increase in total blood volume. The reason for this lies in the importance which the body gives to the maintenance of the arterial pressure.^{10,11} Any threat to the arterial pressure evokes a response of the sympathetic and renin:

angiotensin:aldosterone systems which sustain the arterial pressure at the expense of an expansion of the blood volume and retention of salt and water.¹²⁻¹⁴

Conclusions

The pulmonary circulation is the meeting place of two great convectional transport systems. How it came to be as it is can be elucidated by considerations of evolutionary necessities. First among these is the development of an increasing need for oxygen in the evolving species. Second is the emergence from the waters and the exploration of dry land. The physical requirements of the two convectional systems have necessitated compromises. On the cardiovascular side has come a dependence on a high arterial pressure, fiercely defended by neurohumoral mechanisms at the expense of a retention of water and salt. On the external side has been the need for a large exchange interface, combined with the convenience of an organ of limited dimensions. The system of to-and-fro ventilation into a blind tree of airways carries with it the twin perils of blockage

and flooding which are of everyday concern in the wards.

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