Chapter 2
Fundamental Principles of Gas Exchangers

The quality of a system depends on the quality of the components which form it, as well as the excellence of its organization.

French (1988)

2.1 General Observations

Inaugurating as a simple, plain cell membrane in the primeval unicellular prokaryotes and progressing to the most advanced respiratory systems of the endothermic-homeothems, i.e., the bronchioalveolar lung of mammals and the parabronchial one of birds, the designs of gas exchangers have occurred based on remarkably similar bioengineering principles. The gas exchangers have developed under dynamic environmental conditions, especially those of shifting O_2 and CO_2 levels (Sects. 1.2 and 1.3). In its broadest context, respiration comprises spatiotemporally coordinated biomechanical, biophysical, behavioral, and physiological processes. Together, they effect movement of two vectorial quantities in opposite directions – influx of O_2 from the environment into the organism and efflux of CO_2 to the outside. More specifically, external respiration entails the acquisition of O_2 and in derived animals its transport through properly configured airways and vasculature while internal respiration involves the utilization of O_2 at the cellular level, specifically in the mitochondria, to generate energy mainly in form of ATP. Carbon dioxide (CO_2) and water (H_2O) are the secondary products of internal respiration.

$$6O_2 + C_6H_{12}O_2 \rightarrow 6CO_2 + 6H_2O + \text{energy (ATP)}$$

In a steady, non-limiting state, driven by its utilization at the mitochondrial level, the flow of O_2 from the external environment to the cells is constant. The diversification of the animal life has been accompanied by progressive advancement of the respiratory mechanisms and processes. The functional designs of the gas

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exchangers robustly correlate with the phylogenetic advances of the different animal taxa (e.g., Maina 1994, 1998; Powell and Hopkins 2004). Those animals that have high metabolic rates and therefore large O_2 needs have structurally more complex and functionally more efficient gas exchangers (Chap. 5). Although they differ phenotypically, some structural and functional features have been evolutionary "hard-wired" (e.g., Tenney 1979). Body designs and processes that have stayed constant for a long evolutionary period are conserved. Such are designated as "Bauplans" (="blue prints" = "frozen cores") (e.g., Wagner 1989). Mainly associated with resource procurement (e.g., Alexandrou et al. 2011), such attributes occur in gas exchangers. For example, the "three-ply" (tripartite-laminated) design of the air/water–blood tissue barrier (e.g., Maina and West 2005) has apparently been conserved for ~400 million years (e.g., Power et al. 1999) and diffusion has been the sole means of movement of O_2 across tissue barriers since aerobic respiration started over 2 billion years ago (Gya) (Figs. 1.4–1.6). The rarity of Bauplans manifestly bespeaks of the importance and the immense material cost of establishing and maintaining such highly consequential structures and processes. The question of what structures have been conserved, the basis of their conservation, and the physiological and ecological impacts of such outcomes in many cases remain to be quite determined (e.g., Bacigalupe and Bozinovic 2002; Rozanek and Roubik 2008). Except for the insectan tracheal system where O_2 is conveyed directly to the tissue cells (e.g., Schottenfeld et al. 2010) (Sect. 5.5), the respiratory pathway exhibits hierarchical, i.e., multilevel, organization where the respiratory organ is ventilated with water or air and perfused with blood, processes that bring the respiratory media into close proximity over a large surface area and thin tissue barrier, creating and maintaining a partial pressure gradient of O_2 (ΔPO_2) that drives it (O_2) across the tissue barrier by passive diffusion (e.g., Olmeda et al. 2010). The flux of O_2 correlates directly with the area of the respiratory surface and inversely with the thickness of the tissue barrier. After binding to metal-based carrier-pigments or dissolving in the blood/hemolymph, O_2 is distributed to the rest of the body where at the blood capillary level it diffuses into the surrounding tissues/cells, ultimately entering the mitochondria where energy is produced on their cristae. Because of the distinctive physicochemical properties of water and air (Chap. 3), no one gas exchanger can function with equal efficiency in the two respiratory fluid media, water and air.

Energy is decisive to life from molecular, cellular, ecological, and evolutionary levels. Living organisms are open thermodynamic systems. They continuously exchange matter and energy with the environment. Oxygen is continually taken up and utilized for energy production that is vital to driving the physiological machinery. In terms of modern means of carrying out economic transactions, figuratively, energy is the currency that animals use to purchase and procure services. Metabolic rate defines the pace at which energy is mobilized, transformed, and utilized by an organism to build, service, and maintain its infrastructural integrity and drive the necessary processes that maintain homeostasis (e.g., Calder 1984; Kleiber 1965). The evolutionary success of an organism is foremost determined by the efficiency with which it procures and utilizes O_2. Those species that

can maintain high O_2-to-CO_2 exchange ratio in relation to their body mass can generate high and stable tissue-fluid gas concentrations under different environmental conditions and metabolic states. Ecologically, they are the most successful ones. Predator avoidance, survival, and self-perpetuation mainly depend on the level and the efficiency of energy acquisition and expenditure as well as feeding habits. In thermodynamic terms, death can be defined as a state of zero energy production and with it nil (zero) O_2 consumption (VO_2). The energy in the environment is effectively at equilibrium with that in the lifeless body. Energy production by oxidative phosphorylation has been an irrevocable process since the O_2-consuming pathways were established in some early prokaryotic and eukaryotic cells. Utilizing finite quantities of O_2, eukaryotic sex cells and unicellular organisms have for millennia perpetuated themselves from generation to generation.

A remarkable assortment of respiratory structures has evolved to supply O_2 needs. They range from the primitive water lungs and air gills of the invertebrate organisms to the complex gills and lungs of the higher vertebrates (e.g., Maina 1998) (Chap. 5). The tropical oligochaete swamp worm, *Alma emini*, which subsists in the derelict waterlogged soil of the floating mats of papyrus swamps of East Africa, a generally anoxic and highly reducing habitat (Stephenson 1930; Beadle 1974), presents a particularly interesting respiratory behavior. It constructs a lung when it requires one! On surfacing from the water-logged soil to breathe air, the posterior part of the body, which is highly vascularized, folds up to form a respiratory groove, a lung (Maina et al. 1998) (Figs. 2.1 and 2.2a). When the worm retracts back into the soil, some air is trapped in the grove and from it O_2 extraction continues under the soil (Mangum et al. 1975a). *Alma* can survive for as long as 2 days under anoxia (Beadle 1957). During such a time, it may result to anaerobic respiration or energy may be derived from metabolic breakdown of hydrogen sulfide (H_2S) that exists abundantly in the soil. Symbiotic bacteria which may be involved in such a process occur in the cytoplasm of the cells that line the lung (Maina and Maloiy 1998) (Fig. 2.2b).

Large shifts in the concentrations of the respiratory gases from the tolerable range are harmful to unacclimatized/adapted animals (e.g., Brunelle et al. 2005). Except for fossorial (underground) habitats, on the whole, open terrestrial habitats are not liable to hypoxia or hypercapnia due to the mass (convective) movements and diffusivity which mixes the gases, equilibrating gas-tensions in and between habitats. Animals operate across a range of metabolic (energetic) levels which are to different extents determined by factors such as sex, age, habitat occupied, prevailing environmental conditions (e.g., ambient temperature and O_2 availability), body mass, phylogeny, and lifestyle. These and other selective pressures have acted on the genotype to create various phenotypes, i.e., functional designs. At rest, VO_2 is low during modest exercise, while at peak exercise, when continued activity does not lead to increase in VO_2, maximum VO_2 (VO_{2max}) is reached. The correlation between an animal's environment and its respiratory requirements is a very intimate one. From rest to flight, bats and birds increase their VO_2 by factors that range from 10 to 20 times (e.g., Thomas 1987; Butler 1991) and insects by as much as 100–400 times (e.g., Portier 1933; Weis-Fogh 1967). When exposed to a hypoxic environment, to support the basic metabolic requirement, animals typically

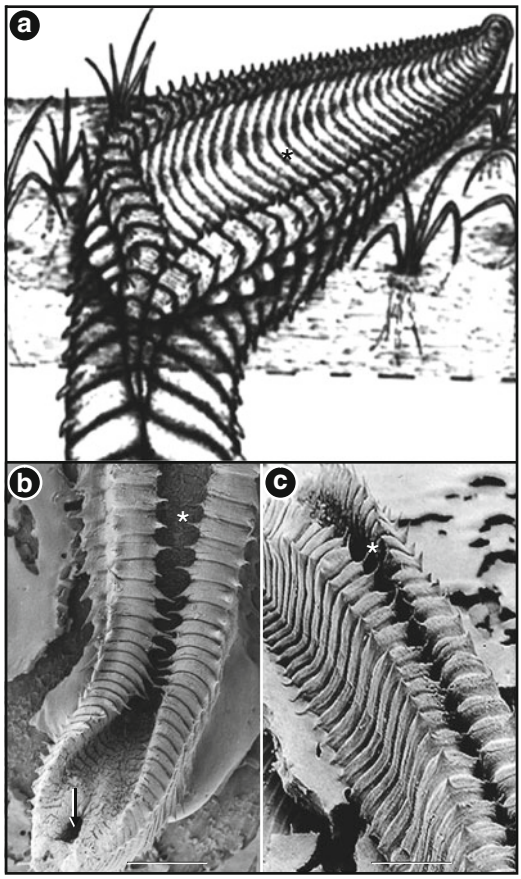

Fig. 2.1 (**a**) Sketch of a respiratory groove (*star*) on the posterodorsal part of the body of the oligochaete swamp-worm, *Alma emini*, which subsists in anoxic, hydrogen sulfide-rich soil. (**b**, **c**) *Alma emini* in different breathing positions. *stars*, respiratory groove; *arrow* (**b**), cloaca. *Scale bar*: 10 cm

extract and transfer the required amount of O_2 to the tissues equivalent to that when in a normoxic one. The respiratory system must be designed with sufficient plasticity to adapt to the extremes of physiological demands for O_2 in shifting states and circumstances. Under hypoxic conditions, it is the availability of O_2 rather than the exchange rate and potential of acquiring it that is limiting. Dependent on factors such as the PO_2, pulmonary ventilatory rate, and blood flow rate, O_2 is secured by the gas exchanger, chemically bound to a carrier (transport) pigment in the capillary blood, and convectively transported to all parts of the body by the circulatory system. Movement of O_2 down the cascade of compartments and tissue spaces, i.e., from the gas exchanger to the mitochondria, is regulated by behavioral and physiological states under which the animal operates. Through an intricate feedback mechanism, O_2 and CO_2 levels in the body spaces and fluids are detected and properly controlled. At the level of gas exchange, the pulmonary diffusing capacity (conductance) of O_2 (DO_2) depends foremost on the diffusion distance (the thickness of the blood–gas/water barrier) and the respiratory surface area (Fig. 2.3) and the O_2-permeation properties of the tissue barriers. In the rainbow trout and the

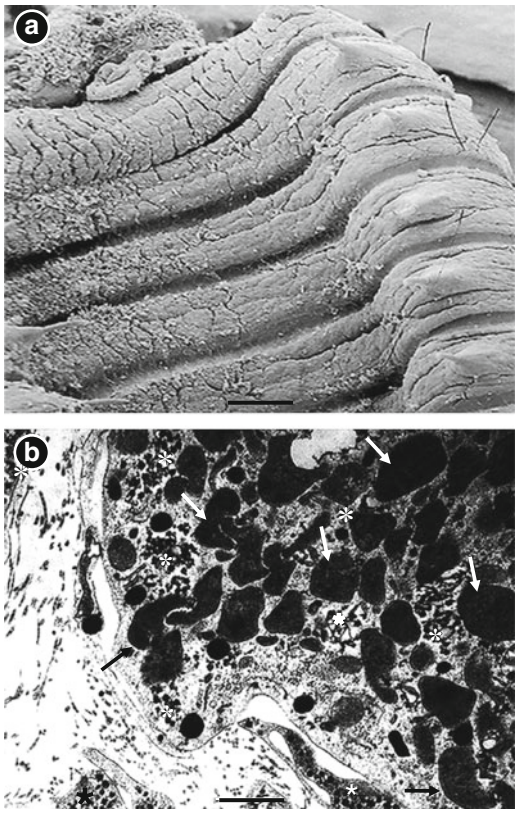

Fig. 2.2 (**a**) Close-up of the respiratory groove of the swamp-worm, *Alma emini*. *Scale bar*: 0.5 cm. (**b**) Cells lining the respiratory groove that contain symbiotic bacteria (*arrows*) that are involved in the detoxification of hydrogen sulfide. *Asterisks*, deposited elemental sulfur and its complexes. *Scale bar*: 0.5 μm

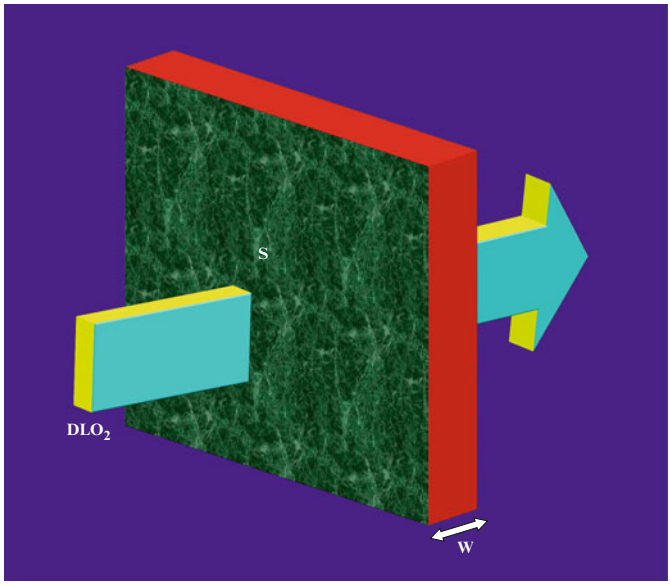

Fig. 2.3 In a gas exchanger, the diffusion capacity of oxygen (DLO_2) correlates directly with the surface area (S) and inversely with the thickness of the tissue barrier (W)

lingcod, e.g., at rest, only about two thirds of the gill's respiratory units, the secondary lamellae, are perfused (e.g., Farrell et al. 1979). Generally, in fish, during exercise, VO_2 can increase 8–10 times (Jones and Randall 1978). In the blue crab, *Callinectes sapidus*, in warm, bottom, and still waters and during low-tide, hypoxia is averted by increasing the ventilation and the lamellar perfusion recruitment (e.g., Farrell et al. 1980; DeFur and Pease 1988), reduction of the thickness of the water–blood barrier (e.g., Farrell et al. 1980), and adjustment of the blood O_2-binding properties (Jensen and Weber 1985). In extreme circumstances when hypoxia is accompanied by high temperature, metabolic rate may drop to conserve O_2 and/or the fish may relocate to less hypoxic waters (e.g., Whitmore et al. 1960). Cephalopods, e.g., *Loligo* and *Octopus*, can increase their VO_2 by a factor of 2–3 times over resting ones (e.g., Wells et al. 1983). Squids which live in cold, deep seawater have large gill surface areas and thin water–blood barrier compared to those which inhabit shallow waters (Madan and Wells 1996). The cephalopod heart mainly works aerobically by largely exploiting amino acids as the substrates for oxidative metabolism (Hoeger and Mommsen 1985). By retracting into the shell, the bivalve mollusc, *Pholas dactylus*, can totally shut down the posterior parts of the gills and at their maximal enlargement, the gills may be three times as long as the shell itself (Knight and Knight 1986). In fish, ion pumping and gas transfer can be synchronized when the gills are exposed to water (e.g., Wood and Randall 1973). The mammalian lung has a large functional reserve (Weibel 1984). DO_2 can increase by a factor of 2. The goat can reach VO_{2max} even under hypoxic conditions and only the smallest mammals utilize the whole of their DO_2 under such a condition (Taylor et al. 1989). Animals that have the highest VO_2, e.g., birds and insects in flight, have exceptionally efficient gas exchangers (Sects. 5.4.4 and 5.5).

In the course of the evolution of the gas exchangers and the respiratory processes and strategies, concerning the acquisition and the utilization of O_2 for metabolic activities, important quantum events have occurred. The most distinctive ones are (a) the transformation of prokaryotic to eukaryotic cells, (b) the change from unicellular to multicellular forms, (c) the transition from water- to air-breathing, (d) the progress from heterothermic–ectothermy to homeothermic–endothermy, and (e) the attainment of energetic lifestyles such as flight. When the O_2 need exceeded that which could be supplied by the existing gas-exchanger, specialization and/or development of a new structure(s) occurred.

In gas exchangers, ventilation, perfusion, and diffusion are the most important mechanisms for the movement, uptake, and transfer of O_2. Physical laws determine the flow dynamics of fluids along tubes/conduits. Convective (bulk = mass) movement of respiratory fluid media (water and gases) requires energy (Fig. 2.3). In a simple unicellular organism, where the surface-to-volume ratio is large and the distances short (Fig. 2.4), diffusion serves for gas exchange. However, as the metabolic rate, size, and structural complexity increase, diffusion fails. At that point, energy-consuming convective means of transporting the respiratory fluid media (Fig. 2.5) became necessary (e.g., Schmidt and Carmeliet 2010) (Fig. 2.6). The dynamics of the flow of a fluid through a long cylindrical conduit very much

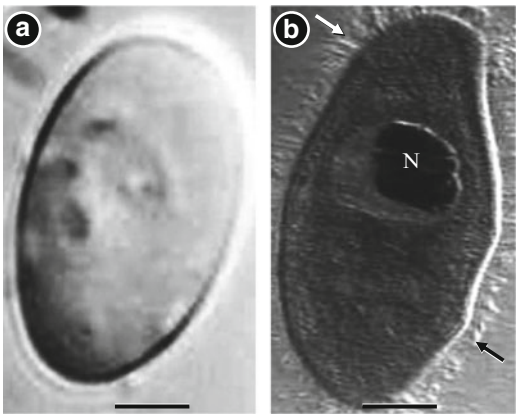

Fig. 2.4 A prokaryotic unicell (**a**) and a eukaryotic unicell (**b**). N (**b**), macronucleus; *arrows*, cilia. *Scale bar*: **a**, 2 μm; **b**, 50 μm

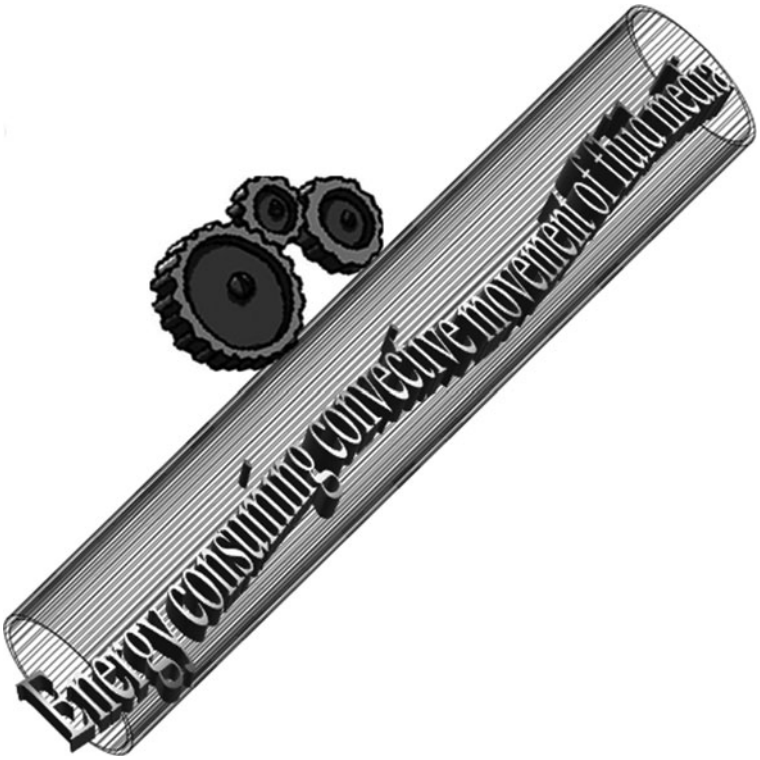

Fig. 2.5 The movement of respiratory fluid media, water and air, requires energy

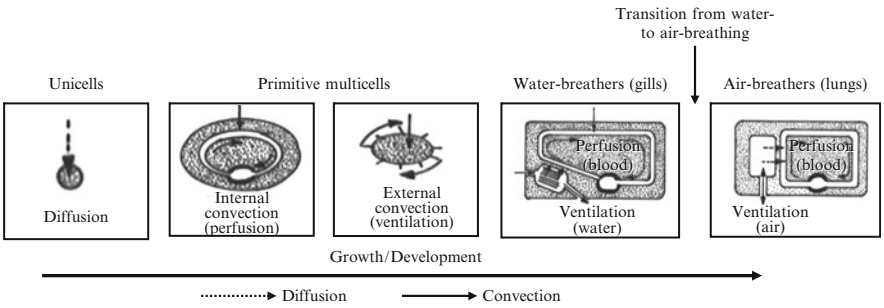

Fig. 2.6 Changes from diffusion driven respiration in simple organisms to perfused and ventilated ones in animals during increase in size and complexity

corresponds to that of the flow of electricity along a wire which is described by Ohm's Law as follows:

$$V = \Delta P \,.\, R^{-1}$$

where V is the current, ΔP is the potential difference between two points, and R is the resistance.

Laminar flow of a Newtonian fluid in a rigid cylindrical tube is described by the Hagen–Poiseuille's equation as follows:

$$Q = \pi r^4 (P_i - P_o).(8\ \eta\ L)^{-1}$$

where Q is volume rate of flow (the volume of fluid flowing past a given point per unit time), r is the internal radius of the tube; L is its length of the tube, P_i–P_o is the difference between the inflow (i) and outflow pressures (o); η is the viscosity; and $\pi.8^{-1}$ is the constant of proportionality.

The Hagen–Poiseuille's equation shows that Q is directly proportional to the viscosity of the fluid and that it relates to the fourth power (2^4) of the radius of the tube (r). All other conditions held constant, in practical terms, reducing the radius by one-half increases the resistance by a factor of 16 (2^4). Regarding the lung, the flow rate or the pressure needed to sustain a given flow of air is greatly affected by even a small change in the diameter of the conduits (airways), with wider branches that possess lower resistance transporting more air. The dimensions of the airways are particularly important during diseases and pathological conditions such as asthma and inflammations where the luminal dimensions change respectively on or after hyperresponsive contraction of the smooth muscles in the wall and narrowing of the airways from presence of secretions and exudates. The Hagen–Poiseuille's equation is only tenable for streamlined flow of an incompressible fluid of constant viscosity. Blood is not a Newtonian fluid. The blood plasma, or the fluid part, contains suspended bodies in the form of red and white blood cells and blood platelets (Fig. 2.7). Although to some extent deformable (e.g., Nikinmaa

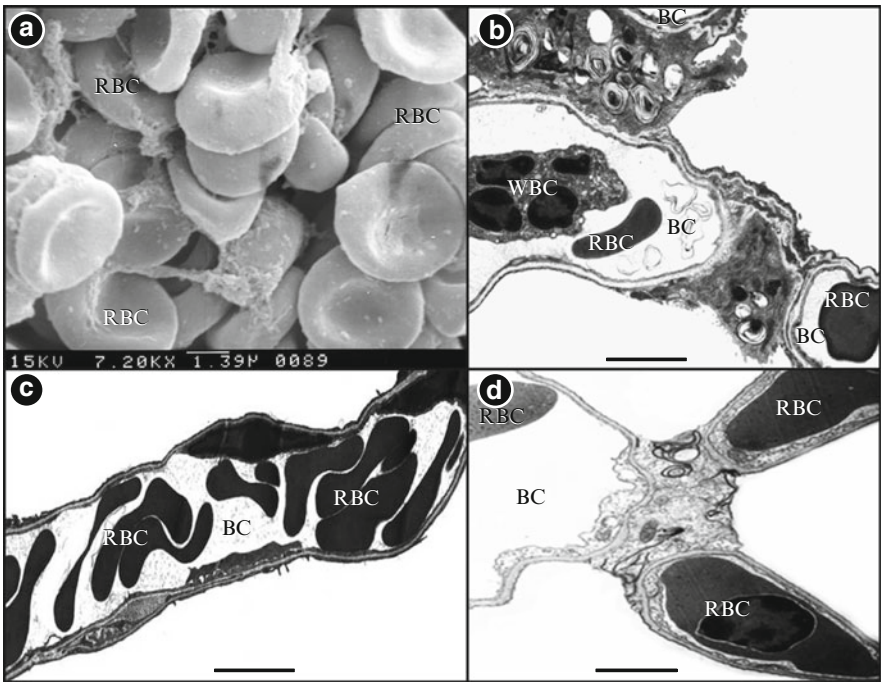

Fig. 2.7 (**a**) Red blood cells (RBC) that transport oxygen on its binding to hemoglobin. (**b**) In the air-breathing vertebrates, a closed circulatory system where the blood plasma and red blood cells are confined to the blood vessels exists. *BC* blood capillaries, *WBC* white blood cell. (**a**–**c**) mammalian lung and **d**, avian lung. *Scale bar*: **b**, 12 μm; **c**, 10 μm; **c**, 4 μm

1990), the diameters of the red blood cell (RBC) are about equal to that of the blood capillaries. The apparent viscosity of blood, which is 2.5 times more than that of the plasma, depends on the hematocrit. In severe anemia, the viscosity of blood is low, while in a case like polycythemia vera, it increases considerably.

In terrestrial vertebrates, high metabolic rates result in higher VO_2 and CO_2 production. During maximum exercise, the flux of the respiratory gases may increase by a factor of more than ten times above the resting level. Gas exchange is determined by temporal and spatial limitations that ensue from finite rates of convection, diffusion, and the reaction kinetics of CO_2 and O_2 with carrier-pigments such as hemoglobin (HB) and hemocyanin. Inert gases, i.e., those that dissolve in blood without reacting chemically with blood, equilibrate much faster than O_2 which reacts with metal-based carrier pigments and CO_2 which reacts with water to form carbonic acid (H_2CO_3). "Reactive," i.e., biochemically active, gases require longer capillary transit time (CTT) at the respiratory site for complete equilibration. While inert gases of equivalent molecular weights take from 15 to 20 ms (e.g., Wagner 1977), O_2 and CO_2 take 430 and 210 ms to reach 99% equilibration. At rest, blood passes through a pulmonary blood capillary in ~0.75 ms. The PO_2 equalizes in 0.3–0.4 s and the PCO_2 in ~0.1 s. End-capillary

PO_2 equilibration is determined by (a) extremely high concentration of CO_2, e.g., during exercise and disease conditions which adversely affect the function of the capillary bed, resulting in shorter CTT (Wagner et al. 1986), (b) thicker tissue barriers, e.g., in conditions like edema, (c) severe hypoxia (low PO_2), e.g., during sojourn to high altitude (Wagner et al. 1986), (d) occurrence of large RBCs which are accompanied by thicker unstirred plasma layers, and (e) conditions like anaemia which are characterized by low HB concentration and RBC count, resulting in low O_2-binding properties (e.g., Nguyen-Phu et al. 1986). The RBCs of the bull-frog (volume ~700 μm^3) take up O_2 at a late five times slower than the smaller RBCs of the goat that have a volume of ~20 μm^3 (Holland and Forster 1966). During extreme exercise, diffusion resistance may hinder end-capillary O_2 equilibration. The CTT decreases to as much as 200 ms (Groebe and Thews 1987). However, on account of the sigmoid shape of the HB-O_2 dissociation curve that brings about large O_2 loading during the initial part of the intracapillary blood transit pathway, even when end-capillary equilibration is not achieved, the amount of O_2 contained in the end-capillary blood is sufficient for the metabolic requirements. In gas exchangers, CTT is determined by the blood-flow rates, the pressure driving blood across the capillary bed, the viscosity of blood, and the capillary density, number, and length (Karas et al. 1987). In the mammalian lung, at rest, CTT scales disproportionately to body mass (kg) to a power (scaling) factor of 0.20 (Lindstedt 1984). The CTTs are shorter in small animals compared to the larger ones (e.g., Swenson 1990). Too short CTTs are averted by capillary recruitment (e.g., Malvin 1988) and opening of the arterio–venous anastomoses. Given that on average the CTTs are longer than the saturation times, all the inert and the "reactive" respiratory gases completely equilibrate as the blood passes through the pulmonary blood capillaries, at least under resting normoxic conditions (e.g., Karas et al. 1987). In the fish gills, the CTTs are ~0.5–3.0 s (Perry and McDonald 1993). They are the same order of magnitude as in the lungs of mammals (Roughton 1945). In birds (e.g., the domestic fowl, *Gallus domesticus*), however, the CTT which was reported by Henry and Fedde (1970) to be 0.31 of a second is relatively shorter. It may explain the lower arterial PO_2 in birds compared to mammals (Jones and Johansen 1972).

Morphometric models have shown that the RBCs contribute the greatest resistance to O_2 diffusion (e.g., Hallam et al. 1989; Maina et al. 1989a). Unlike in the mammalian lung, due to lack of carbonic anhydrase in the capillary endothelial-cells of the fish gills (e.g., Lessard et al. 1995), the piscine RBCs seem to be the only site for bicarbonate ($-HCO_3^-$) dehydration (e.g., Perry and Laurent 1990). The relatively long transit time of blood in the secondary lamellae of the fish gills (Hughes 1972a), the high capacitance of CO_2 in water, and the highly efficient countercurrent system of the gills (Sect. 5.2) may account for the exceptional efficiency of the gills in the elimination of CO_2. The differences in the equilibration time courses in the inert gases and the "biochemically active" gases such as CO_2 and O_2 can be attributed to the ratio of the solubility of the gases in the membrane (tissue barrier) to that in blood (which for inert gases is unity), a value that is several orders of magnitude lower than for CO_2 and O_2 (Piiper and Scheid 1980). The greater solubility of O_2 and CO_2 in blood relative to the membrane is due to the

reversible chemical binding and reaction with HB and other proteins in the RBCs and the blood plasma. The rate at which the partial pressure of a particular gas builds up is totally dependent on its solubility in blood. The more soluble a gas is, the slower will be its rate of change of partial pressure for a given quantity of gas transferred. The rate of equilibration of CO_2 in any solution is significantly dependent on the buffering capacity of the fluid. The rate-limiting steps in O_2 transfer can be attributed to both the diffusion resistances and the chemical reactions in an inhomogeneous medium. Unlike for CO_2 exchange and in the Bohr–Haldane effects, these rapid processes occur simultaneously and do not require enzymes or membrane transport carriers.

2.2 Mechanistic Essential: Diffusion

Also called "Brownian motion," diffusion is a state in which atoms or molecules move because of their random thermal activity. Only of historical interest now, at the beginning of the twentieth century, it was considered, even by as eminent physiologists as Christian Bohr (1855–1911) and John Scott Haldane (1860–1936) (for review of the controversy see, e.g., Milledge 1985; Cunningham 1986; West 2004) that the PO_2 in the pulmonary blood capillary blood was greater than that in the alveolar air. It was therefore supposed that the flow of O_2 through the blood–gas barrier happened "uphill," i.e., O_2 was "pumped" or "secreted" into the capillary blood by an active (energy-requiring) process. This was particularly envisaged to occur during exercise when VO_2 was high and during exposure to hypoxia. While even presently the ΔPO_2 at the alveolar level still has to be determined indirectly (because of technical difficulties), based on more precise arterial and venous blood gas measurements (e.g., Comroe 1974; Weibel 1984; West 2008), it is now accepted beyond a shadow of a doubt that across microscopical biological distances, O_2 moves entirely by simple passive diffusion (e.g., Schmidt and Carmeliet 2010). In a well-ventilated and perfused vertebrate lung, the alveolar PO_2 is normally higher than the arterial one (e.g., Karas et al. 1987). Hemoglobin (HG), myoglobin (MG), and cytochrome P_{450} have been associated with intracellular storage of O_2. A poorly understood process termed "facilitated-diffusion" or "carrier-mediated O_2 transfer" was claimed to transport O_2 in the muscle tissue (e.g., Burns et al. 1975; Braulin et al. 1986; Wittenberg and Wittenberg 1989, 2003) and in the placenta (e.g., Burns and Gurtner 1973). The process may become important under conditions of reduced O_2 flow such as in case of interstitial edema (e.g., Burns et al. 1976) and under hypoxic conditions (Longmuir 1976). Myoglobin is an important O_2-binding hemoprotein in striated muscle (e.g., Ordway and Garry 2004). Since diffusion is a physical process, the tissue barrier is functionally a passive contributor to the movement of O_2 and CO_2 through it. Over the evolutionary time, notwithstanding the vast changes that have occurred in the structure and function of the gas exchangers, the movement of O_2 across the tissue barriers universally occurs by passive diffusion. While the sites

and forms of gas exchangers have changed greatly, the means by which O_2 travels through barriers that separate biological compartments has remained the same. This is a rare case of conservation of a physicobiological process/mechanism. It could be argued that diffusion (a passive process) was elected in the primeval facultative aerobic prokaryotes and "hard-wired" into the respiratory system because it grants an energy-saving and highly cost-effective way of providing O_2. Incontrovertibly, if O_2 was obtained by an active process, considering that acquisition of O_2 is a continuous process and large amounts of O_2 are particularly required during states and conditions such as exercise, the energetic cost of respiration would be unmanageably high to render the process uneconomical and probably untenable within the feasible biological designs.

As means of moving O_2 across tissue barriers, diffusion is only efficient over very short distances. A typical molecule takes 0.5 ms to travel across a distance of 1 μm (e.g., Levy et al. 2006). The time needed for diffusion increases with the square of the distance over which it occurs. Thus, if the diffusion distance increases tenfold, the time required to reach a particular level of equilibrium increases 100 times. Theoretically, the time needed for a typical molecule with a diffusion coefficient of 1×10^{-5} cm^{-2} s^{-1} to travel distances of 1 mm (10^3 μm) and 1 cm (10^4 μm) is respectively 8.3 min and 14 years (Levy et al. 2006)! Diffusion of O_2 through water is a very slow process. Krogh (1941) estimated that it would take ~42 years for an O_2 molecule to travel a depth (a distance) of 250 m! After combining with the HB, O_2 exerts negligible back pressure. This creates the ΔPO_2 that maintains the flow of O_2. In a healthy lung, diffusion quickly equalizes the mixed venous gas pressures with the alveolar ones. According to Graham's law, the rate of diffusion of a gas is directly proportional to the velocity of its molecules which is in turn inversely proportional to the square root of its density. Whether in a gas or in a liquid medium, larger gas molecules diffuse relatively more slowly. Based solely on their molecular weights, O_2 (=32) diffuses faster than CO_2 (=44). In the vertebrate lungs, O_2 and CO_2 diffuse between a gaseous environment and capillary blood across a thin fluid (water) layer (the hypophase) that lines the alveolar surface (e.g., Ward and Nicholas 1984; Bastacky et al. 1993, 1995; Freites et al. 2003; Pavelka and Roth 2005). Since the relative solubility of CO_2 and O_2 in the aqueous phase at 37°C and 1 atm is ~24:1, because of its greater solubility in water, the concentration of CO_2 in the aqueous layer is greater than that of O_2. This explains why CO_2 diffuses faster between the alveolar gas and the capillary blood than O_2, although CO_2 diffuses less rapidly within the alveolus.

As means of transport of O_2, diffusion has had a profound effect on the shapes and the sizes of organisms and animals in general (e.g., Burggren and Roberts 1991). In the unicellular organisms (Fig. 2.4), some simple multicellular organisms and young embryos, O_2 transfer occurs entirely by diffusion across the plain (unspecialized) cell membrane or body wall (e.g., McMahon and Wilkens 1983; Schmidt and Carmeliet 2010). Larvae of many insects rely on diffusion for gas transfer across the integument (Fraenkel and Herford 1938). With their small, long, thin bodies, the dragonflies (Fig. 2.8a) and stick insects (e.g., *Dixippus morosus*) (Fig. 2.8b) strikingly display the evolutionary trade-offs between size and shape in

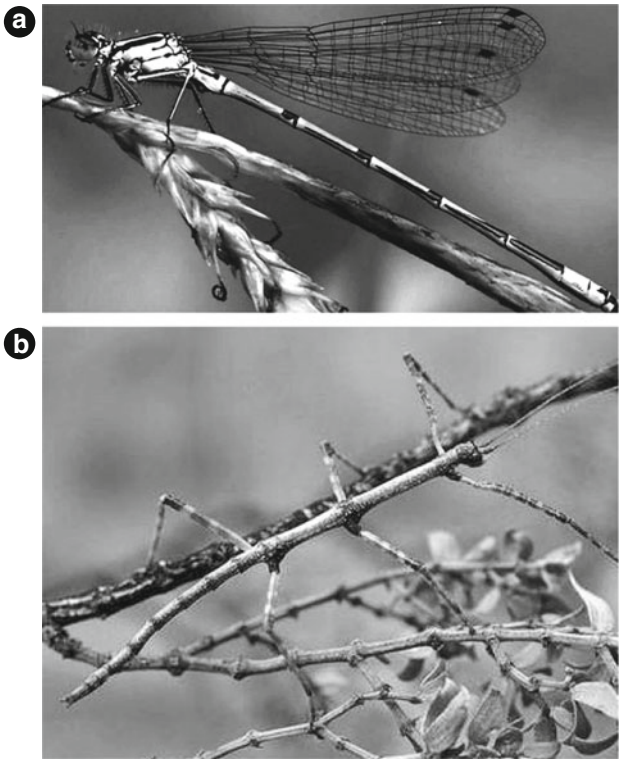

Fig. 2.8 A dragon fly (**a**) and a stick insect (**b**) showing their thin and long bodies that have been compelled by need to supply oxygen by diffusion over short distances

insects which particularly utilize diffusion as the only means of acquiring O_2. The flux of the respiratory gases into and out of the body is essentially regulated by the rates at which O_2 is consumed (utilized) (VO_2) and CO_2 produced at cellular level. Because the simplest of the organisms rely entirely on diffusion to procure O_2, generally, respiratory sites are not structurally conspicuous below the level of the molluscs and the arthropods. The movement of O_2 is driven totally by the prevailing partial pressure difference across the barrier (the cell membrane) and nothing else. During the passive process of diffusion, the water/air–blood barrier plays no direct role in the movement of O_2 through it.

Estimations of the largest size (volume) that an organism can theoretically reach while utilizing diffusion as the only means of obtaining O_2 have differed between investigators. According to Harvey (1928), this can be calculated as:

$$r = \sqrt{\text{C.6Kt. } VO_2}^{-1}$$

where r is the radius, Kt is the Krogh's diffusion constant, C is the partial pressure of O_2 across the cell membrane, and VO_2 the O_2 consumption. In a normobaric

environment and at moderate VO_2, Rashevsky (1960) calculated that the maximum radius of a spherical cell where anoxic state does not form except at the center (i.e., the farthest point from the surface) is 0.5 mm. Krogh (1941) estimated that the radius of a spherical organism that consumes O_2 at a rate such that the PO_2 is zero (0 = nil) at the center, the PO_2 at the surface of the sphere is 0.21 of an atmosphere (160 mm Hg = 21 kPa), the K_t is 1.105 $cm^2\ min^{-1}\ atm^{-1}$, and the VO_2 is 0.02 $cm^3\ min^{-1}$ (a realistic value for a protozoan) would theoretically be 0.25 mm. In addition, Krogh (1941) calculated that for a homogenous spherical organism of a radius of 1 cm and a VO_2 of 100 $cm^3\ kg^{-1}\ h^{-1}$ (about half that of a resting person), an external PO_2 of 25 atm or 19,000 mmHg ($2.5.10^3$ kPa) would be needed to sufficiently supply O_2 up to its center by diffusion. According to, e.g., Schmidt-Nielsen (1990), when O_2 needs are high, at one atmosphere pressure, diffusion suffices in organisms that measure up to 1 mm in diameter and through animal tissues that are 2–5 mm thick. A paramecium (volume, 0.0006 cm^3; VO_2, 1.3 ml $g^{-1}\ h^{-1}$; and diameter, 0.11 cm) requires a PO_2 of 0.73 of an atmosphere (Prosser and Brown 1962). Given that such high value (PO_2) does not naturally occur, these calculations show the flaws inherent in the mathematical models applied to determine the hypothetical sizes that organisms can attain, if diffusion was the only means of acquiring O_2.

For a spherical structure, volume increases as the cube while surface area increases as the square of the change in size. If the metabolic rate remains constant, O_2 transfer by diffusion therefore decreases with increase in size. It is for the fact that spherical shape confers the smallest surface-to-volume ratio that except for eggs and embryos that come close to it, no organism is absolutely globular in shape. To offset the inadequacy of decreasing surface-to-volume ratio with increasing body mass, the shapes of many organisms are irregular, long, or are greatly attenuated (Fig. 2.8). Those organisms that live in well-oxygenated milieu and have low VO_2 can, however, attain relatively larger body sizes. Pelagia that can grow to a diameter of ~6 cm (Henze 1910) and the coelenterate, *Cynea,* that reaches one of 2 m reportedly utilize diffusion for their O_2 needs (Krogh 1941). The tropical earthworms that weigh as much as 1 kg in body mass, e.g., *Rhinodrilus fafner* and *Megascolides australis* and are known to reach lengths of 2.2 m and diameters of 24 mm utilize cutaneous diffusion for their O_2 need (Stephenson 1930). In an egg-mass of developing embryos of the sand snail, *Polinices sordidus,* which weighs as much as 210 g (Shepherd and Thomas 1989) and have a radius of as much as 40 mm, those eggs farthest from the surface experience extreme hypoxia ($PO_2 < 1$ kPa), even when the PO_2 in the layer of water surrounding them may be moderately high ($PO_2 > 10$ kPa) (Booth 1995). The water inside a spawn of *Rana temporaria* is only 3–16% saturated with O_2 while ~50 cm away from the egg cluster it is 136% saturated with it (Savage 1935).

Since some structures and organisms like the amphibian eggs develop to sizes greater than those theoretically predictable and the PO_2 inside the cell surpasses that which can be met exclusively by diffusion, it has been considered plausible that another or other processes is/are involved in gas transfer (e.g., McDougall and McCobe 1967). The amphibian eggs are restricted to a diameter of 9 mm

(e.g., Carroll 1970) while in the much larger eggs of reptiles and birds, where diffusion is insufficient for moving O_2, a well-vascularized chorioallantoic membrane promotes uptake and transport of O_2 (e.g., Wangensteen et al. 1970; Wangensteen and Rahn 1970; Wangensteen 1972; Luckett 1976; Wangensteen and Weibel 1982). In the Protozoa, protoplasmic streaming, a circulatory-like process that occurs in living cells, may enhance intracellular gas transfer (e.g., Andrews 1955). Mechanical vibration or agitations of the respiratory fluid medium appear to increase permeability of tissues by the respiratory gases (Longmuir and Bourke 1960). Organs and structures such as the heart and the diaphragm that mechanically contract, change in muscle tone, and physical interaction, e.g., between moving RBCs and the vascular endothelial cell wall, may promote gas transfer at the tissue and cellular level.

According to Fick's law of diffusion, the diffusive conductance (Q), i.e., the net rate of diffusion or the volumetric rate of gas transfer by diffusion of a gas (e.g., O_2) between compartments A and B is directly proportional to the O_2 permeation constant (K_t) for O_2 across the tissue barrier (K_tO_2), the respiratory surface area (S) (Fig. 2.3), and the ΔPO_2 between the gas exchange compartments [PO_2(A) – PO_2(B)], but is inversely proportional to the thickness of the tissue barrier (τ) (Figs. 2.3, 2.9, and 2.10).

$$Q = K_tO_2 \,.\, S \,.\, [PO_2(A) - PO_2(B)].\ \tau^{-1}$$

K_tO_2 is the product of the diffusion coefficient (d) which is determined by the physical properties, i.e., the materials attributes of the tissue barrier, and the solubility of O_2 in it (β) ($K_tO_2 = d.\ \beta^{-1}$). At 38°C, mainly due to the differences in their solubilities, K_tO_2 is ~25 times greater for CO_2 than for O_2. Since d and β are

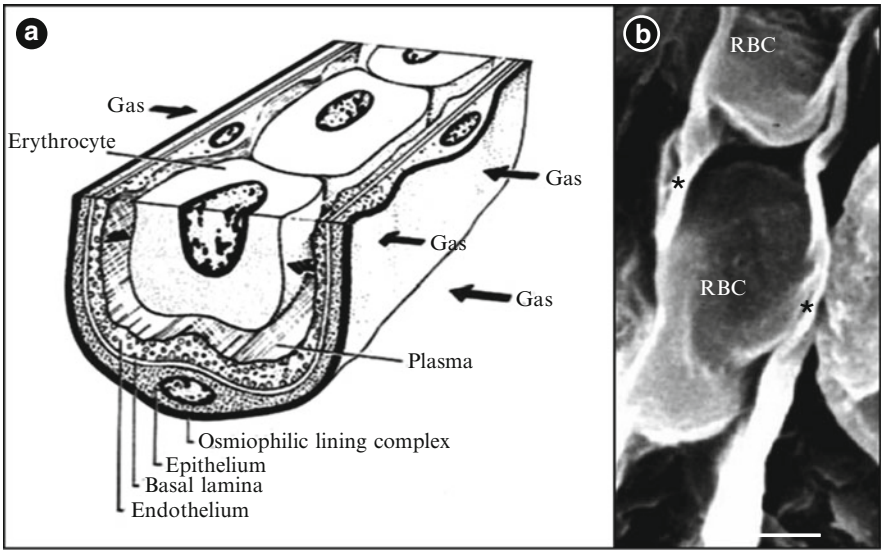

Fig. 2.9 (**a**) Schematic illustration and (**b**) a blood capillary (**b**) showing the tissue barrier across which oxygen has to diffuse in the lung (*star*). The red blood cells (RBC) contains hemoglobin which chemically binds oxygen for distribution to the rest of the body. *Scale bar*: 5 μm

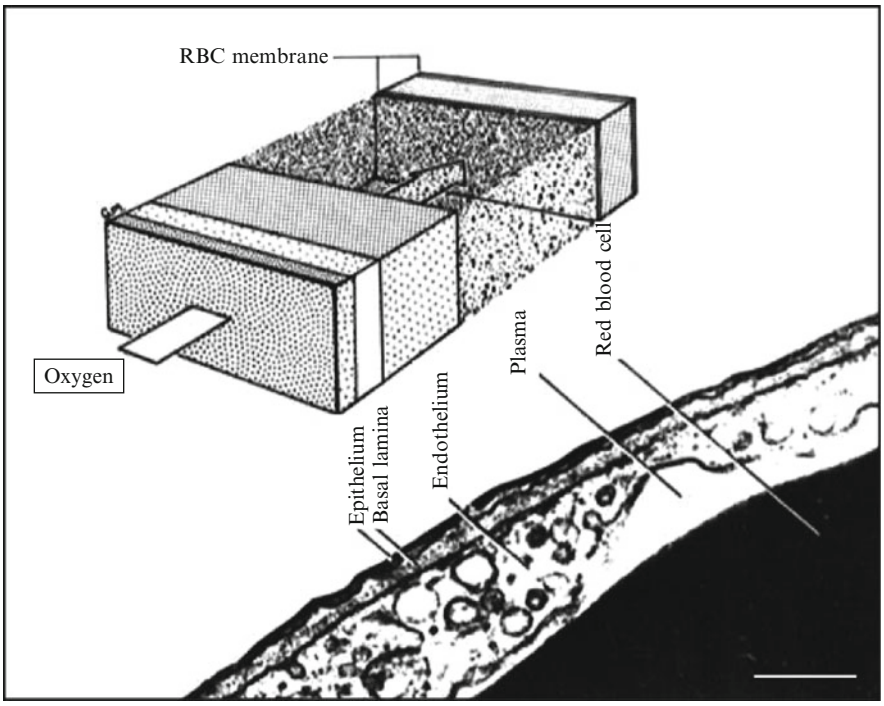

Fig. 2.10 A stereogram showing the barriers across which an oxygen molecule passes to bind to hemoglobin molecules. The transfer is dependent on the surface area, the thickness of the barrier, and the permeation constants of the tissues of the barrier. An electron micrograph of the blood–gas barrier of the lung of the black-headed gull, *Larus ridibundus* is given to show the specific barriers. *Scale bar*: 0.5 μm

affected by temperature in opposite directions, with d increasing and β decreasing, on the whole, temperature has little effect on K_tO_2.

From the terminal respiratory units of gas exchangers, the diffusion pathway for O_2, the so-called air–hemoglobin pathway (AHP), can be broken up into a very thin surfactant lining, an aqueous layer (the hypophase), the tissue barrier, a plasma layer, the membrane of the RBC, and the cytoplasm of the erythrocyte (Figs. 2.9–2.11). Being on the whole extremely thin and physically fluid in nature, the surfactant and the hypophase are presumed to contribute relatively little to the resistance that O_2 encounters as it travels along the AHP. The reciprocal of resistance is conductance or diffusing capacity. The physiological diffusing capacity of the lung for O_2 (D_LO_{2P}) defines the lung's conductance of the gas per unit time per unit partial pressure gradient (e.g., Comroe 1974). It is estimated as the ratio of the transfer or consumption of O_2 (VO_2) to the mean alveolar gas tension (P_AO_2) and the mean pulmonary capillary gas tension (P_CO_2). Thus:

$$D_LO_{2P} = VO_2.(P_AO_2 - P_CO_2)^{-1}$$

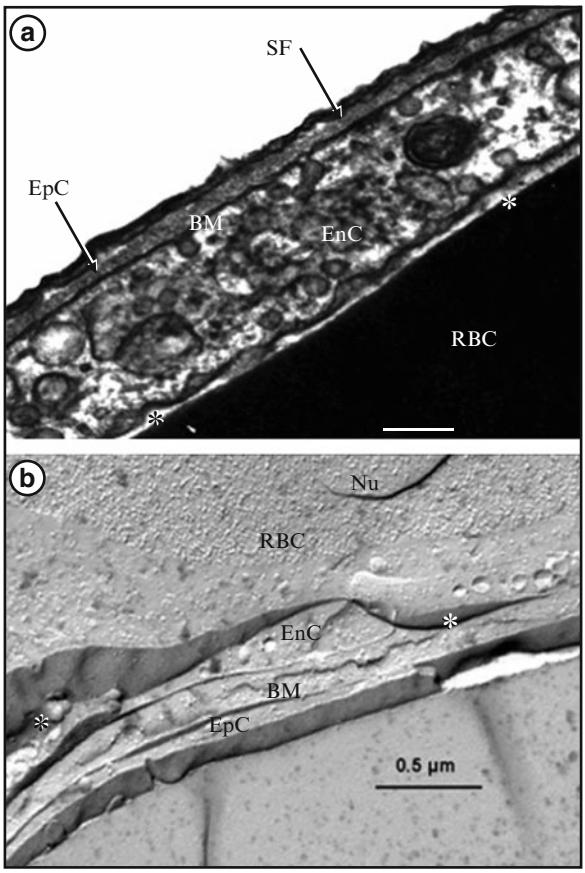

Fig. 2.11 The components of the blood–gas barrier of the lung of the domestic fowl, *Gallus domesticus*. *EpC* epithelial cell, *BM* basement membrane, *EnC* endothelial cell, *SF* surfactant, *RBC* red blood cell, *Nu* nucleus, *asterisk*, plasma layer. *Scale bar*: **a**, 0.2 µm

Mathematical integration of morphometric parameters such as surface areas (S) of the blood–gas barrier (BGB) and that of the blood plasma (BP), the harmonic mean thicknesses of the BGB (τht) and that of the plasma layer (τhp), and the relevant K_ts, i.e., those of the BGB (K_tO_2) and blood plasma (K_pO_2) allow the anatomical diffusing capacities of the BGB (tissue barrier) (D_tO_2) and that of the plasma layer (D_pO_2) to be calculated (Weibel 1970/71).

$$D_tO_2 = K_tO_2.S_{(BGB)}.\,\tau ht^{-1}$$

and

$$D_pO_2 = K_pO_2.S_{(BP)}.\,\tau hp^{-1}$$

D_tO_2 and D_pO_2 correlate directly with S and K_ts and inversely with τht and τhp. The commonly used values of K_tO_2 for the BGB for O_2 is 4.1×10^{-8} cm^2 s^{-1} Pa^{-1} and for blood plasma, the minimum value for K_pO_2 is 4.0×10^{-8} cm^2 s^{-1} Pa^{-1} and the maximum one 5.4×10^{-8} cm^2 s^{-1} Pa^{-1}) (1 mbar = 10^2 Pa).

The DA of the erythrocytes (DeO_2) is calculated as the product of the O_2 uptake coefficient (Θ_{O2}) and the volume of the pulmonary capillary blood volume (Vc) as follows:

$$DeO_2 = \Theta O_2 \,.\, Vc$$

The commonly used values of ΘO_2 are 1.13 $mlO_2\ s^{-1}\ Pa^{-1}$ (maximum value) and 3.13 $mlO_2\ s^{-1}\ Pa^{-1}$ (maximum value).

The total anatomical diffusing capacity of the lung for O_2 (DLO_{2A}) is calculated from the reciprocals of the resistances through the tissue barrier (DtO_2), the plasma layer (DpO_2), and the erythrocytes (DeO_2).

Thus:

$$DLO_{2A}{}^{-1} = DtO_2{}^{-1} + DpO_2{}^{-1} + DeO_2{}^{-1}$$

Among the air-breathing vertebrates, the thickness of the blood–gas (tissue) barrier, which comprises an epithelial cell, a basement membrane, and an endothelial cell (Figs. 2.9–2.11) decreases from the amphibian, the reptilian, the mammalian, and the avian lungs (e.g., Meban 1980; Perry 1983; Gehr et al. 1981; Maina 1989a; Maina et al. 1989a). In the vertebrate gas exchanger, some of the structural elements, e.g., the surfactant (e.g., Power et al. 1999) and the tripartite design of the tissue barrier have been highly conserved (e.g., Maina and West 2005). Diseases and conditions that lower the DLO_{2A} do so by reducing the surface area and/or increasing the diffusion distance. Examples of the former conditions and states include the collapse of parts of the lung (e.g., atelectasis) and break-down of the interalveolar septa (e.g., emphysema) which generate abnormally larger terminal air spaces while the latter occurs in conditions such as fibrosis or accumulation of fluid in the blood–gas (tissue) barrier (edema). The thickness of the plasma layer and the red blood cell cytoplasmic distance (space/distance in the red blood cell across which O_2 travels before binding to the haemoglobin) (Figs. 2.10 and 2.11) can increase in various conditions such as anaemia. The impairment of the AHP leads to what has functionally been termed "physical block to diffusion."

In the mammalian lungs, D_LO_{2p} is constantly lower than D_LO_{2m} (e.g., Siegwart et al. 1971; Crapo and Crapo 1983; Weibel et al. 1983). There are indications that a similar relationship exists in birds (e.g., Meyer et al. 1977; Scheid et al. 1977; Burger et al. 1979). During the fixation of the mammalian lung by intratracheal instillation, a standard technique for tissue preparation for morphometric analysis, the alveolar surface area is stretched out to that at functional residual capacity (e.g., Siegwart et al. 1971; Weibel 1973). On assumption that the entire BGB is utilized for gas exchange, D_LO_{2m} therefore predicts the maximum possible diffusing capacity of the gas exchanger under conditions where ventilation and perfusion (V/Q) are optimal, i.e., V/Q inequalities are nonexistent. In a healthy mammalian lung, at VO_{2max}, D_LO_{2p} approaches D_LO_{2m} (Weibel 1990). It is envisaged that D_LO_{2p} underestimates the diffusing capacity of a gas exchanger mainly on account of prevailing regional V/Q inhomogeneities. In birds, the exceptionally high VO_2 of

the nucleated erythrocytes (e.g., Lutz et al. 1973) may lower the D_LO_{2p}. Bats, the only volant mammals, have higher D_LO_{2m} than birds and nonflying mammals (e.g., Maina and King 1984; Maina et al. 1991).

Generally, the gas exchangers that operate by diffusion alone occur in the simple and/or low metabolism animals. Interestingly, in vertebrates, through a process called apneic oxygenation (e.g., Malan 1982; Szewczak and Jackson 1992), in states such as aestivation (hibernation) when the respiratory quotient is less than 1 and the metabolic rates particularly low, during long apneic periods, a significant amount of resting O_2 need is met by diffusion down the respiratory tract through an open glottis. In the African lung-fish, *Protopterus aethiopicus*, during aestivation which has been reported to be as long as 5 years (e.g., Lomholt et al. 1975; DeLaney et al. 1974; DeLaney and Fishman 1977), O_2 moves from the atmosphere down the trachea to the lung by diffusion. When breathing pure O_2, dogs have been experimentally kept alive for an hour on diffusion respiration alone (Lambertsen 1961). Diffusion lungs occur in the pulmonate gastropods, e.g., in *Trichotoxon copleyi* (e.g., Ghiretti 1966; Maina 1989b) (Fig. 2.12), in the Arachnidae (the Scorpionidae, Padipalpi and Araneidae) (e.g., Paul et al. 1987; Fincke and Paul 1989), in a chilopod (Scutigera), and in the tracheate isopods particularly in the Porcellionidae. The largest "diffusive lungs" are those of the African pulmonate snails, *Achatina* and *Bulimus*, which have a volume of up to 500 cm^3 (Krogh 1941). In the freshwater pulmonates, *Planorbis corneus* and *Lymnea stagnalis*, the PO_2 respectively increases to 16–18 kPa (a value that is greater than that in the alveolus of the mammalian lung of ~13 kPa), in spite of absence of ventilatory activity. The PO_2 has to drop to a low of 2.7 kPa before the lung reopens (Precht 1939; Jones 1961). The mantle cavity of the diffusive lung of *T. copleyi* is very well vascularized (Fig. 2.12), is surrounded by a strong ring of muscle, and some parts of the blood–gas barrier are as thin as 0.2 μm (Maina 1989b). According to, e.g., Dahr (1927), in such lungs, a very small PO_2 of ~0.3 kPa is sufficient to deliver adequate amount of O_2 by diffusion. In *Arion* and *Helix*, at a PO_2 of 2 kPa, the pneumostome opens 15–30 times in 30 min and remains open for ~7 min (Dahr 1924). During the evolutionary transformation of simple unicellular to the large, complex multicellular organisms, at different points, development of the mechanisms of perfusion and ventilation (Fig. 2.6) enhanced the transfer of O_2 above that which could be supplied by diffusion alone.

2.3 Mechanistic Essential: Ventilation

Ventilation entails mass renewal of the external respiratory fluid medium (water/air) from the proximate of a gas exchanger by passive and/or mechanical effort. The former entails, e.g., placement of the body or gas exchanger in a current of moving respiratory (fluid) medium (air/water) and the latter, e.g., movement through a fluid medium or active transporting (pumping) of the medium in-and-out of the gas exchanger. Considering that it is more costly and takes time to evolve (develop)

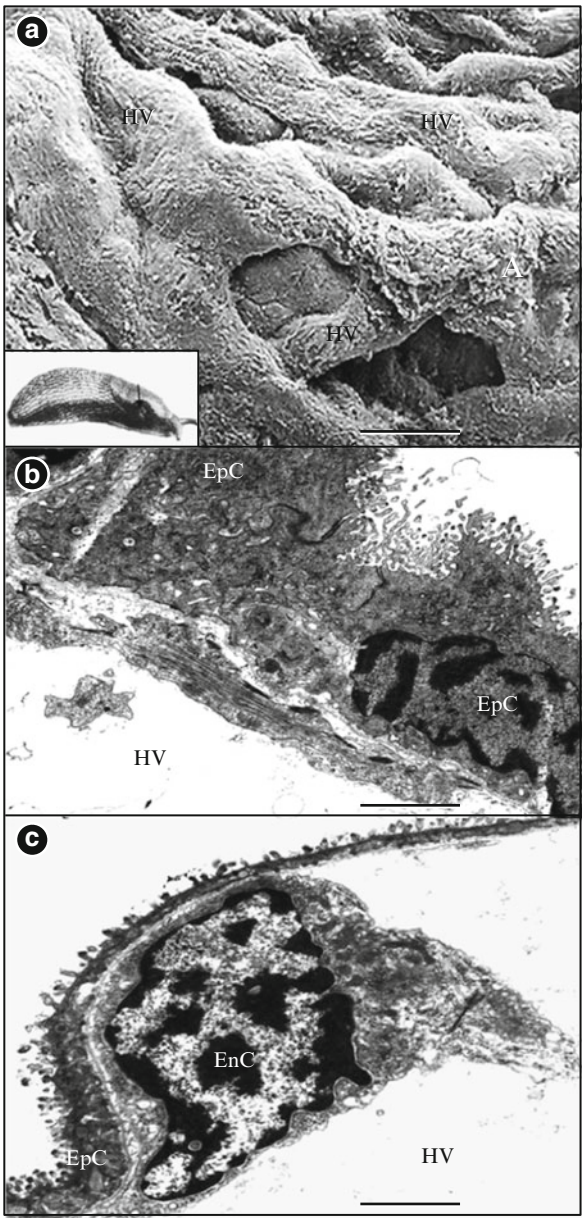

Fig. 2.12 Lung of the pneumonate gastropod, *Trichotoxon copleyi* (*arrow*, *arrow*) showing the vascularization of the surface of the lung (**a**) and the barrier across which O_2 diffuses (**b**, **c**). *HV* hemolymphatic space, *EpC* epithelial cells, *EnC* endothelial cell. *Scale bar*: **a** 30 μm; **b** 25 μm; **c** 10 μm

anatomical structures, it is conceivable that as means of promoting gas exchange, after diffusion could no longer suffice as means acquiring/supplying O_2; ventilation, at least through locomotion, may have come before perfusion, at least in some animals (Fig. 2.6). In simple organisms, physical displacement combines the activities of food acquisition, predator avoidance, and gas exchange. By

convective/mass movements of the respiratory fluid media (water/air and blood), the processes of ventilation and perfusion create and maintain partial pressure gradients of O_2 (ΔPO_2) and CO_2 (ΔPCO_2) across the tissue barriers, i.e., the water/air–blood barriers. In the animal kingdom, the means by which the gas exchangers are ventilated differ. To a large extent, they show the limitations that have obligated the need to optimize the movement of the respiratory fluid media, the functional designs of gas exchangers, and the physicochemical properties of the respiratory fluid media (Sects. 3.2 and 3.3). In organisms/animals which live in torrential waters (rheophilic species), the PO_2 in the water is equal or almost equal to the atmospheric one (i.e., the water is saturated with O_2), e.g., in the hill-stream fish, *Danio dangila*, which inhabits hyperoxic water (9 $mgO_2\ L^{-1}$) (Ojha and Singh 1986), the gills and the skin are passively ventilated with water, an energy-saving process. Except for the fresh-water limpets, *Ancylus fluvialis*, and *Acroloxus lacustris* (Berg 1951), invertebrates which live in running water are similarly passively ventilated with moving water. Such animals have higher metabolic rates compared to those that live in sluggish or standing water (e.g., Fox et al. 1935; Walshe 1948). In sponges, the beating of the cilia of flagellated cells (choanocytes) drives water through numerous incurrent pores or ostia into ramified water-channels which are ~1 mm in diameter. During intense activity, up to 90% of O_2 is extracted from the water passing through the pores (Hazelhoff 1939). In the coelenterates, constant water flow by movements of cilia occurs across the gastro-vascular canals.

In primitive aquatic animals, e.g., bivalve molluscs, amphioxus, and ascidians, movement of water across the gills is brought about by cilia while in advanced fish, the transfer is achieved by the more sophisticated branchial pumps. In amphioxus, *Branchiostoma lanceolatum*, the gills do not play an important function in gas exchange (Schmitz et al. 2000). Tubiculous polychaetes rely on ciliary currents (e.g., *Nephtys*), peristalsis (e.g., *Arenicola*), or undulating movements of the body to ventilate the body cells (e.g., *Chaetopterus*). In molluscs, where the gills are largely used for feeding and respiration, water is moved across the gills by the beating of cilia which are located on the gills (Borradaille et al. 1963). The echinoderms breathe through movable tubes (podia) which project into basal dilatations (ampullae) that lengthen via openings in the calcaneous outer body cover (e.g., Steen 1965). Hemolymph that lacks respiratory pigments is moved by ciliary action into the microcirculatory units. In the sea-urchin, *Strongylocentrotus droebachiensis*, the podial respiratory surface area which becomes a constraining factor to O_2 uptake only at higher temperatures (Steen 1965). At 19°C, the VO_2 (2 $cm^3\ h^{-1}$) is directly proportional to the respiratory area while at 6°C, 80% of the area is redundant. In the sea-urchin, a 70-g specimen has about 100 podia which are about 20 mm long and 0.4 mm in diameter. It provides a surface area of ~250 cm^2 and the thickness of the diffusion distance (podial) is ~15 μm (Steen 1965). The soft-bodied cucumbers (Holothuroidea) utilize an internal respiratory tree-like (arborescent) organ that is rhythmically ventilated by muscular contractions. *Holothuria tubulosa* replenishes the water in the respiratory tree every 1–4 min. The water that is expelled has an O_2 content of ~50–80% of that of the surrounding

water (Hazelhoff 1939). Fish embryos develop rhythmic contraction of the tail muscles before the respiratory movements start to show motor response to hypoxia (Polimanti 1912). To a small extent, beating of cilia moves water currents into the molluscan mantle cavity. Some burrowing annelids, e.g., marine echiuran worm, *Urechis caupo* (Wells 1949; Mangum 1985) generate a water current over their bodies and in the tubes by undulating their bodies in water through peristaltic contractions of muscles in their body wall. In the urodele, *Necturus*, regular movements of the external gills replace the water on the surface of the gills. In the shelled *Nautilus* (a paleontological relic of more than 2,000 extinct genera of Nautiloids and Ammonoids), when mantle movement is not possible, the ventilatory stream of water is generated by movements of the fused collar and funnel folds, the "wings" which produce small pressure differences in the order of 0.1 kPa (Wells and Wells 1985). The ventilatory frequency which is 35 times per minute at 16°C increases with rise in temperature and the stroke-volume ranges from 5 to 22 cm^3 for a 395 g animal. In a fixed specimen of *Nautilus* (470 g), the volume of the mantle-cavity is 75 cm^3 (Packard 1972). In *Octopus vulgaris*, respiratory movements decrease with increasing body mass (Polimanti 1913).

In the oegopsid cranchid squids, the flow of water over the gills is generated by movement of the ammonia storing coelomes that regulate buoyancy (Denton et al. 1958; Clarke 1962). The urodele salamanders (Family: Plethodontidae) which do not have lungs or gills rely entirely on cutaneous respiration (e.g., Gatz et al. 1974; Piiper et al. 1976). Physical movement or positioning of the body in a stream of flowing water is the only ventilatory possibility. In marine and fresh water bivalves (Zinkler 1966; McMahon 1988), crustaceans (Hughes et al. 1969; Taylor 1982), polychaetes and oligochaetes (Mangum 1963), and holothurians (Newell and Courtney 1965), hypoxia increases ventilation. In cephalopods, hypoxia reduces respiratory frequency (Frederiq 1878) while exercise (Ghiretti 1966) and hypecapnia (Winterstein 1925) increase it. In some crustaceans, e.g., the crayfish, *Astacus leptodactylus* (Angersbach and Decker 1978), and the crabs, e.g., *Cancer productus* (McMahon and Wilkens 1977), *Cancer pagurus* (Bradford and Taylor 1982), and *Potamon niloticus* (Maina 1990a), dedicated mouth part appendages, the scaphognathites (flattened exopodites of the maxillae), mechanically ventilate the gills which are covered by lateral extensions of the carapace, the branchiostegites (Lockwood 1968; Burggren et al. 1974). In some species of crabs, e.g., *Carcinus maenas* and *C. guanhumi,* the direction of the flow of air can be reversed (Taylor and Butler 1978; Burggren et al. 1985). The disposition between the flows of water and blood in the gill lamellae is counter-current (e.g., Yonge 1947; Hughes et al. 1969). In species that burrow into substrates, the direction of the ventilatory current can be reversed when the animal is covered by particulates (e.g., Dyer and Uglow 1978). With the exception of *Holthuisana transversa* (Greenaway and Taylor 1976), where tidal ventilation is caused by movements of the membranous thoracic wall, the scaphognathites ventilate the gills and the lungs of the land crabs when the animal is in air (e.g., Al-Wassia et al. 1989), particularly when they are exposed to hypercapnea. The movements of the scaphognathites of *Coenobita clypeatus* in air

produce pressure wave forms that are equivalent to those generated by the scaphognathites of the water-breathing crabs (McMahon and Burggren 1979).

Among the land crabs, the ventilatory mechanism in *Holthuisana transversa* is unique (Taylor and Greenaway 1979). The energetic cost equals that of the vertebrate respiratory systems. In *Ocypode saratans*, the scaphognathites beat at a rate of 53 times per minute in an immersed crab, 218 times per minute when active in air, 43 times per minute at rest in air, and 235 times per minute in a hypercapnic environment (Al-Wassia et al. 1989). The irregular beating of the scaphognathites is neurogenically synchronized to that of the heart (e.g., Young and Coyer 1979). On account of changing the dimensions of the gill lamellar blood-vessels, scaphognathite activities that produce pressures of −0.53–0.93 kPa may considerably affect the perfusion of the gills and the lung (Blatchford 1971). In the crab, *Carcinus maenas* (e.g., Wheatly and Taylor 1979) and the crayfish, *Orconectes rusticus* (McMahon and Wilkens 1983), air is forced through water held in the branchial cavity by means of the scaphognathites beating in the opposite direction. In the amphibious ghost crab, *Ocypode saratan*, heart rate changes with ventilation. At four times the rate of the gills, the lungs are only perfused with blood when the crab is exposed to air (Al-Wassia et al. 1989). Ventilation of the respiratory sites by oscillatory movements of special appendages takes place in some polychaetes (e.g., *Chaetopterus*), amphipods (e.g., *Gammarus*), isopods (*Idotea*), and crustaceans, e.g., *Cancer pagurus* (Bradford and Taylor 1982). The currents produced by such activities also deliver food, i.e., small microorganisms such as *Chirocephalus, Artemia,* and *Daphnia*.

Diverse ventilatory mechanisms occur in the gills (Sect. 5.2) and the accessory respiratory organs (ARO) of bimodally-breathing fish (Sect. 5.3). The gills are ventilated with water by a four-phase pressure-suctional buccal force pump while the air-breathing organs are ventilated tidally. In fish, pressure difference of ~0.4 kPa (3 mmHg) fill up the mouth while those of 0.7–1.3 kPa (~5 to ~10 mmHg) convey the water across the gills (e.g., Hughes and Shelton 1958). Fish which swim strongly and continuously such as the mackerel, the tuna, and some sharks (elasmobranchs) utilize ram ventilation, where gills are essentially ventilated by forward movement. Some of them cannot achieve optimum oxygenation of blood when stationary or if they are confined to a small space. The bimodal-breathing fish use a modified buccal force-pump to ventilate its ARO (Fig. 2.13). Air is forced into the chamber containing the organ(s) and exhalation is considered to be a passive process (e.g., Farrell and Randall 1978). In some air-breathing fish, e.g., *Anabas testudineus* (Peters 1978) and *Clarias mossambicus* (Maina and Maloiy 1986), where the inhalant and exhalant apertures are respectively contained in the pharyngeal and opercular cavities, the buccal and opercular pumps may generate unidirectional air flow over the labyrinthine organ which is located in the suprabranchial chamber (Fig. 2.13b and d) (Sect. 5.3). The cephalopods and molluscs have evolved a through-flow ventilatory mechanism which fits between the bidirectional (tidal) one of the air-breathers and the unidirectional one of the water-breathing fish. The inspired and expired water flows pass through different apertures (e.g., Gosline et al. 1983). With an O_2 extraction index

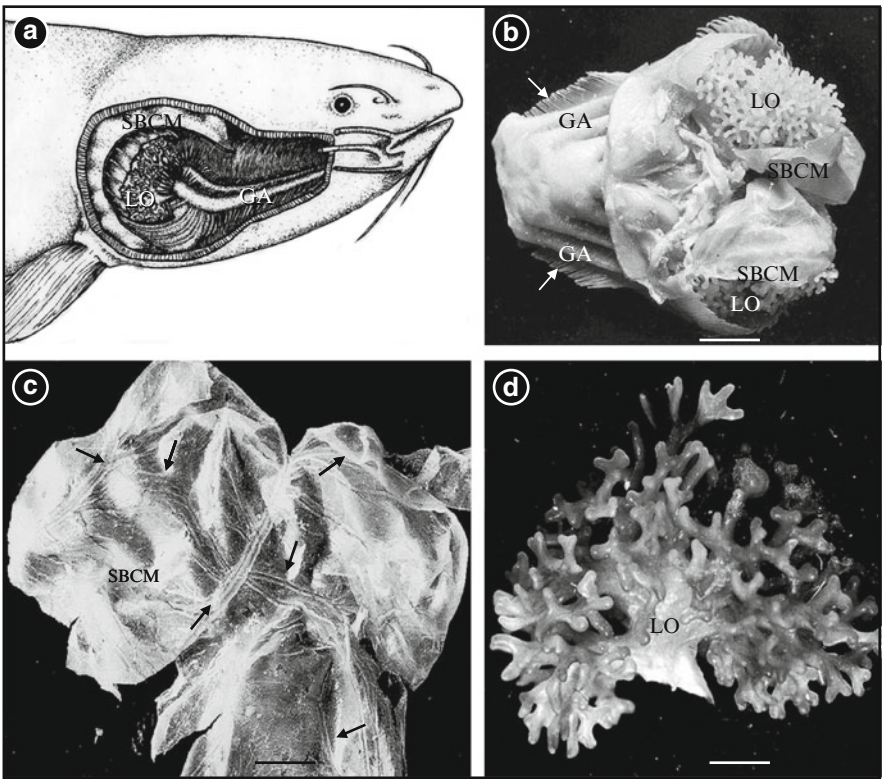

Fig. 2.13 (**a**, **b**) The respiratory structures of the bimodally breathing catfish, *Clarias mossambicus* showing the gills arches (GA), labyrinthine organ (LO), and the suprabranchial chamber membrane (SBCM). (**c**) Surface of the suprabranchial chamber membrane. (**d**) The labyrinthine organ. *Arrows* (**b**), gill rakers and (**c**) blood vessels. *Scale bar*: **b**, 0.2 mm; **c**, 0.15 mm; **d**, 0.15 mm

of 33–72%, in the octopus, the arterial PO_2 may be higher than that in the out flowing water (Johansen and Lenfant 1966). In *Nautilus*, there are two pairs of gills and the funnel is the main contractile structure (Ghiretti 1966). In the holothurians, e.g., sea-cucumber and the cephalopods, the cloaca pumps water tidally across the branched diverticula of the hind-gut that forms the respiratory tree. When in O_2-saturated water, for the sea-cucumber, *H. forksali*, out of the total O_2 need, 60% of it is transferred across the cloaca, with the rest passing over the skin (Newell and Courtney 1965). About ten successive cloacal contractions, each of which transfers ~1 cm^3 of water into the animal, are followed by body contractions which eject it. When cloacal respiration stops, VO_2 decreases (Lutz 1930). Tidal breathing of water across the hind-gut also occurs in annelids, e.g., *Urechis caupo* (e.g., Menon and Arp 1992) and insects, e.g., dragon-fly nymph (*Aeshna*) (Fig. 2.14), via the branchial apertures in lamprey eels and via the mouth in some amphibians and reptiles, e.g., the soft-shelled turtle, *Amyda*. In such simple structures, the primary

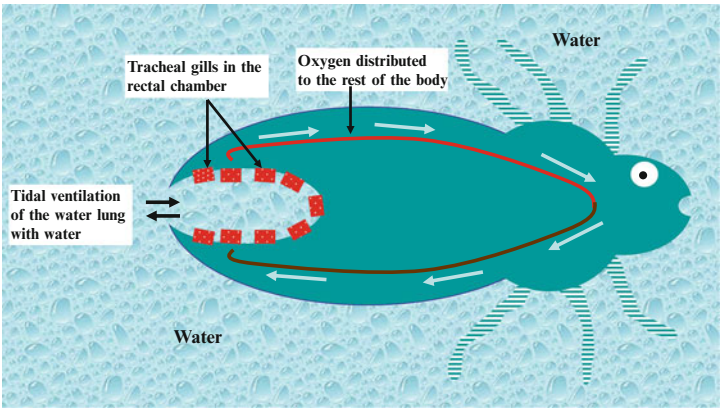

Fig. 2.14 Rectal tracheal gills of the dragonfly. The rectum is ventilated tidally. After Hughes (1982)

functions are olfaction and/or feeding and not respiration; they are collectively called "water lungs." Under normoxia, in *U. caupo*, hind-gut ventilation with seawater occurs at a rate of ~0.7 cm^3.g body wt^{-1} (e.g., Menon and Arp 1992). At a PO_2 of 4 kPa, this rises to ~2 cm^3. The mucosa of the hind gut contains collagenous and elastic tissue fibers which may allow greater expansion when filling with water under hypoxic conditions (Menon and Arp 1992). An analogous rectal-gill mechanism occurs in the echiuran-worm, *Arhynchite pugettensis*, where large cloacal diverticula exist (Manwell 1960). In the diving turtle, *Sternothaerus minor*, 30% of O_2 is conveyed by rhythmic contractions that maintain flow of water into and out of the buccopharyngeal cavity (Belkin 1968).

2.4 Mechanistic Essential: Perfusion

Typically, organisms with a diameter exceeding 1 cm require a circulatory system (e.g. Krogh 1941; Burggren and Pinder 1991). In both the closed and the open circulatory systems, hemolymph/blood is convectively moved through the body and across the gas exchanger. To different extents, this increases the transfer of respiratory gases across the water/air–blood barriers and through the blood capillaries to the tissues/cells. The ΔPO_2 and ΔPCO_2 are directly maintained by the constantly moving respiratory fluid and indirectly by consumption (utilization) and production of O_2 and CO_2 in the cells, respectively, specifically in the mitochondria. The importance of perfusion in gas exchange was shown by Krogh (1941) who estimated that for an organism with a diameter of 2 cm and having a VO_2 of 100 cm^3 kg^{-1} h^{-1}, an external PO_2 of 25 atm would be necessary to supply O_2 to all the parts of the organism but when the external (respiratory) medium is

separated from an internal circulating medium by a 50 μm thick barrier, only a PO_2 of about one-quarter of an atmosphere is needed. Mature animals with an elementary circulatory system close to the surface of the body (e.g., earthworms and echinoderms), where the blood/hemolymph is moved by a heart or hearts and not cilia, can grow up to body masses of a few grams and a length of 30–40 cm while relying totally on the skin for procurement of O_2, provided that they live in water or in a humidic environment. In many of such animals, directional flow of the blood/hemolymph and therefore presence of a true circulatory system may not exist. Contraction of the body muscles may further promote the transport of the respiratory gases. In organisms such as Chaetopoda, Synapta, and Pantopoda, there is no functional circulation because the coelomic fluid is kept in motion by cilia (e.g., Lindroth 1939). The blood of the earthworms which has a high O_2 affinity ($P_{50,}$ 0.3–1.1 kPa) is highly sensitive to temperature (e.g., Laverack 1963) and has a high O_2-carrying capacity of 8–12% by volume (Haughton et al. 1958). The giant earthworm, *Glossoscolex giganteus*, which attains a body mass of 600 g, a length of 120 cm, and a width (diameter) of 2–3 cm has blood with a P_{50} of 0.9 kPa at 20°C, a pH of 7.5, and a small Bohr-shift (Johansen and Martin 1966). By controlling cutaneous perfusion (Burggren and Feder 1985) and external body surface area (Noble 1925), the hairy frog, *Astylosternus robustus*, controls gas exchange across the skin. In the higher vertebrates, the skin is highly impermeable to O_2 and in the human being only 0.2% of the VO_2 passes through it (Krogh 1941). Nemertines have two large longitudinal blood vessels and in those species that have hemoglobin, oscillatory, i.e., back and forth, movement of blood is common (Hyman 1951).

In some annelids, closed circulation with well-developed blood vessels that have pulsatile primitive "hearts" exist. In some teleosts and elasmobranchs, venous return is brought about by the caudal hearts that are situated close to the tail and the contraction of the skeletal muscles (e.g., Satchell 1992). Secondary hearts exist in the circulatory system of the decapod crustaceans (Steinacker 1975) where locomotory movements produce large pressure changes which enhance the flow of the hemolymph (Belman 1975). In the Atlantic hagfish, *Myxine glutinosa*, the oscillations in the dorsal aortic blood pressure correlate with the contractions of the gill musculature, a process which may be concerned with moving blood (Johansen 1960). Such a mechanism, however, does not appear to occur in the gills of the Pacific hagfish, *Eptatretus stoutii* (Chapman et al. 1963). In most gastropods, to ascertain forward flow of blood, passive valves exist in different parts of the body (Jones 1983). The weight-specific volume of blood is greater in animals with an open circulatory system than in those with a closed one (Prosser 1961) and the peripheral resistance and blood pressures are generally low (Jones 1983). In crustaceans, the blood volume constitutes ~30% of the body mass (Prosser 1973), in the gastropod molluscs 25–30%, in the bivalves it is as much as 60%, and in the dog it forms only 8.3%. In general, the circulatory system does not play a significant respiratory role in most tracheates, especially insects, where O_2 is delivered directly to the cells from the atmosphere (Sect. 5.5). In mammals, the relative blood volume decreases with body size (Gregersen and Rawson 1959).

Invertebrates such as crustaceans and molluscs have an open circulation where a capillary system between the arteries and veins is for the most part lacking. The blood returns to the heart essentially at random through a system of open disseminate tissue spaces (sinusoids) that are not bordered (lined) by uninterrupted (continuous) endothelial cells as in the endothelial lining of the blood capillaries of a closed circulatory system (e.g., McMahon and Wilkens 1983) (Fig. 2.7). The large volume of fluid that is found in the intercellular space grants mechanical support for locomotory activity and feeding movements (e.g., Jones 1983; Russell and Evans 1989). With a smaller blood volume, a closed circulatory system affords fast return of blood compared to the relatively sluggish one of the large volume open circulation. An open circulation meets the needs where O_2 demands are low and the diffusion distances small (Farrell 1991). In the terrestrial slug, *Deroceras reticulatum*, heart rate increases during feeding. This can be ascribed to the need for high hemocoelic pressure that is required to enlarge the odontophore (Duval 1983). Gas exchange through the surface of the body together with a primitive circulatory system occurs in the leeches, the oligochaetes, and some polychaete annelids. In the more advanced animals, the arrangement of the circulatory system is more complex. In some large earthworms, blood pressures are as high as 2.5 kPa and the flow of the blood is fast (Johansen and Martin 1966). In the black-lip abalone, *Haliotis ruber*, ventricular pressure ranges from 0.4 to 1.2 kPa (~19 mmHg) and the heart rate increases with the temperature of the water, with the maximum rate being reached at 22°C (Russell and Evans 1989).

The gastropod and the cephalopod molluscs are phylogenetically the first extant animal taxa that display a conspicuous circulatory system (e.g., Wells 1983; Andrews and Taylor 1988). The heart is structurally well organized and constantly pulsates to impart directional blood-flow. In the pneumonate gastropod molluscs, the systolic pressure is as high as 4 kPa (~30 mm Hg) (Jones 1983; McMahon and Wilkens 1983). The systolic peak blood pressure rises to as high as 6.7 kPa in some terrestrial crabs (Cameron and Mecklenburg 1973). Beyond the gills which contribute 40% of the peripheral resistance, the pressure gradually drops to zero (Bourne and Redmond 1977). The closed circulation in the cephalopods constitutes the initial adaptation for a more efficient gas-transport system. With certain exceptions, in gastropods and bivalves, the most common response to hypoxia is bradycardia (DeFur and Mangum 1979; Russell and Evans 1989). The pinnacle of the development of the circulatory system was reached with the double-circulation where the arterial and venous blood volumes were completely separated both in the heart and peripherally. It took ~300 million years for a double-circulatory system to develop from the single-circulatory one, where arterial and venous blood mix, especially in the heart. A pulmonary vein and a partially divided heart first developed in the lungfishes (Order: Dipnoi). This marked a pivotal transition point in the transformation from open to closed circulatory systems (Bugge 1960; Satchell 1976). Pulmonate amphibians have a pulmonary vein and absolute or partial division between the right and the left atria. It is only in crocodiles (e.g., Axelsson et al. 1989; Nilsson 1994; Axelsson 2001) and post embryonic endotherms, mammals and birds, where a four-chambered heart exists. In mammals

and birds, separate pathways convey venous blood (right half) and the arterial blood (left half). The pulmonary and systemic circuits are completely separated. The pulmonary circuit, which handles the whole of the systemic venous blood, is a low resistance circulatory system, having a pressure of 1.7 kPa (~13 mmHg) on average (Rushner 1965). In fish, gill vascular resistance is between one half and one third of that in the systemic circulation (Cameron et al. 1977), with the difference being much greater (~10 times) in mammals and birds (Langille and Jones 1975). The gills of the amphibious ghost crab, *Ocypode saratan*, are perfused with blood both in immersed and air-breathing states while the lungs are perfused with blood only while animal is in air (Al-Wassia et al. 1989).

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