PULMONARY AND RENAL PRESSURE-FLOW RELATIONSHIPS: WHAT SHOULD BE TAUGHT?

Barbara E. Goodman

University of South Dakota, Division of Basic Biomedical Sciences, School of Medicine, Vermillion, South Dakota 57069

This article is from a symposium presented at the annual meeting of the Human Anatomy and Physiology Society (HAPS) on June 11, 2000. The presentation was funded under the auspices of a National Science Foundation Course, Curriculum, and Laboratory Improvement Program entitled “Development of Active Learning Materials for Physiology and Functional Anatomy: A Cooperative HAPS-APS Initiative.” This symposium was part of the first module to be developed on “gradients and conductances: what flows where and why?” This presentation was designed to model the usefulness of the general model of gradients and conductances in the physiology and pathophysiology of the respiratory and renal systems. Thirteen different examples of pressure-flow-resistance and concentration-flux relationships are introduced; several ideas for active-learning activities and simple figures appropriate for undergraduate physiology classes are included. The symposium assumes that undergraduate students have already learned about diffusion, osmosis, and the basic principles of cardiovascular physiology. The presentation was designed to follow a symposium entitled: “Cardiovascular pressure-flow relationships: what should be taught?”

Key words: concentration-flux; airflow; blood flow; Starling’s hypothesis

One of the key concepts that reoccurs throughout physiology is the importance of gradients and conductance for normal body functions or what flows where and why? These key concepts, also known as general principles or general models of physiology, are vital to the function of numerous organs and systems in the body (1). However, because physiologists often use different terminology for and different approaches to describing these general models in the various body systems, students often totally miss that they are seeing the same general principle again. The key concept of gradients and conductance involves the principle that the movement or flow of something is related to a driving force or gradient divided by a resistance (R). For the respiratory and renal systems, this key concept includes pressure (P)-flow-R relationships for air during breathing and for the formation of tubular fluid in the kidneys, P-flow-R relationships for blood, and P-flow or concentration-flux relationships for diffusion of gases and the movement of solutes and water across barriers.

KEY CONCEPTS OF P-FLOW-R IN THE RESPIRATORY SYSTEM

This section will look at P-flow-R relationships important in respiratory physiology. First, we will look at the importance of the P-flow-R relationship for airflow during breathing in the lungs. Second, we will look at the importance of the P-flow-R relationship for blood
flow in the pulmonary circulation. Last, we will look at the importance of the P-flow or concentration-flux relationship for passive transport across the blood-gas barrier including diffusive transport for gases and water balance.

Activity 1: assuming that the students have already learned about P-flow-R relationships for blood flow in the cardiovascular system, you might want to open this section with an activity having the students in small groups discuss how the cardiovascular pump and blood flow are the same as or differ from the respiratory "pump" and air flow (7).

P-Flow-R Relationships Involved in Air Flow

How is P gradient involved? First, we will look at P-flow relationships for breathing in the respiratory system by investigating the importance of the P gradient (ΔP) portion of the relationship [flow in the airways = (P_mouth - P_alveoli)/R_airways] (Fig. 1). The respiratory system can be modeled as one large air-filled balloon pushed into and surrounded by a balloon with insides coated with a very thin layer of liquid. This gives three compartments in which to measure P (Fig. 2) (6). They are: the outside compartment (the outside of the outer balloon, equivalent to the chest wall), the small liquid-filled compartment (between the 2 balloons, equivalent to the intrapleural space), and the air-filled compartment (inside the inner balloon, equivalent to the alveoli and conducting airways of the lungs). Respiratory physiologists generally relate the pressures in these three compartments to each other by making the atmospheric P (outside the chest wall) the reference P, or zero. Thus, if the person is at sea level where the atmospheric P is 760 mmHg, then the pressure outside the mouth will be 0 mmHg. When the glottis is open and no air is flowing in the lungs, then the P inside the alveoli will also be 0 mmHg.

During development, the rib cage with its associated pleural membranes grows at a faster rate than the lungs with their associated pleural membranes. The outside of the inner balloon would be the location of the visceral pleural membrane, whereas the inside of the outer balloon would be the location of the parietal pleural membrane. Thus the coupling of the visceral and parietal pleural membranes together by the thin layer of liquid (pleural fluid) opposes the tendency of the rib cage to increase in size (without the lungs) and the tendency of the lungs to decrease in size (without the rib cage; see Fig. 7) (6). Therefore, this tendency for the pleura to pull apart makes the P in the pleural space (between the 2 balloons) less than the atmospheric P (subatmospheric) or negative (if the atmospheric P is the reference P of 0; Fig. 3) (6). This negative P can be looked at as similar to a vacuum that would tend to suck air in.

During the inspiration phase of normal quiet breathing, the P in the pleural space (known as intrapleural or intrathoracic P) will change from -4 mmHg before
inspiration to $-6$ mmHg during inspiration to $-4$ mmHg during expiration (Fig. 3-5) (6). During inspiration, the diaphragm contracts and moves down and the external intercostal muscles contract causing the ribs to move upward and outward, both muscles increasing the size of the thoracic cavity. As the chest expands, the coupled lungs also expand, leading to lower P in the alveolar spaces (Fig. 4) (6). Thus, during inspiration, the alveolar P becomes $-1$ mmHg lower than the atmospheric P at the mouth (0 mmHg). This driving force ($\Delta P$) leads to airflow into the lungs during inspiration.

During the expiration phase of normal quiet breathing, as passive expiration occurs (simply relaxation of the muscles that contracted during inspiration), the elastic recoil of the lung tissue leads to a slight increase in the alveolar P ($-1$ mmHg greater than the atmospheric P at the mouth of 0 mmHg) (Fig. 5) (6). This driving force ($\Delta P$) leads to airflow out of the lungs during expiration. Thus, during the normal quiet-breathing cycle, the intrapleural P is always sub-atmospheric and the alveolar P compared with the atmospheric P changes from slightly lower than during inspiration to the same as to slightly higher than during expiration to the same as again.

**Activity 2:** one can demonstrate $\Delta P$s in the lungs during normal quiet breathing by having the students take a deep breath and then stop the movement of their chests at the end of inspiration. Students should not “hold their breaths” but should simply stop the movement of their chests. In this glottis-open position with no airflow, the air P in the combined alveoli equals the atmospheric P (7).

On the other hand, during a voluntary maximal forced expiration, the atmospheric P at sea level is still 760 mmHg (or the reference P of 0 mmHg). A maximal forced expiration is also known as a forced expiratory maneuver and involves someone inhaling maximally to total lung capacity and then exhaling as hard and as fast as possible. By using the abdominal
and internal intercostal muscles to facilitate this active expiration, intrapleural Ps much higher than atmospheric P are actually generated. Thus, during a maximal forced expiration, the intrapleural P can reach +26 mmHg and the corresponding alveolar P can reach +31 mmHg (due to the additional elastic recoil force of 5 mmHg for the lung tissue; Fig. 6) (6). Thus the driving force ($P_{alveoli} - P_{mouth}$ or $\Delta P$) for the flow of air out of the lungs during maximal forced expiration is much larger [(31 – 0 mmHg)] than the driving force (1 – 0 mmHg) during normal quiet breathing]. In a healthy individual, airflow out of the lungs will be much faster during a forced expiration than during normal quiet breathing. The body adjusts to using varying degrees of active expiration when one is exercising or when suffering from cardiopulmonary diseases. Thus positive intrapleural Ps are frequently found in normal healthy individuals either voluntarily or during exercise.

**How is R involved?** Activity 3: a lung cancer has grown into the walls of the bronchioles, narrowing their luminal spaces. What has happened to R to airflow in these bronchioles? (7)

Next, we will look at P-flow-R relationships for breathing in the respiratory system by investigating the importance of the R component of the relationship [flow in the airways = ($P_{mouth} - P_{alveoli}$)/$R_{airways}$]. But first we need to investigate the effects of the changes in P across the “wall” of the lung tissue. In normal, healthy individuals, the relevance of the intrapleural P to breathing is generally not clear until one looks at the importance of the actual P difference between the air spaces in the lungs and the pleural spaces. This P difference is known as the transmural (across the wall) or transpulmonary P and is equal to the alveolar P minus the intrapleural P. Let’s start with a simple example of the importance of this P difference.

**Activity 4: a stabbing victim is brought into the emergency room with a knife wound between his ribs on the left side of his chest. What is the intrapleural P in the pleural space surrounding the left lung? What happens to the left lung? What happens to the chest wall on the left side?** (7)

A stab wound brings atmospheric air (0 mmHg) into that pleural space. Before the stabbing and at rest before inspiration, the transmural or transpulmonary P for the left lung was [0 mmHg – (–4 mmHg)] or +4 mmHg, tending to keep the alveoli open. However, after the stabbing and at rest before inspiration, the transpulmonary P for the left lung was [0 mmHg – 0 mmHg] and the left lung now uncoupled from the parietal pleura inside the left side of the thoracic cavity will collapse to its resting state (a small volume, 0.5 liter called minimal volume). Simultaneously, the uncoupled chest wall on the left side will expand to its resting state, which is bigger than normal (Fig. 7) (6).

**Activity 5: one can demonstrate the strength of coupling of the lungs to the chest wall by the small amount of liquid in the pleural space by taking a syringe filled with water and observing the difference in force needed to expand the syringe volume when the tip is open to the air compared with when the tip is plugged by a cap. The cohesive forces between the water molecules cause the liquid inside the syringe to strongly resist expansion.** (7)

Thus the transpulmonary or transmural P represents the likelihood of the lung structure being expanded or compressed, if possible. We are now beginning to get into the component of R to airflow (dependent on airway diameter) in the P-flow-R relationship in the airways of the lungs. Another example of the impor-

**FIG. 6.** The pressures in the 3 compartments during a maximal forced expiratory maneuver.
tance of this transpulmonary $\Delta P$ can be seen with the maximal forced expiration described above (Fig. 8) (6). In a normal healthy person, during forced expiration the intrapleural $P$ does not become equal to or greater than the adjacent airway $P$ until very low lung volumes are reached. Where these two $Ps$ become equal (transpulmonary $\Delta P$ equals 0) is known as the equal $P$ point. When the intrapleural $P$ is greater than the adjacent airway $P$, then the negative transpulmonary $\Delta P$ ($P_{\text{airway}} - P_{\text{pleural}}$) tends to compress the airway. In normal healthy people, compression only occurs at the very low lung volumes when the air being exhaled has reached the relatively protected airways (such as the cartilaginous trachea). Thus this force tending toward airway compression does not lead to a significantly decreased radius of these extreme upper airways that are neither compressible nor expandable. However, increasing one’s effort to generate flow by more forced active expiration does not always lead to increased expiratory flow, because eventually the negative transpulmonary $\Delta P$ (higher intrapleural than airway $Ps$) will counteract the increased expiratory effort by compressing airways that have less supportive wall structure. When airway radius is reduced, then there is increased frictional R to flow of air in those airways, and the decreasing expiratory airflow will reach and remain at a constant flow rate. This phenomenon leads to the effort-independent portion of the flow-volume relationship and demonstrates dynamic airway compression. Flow-volume relationships (inspiratory and expiratory curves with lung volume on the $x$-axis and flow on the $y$-axis) for varying degrees of effort in an expiratory maneuver are evaluated clinically to characterize pulmonary function. Dynamic airway compression often occurs at different lung volumes for patients with pulmonary diseases than in normal, healthy individuals.

Clinical implications of airway $P$-flow-$R$ relationships. The compression of the upper airways during expiration causes increased frictional R to airflow. On the basis of $P$-flow-$R$ relationships, positive end-expiratory $P$ (PEEP) or continuous positive airway $P$ (CPAP) are used clinically to keep airways open when mechanical ventilation is needed (Fig. 9). By using PEEP or CPAP, the airway $P$ at the end of expiration does not fall to zero. Positive $P$ is maintained inside the upper airways and the alveoli even at the end of expiration. Thus compression and/or closure of the airways at the end of expiration are diminished, airflows are enhanced, and thereby the patient maintains better oxygenation.

Work of breathing. The body must utilize energy to generate the muscle movement for the $P$-volume work for breathing. Normal, quiet breathing consumes a mere 1–2% of the total body energy requirement at rest. However, in heavy exercise and with cardiopulmonary disease, the demand for energy simply to breathe can rise to greater than 30% of the total body energy expenditure. The work of breathing requires sufficient energy to overcome four different...
factors. These factors include 1) the inertia of the respiratory system, 2) the frictional R of the lung tissue itself, 3) the elastic recoil properties of the lungs and chest wall, and 4) the frictional R to the flow of air in the airways. Normally the inertia of the respiratory system and the frictional R of the lung tissue make negligible contributions to the total work of breathing. Therefore, in a normal healthy individual, 70% of the total work of breathing is to overcome the elastic recoil of the lung tissue and 30% is to overcome the frictional R to the flow of air in the airways.

Simple analogy for understanding the work of breathing. A simple piston within a larger compartment pushing air into a fixed-wall tube can be a good analogy to help students understand how the respiratory system controls the flow of air in the airways (Fig. 10) (4). The “work of breathing” is the total force that needs to be exerted on the piston to move it (to inhale and sometimes exhale). The “stroke volume” is the volume of air in the compartment (the lungs). The R to flow in the combined airways is related to the diameter of the fixed-wall tube.

One can also use the piston analogy to better understand the two major categories of lung diseases. Lung diseases affecting lung volumes can be visualized as a smaller compartment containing the piston. Lung diseases with narrowed airways can be visualized as air exiting via a smaller diameter fixed-wall tube.

**Restrictive lung diseases.** If a patient has increased elastic recoil of the lung tissue (such as in fibrosis or sarcoidosis where the lung tissue becomes stiffer and thus harder to expand), the resultant disease decreases the achievable lung volume and is known as a **restrictive lung disease**. Thus the stroke volume component in the piston analogy is decreased in restrictive lung diseases. With each breath, a lower volume of air moving in or out of the lungs is possible. Any disease/condition in which the ease of expanding the lungs or chest is diminished fits into the category of restrictive lung diseases. These conditions could include the stiffening of the lung tissue itself described above, diseases of the thoracic cage, such as curvature of the spine, diseases of the nerve supply to the respiratory muscles or the muscles themselves, such as polio or muscular dystrophy, abnormalities such as air or excess water in the pleural space, etc. Because these conditions all make it more difficult to expand the lungs, they lead to lower stroke (lung) volumes. With the lower lung volumes of restrictive lung diseases/conditions, less air is available to flow out of the lungs during a forced expiration.

**Obstructive lung diseases.** If a patient has increased R to the flow of air in the airways (such as in bronchitis or asthma where the airway diameter becomes smaller), the resultant disease is known as an **obstructive lung disease**. This can be visualized in the piston analogy as a decreased diameter of the fixed wall tube. Obstructive lung diseases/conditions in-
clude the bronchoconstriction and increased secretions of asthma and/or bronchitis as well as any tumor that compresses the airway, an object blocking the airway after aspiration, the histamine-induced bronchoconstriction of allergies, and the tissue destruction of emphysema.

**Asthma—an Obstructive Lung Disease on the Rise**

From 1982 to 1994, there was a 72.3% increase in the number of children with asthma in the United States (2). Currently more than 4.8 million U.S. children suffer from the disease, with children in inner cities at higher risk. An asthma attack is caused by hyperreactive airways leading to excessive bronchoconstriction (very narrow diameters) after a “trigger” is encountered (Fig. 11) (7). In addition, asthma is characterized by increased inflammation in the airways leading to increased secretions there. Due to the very narrow airways, someone with asthma may have diminished lung function at all times but will have greatly diminished lung function during an attack. The major symptom of an asthma attack is feeling like it is impossible to breathe (known as dyspnea, or difficulty in breathing). In long-term, poorly managed asthma, the patient often develops hypertrophied or enlarged airway muscles and mucus glands leading to airways with permanently smaller diameters than those in healthy individuals. The best management of asthma appears to involve early diagnosis, the avoidance of the triggers, frequent use of corticosteroids to keep down the inflammatory response, and the use of bronchodilators only when necessary to improve breathing.

**Emphysema—Obstructed Airways During Exhalation**

The decrease in airway diameter found in all obstructive lung diseases/conditions increases the work of breathing by increasing the frictional R to the flow of air in the airways. Emphysema is a unique member of the group of obstructive lung diseases, because the disease process actually affects the lung tissue itself (by destroying it and thereby decreasing elastic recoil) and thus only indirectly affects the diameter of the airways. In emphysema, the destruction of the lung tissue by an enzyme imbalance both in the walls of the alveoli and of the airways, eliminates the support structure that tends to keep the upper airways open. For a patient with emphysema during a forced maximal expiration, increased frictional R delays the flow of air out of the lungs and there is less structural support to keep the upper airways open. Therefore, the equal P point and dynamic airway compression described above happen much earlier during expiration (at higher lung volumes). A patient with emphysema can easily inhale due to the abnormally stretchable damaged lung tissue but cannot easily exhale due to earlier airway collapse and thereby the trapping of a higher volume of air in the lungs at the end of exhalation. This repeated trapping of air in the lungs leads to permanent lung changes that enlarge the lung and the chest and cause the “barrel-chested” look of patients who have had emphysema for a long time. With the smaller diameter airways, it takes a lot longer for air to flow out of the lungs during a forced expiration. Thus the R component of the P-flow-R relationship for airflow during breathing is directly responsible for the symptoms of chronic obstructive lung diseases. The use of the simple piston analogy as the basis for these differences leads to logical interpretations of the forced expiratory maneuvers used clinically as pulmonary function tests to diagnose and evaluate both obstructive and restrictive lung diseases.

*Activity 6: you might want to distribute straws to the students at this point to demonstrate how difficult it*
would be to breathe through the much narrower airway of an asthma or emphysema patient (7).

P-flow-R relationships involved in blood flow. The pulmonary circulation critical to the primary gas exchange function of the respiratory system is both similar to and different from the systemic circulation; however, the standard key concepts of the P-flow-R relationship for blood flow are still valid. The pulmonary circulation arises from the right ventricle bringing deoxygenated blood to the lungs via the pulmonary arteries. After oxygenation across the blood-gas barrier of the lungs where the blood in the pulmonary capillaries comes in close contact with the air in the alveolar spaces, the pulmonary circulation returns to the left atrium of the heart via the pulmonary veins. With each heartbeat, the pulmonary circulation receives all of the cardiac output from the right ventricle (Fig. 12). The pulmonary circulation includes an extensive network of pulmonary capillaries surrounding the alveoli. A good analogy for the pulmonary capillary network is that blood flows in an area that is similar to an underground parking garage with the ceilings and the floors being the extensive blood-gas barrier with air on the other sides. The P difference ($\Delta$P) for the blood flow through the pulmonary circulation is 12 mmHg at the right ventricle to 8 mmHg at the left atrium. The vessels of the pulmonary circulation are more expandable than those in the rest of the body, and new blood vessels are recruited as needed (Fig. 13) (3). This recruitment and distension of blood vessels in the pulmonary circulation is important for the reserve function of the lungs that facilitates more oxygenation of blood when needed in exercise and disease. When new parallel vessels are recruited or distended as the blood flow increases, the total R to blood flow in the pulmonary circulation decreases. Thus changes in blood flow (perfusion) of the lungs are known to occur when recruitment and distension lead to decreased R to flow, for example in pulmonary hypertension.

A unique challenge for the respiratory system is that to maintain its primary gas exchange function most effectively, the ventilation and the perfusion to various areas of the lungs need to be well matched. This means that gas exchange is better if just the right amount of air comes in contact with just the right amount of blood and oxygen and carbon dioxide can quickly move back and forth between the two compartments. Thus ventilation/perfusion matching is important in normal, healthy individuals, and ventilation/perfusion mismatching can be the major cause of poor gas exchange in numerous cardiopulmonary diseases. The ideal situation would be to have the same volume of air and blood coming to an area and having plenty of time for gases to equilibrate between the two compartments. Sometimes in diseases, alveoli may be unventilated or poorly ventilated (for example, due to excess water in the airspaces or their own high R airways). If the blood continued to perfuse these poorly ventilated areas of the lungs, the blood leaving those areas would fail to be sufficiently oxygenated and would contribute less well-oxygen-
ated blood into the total blood leaving the lungs (Fig. 14) (4). This is known as wasted blood for gas exchange or a **shunt** of blood and is one extreme of ventilation-perfusion inequality. Sometimes in diseases, pulmonary capillaries may be clogged or narrowed (due to emboli or clots). If the air continued to ventilate these areas of the lungs, the air to those areas would not be contributing to total gas exchange. This is known as wasted air for gas exchange or an alveolar **dead space** (the dead space air of the upper airways is so-called because it is not involved in gas exchange at all) and is the other extreme of a ventilation-perfusion inequality.

Whereas both kinds of ventilation-perfusion mismatching will lead to poorer total oxygenation of the blood in the pulmonary veins returning to the right atrium, fortunately the lungs have their own **local compensatory control mechanisms** to adjust ventilation and perfusion to various regions. Local chemically sensitive cells cause changes in the diameter of either pulmonary blood vessels or bronchioles to better balance the ventilation and perfusion in that region. Thus, for low ventilation in an area of the lungs, the decreased oxygen there and/or increased carbon dioxide will lead to constriction of precapillary sphincters so that less blood is “wasted” by perfusing that poorly ventilated area. Likewise, for low perfusion in an area of the lungs, the increased oxygen and/or decreased carbon dioxide will lead to constric-
tion of bronchioles so that less air is wasted by ventilating that poorly perfused area.

You might want to show the visual model of the “sliding rectangles” concept of ventilation/perfusion matching here (5).

**Pressure-Flow or Concentration-Flux Relationships for Diffusion of Gases and the Movement of Water Across Barriers**

**How do gases cross the blood-gas barrier?** Gases are transported across the blood-gas barrier (the alveolar capillary membrane) by the concentration-flux relationship known as Fick’s First Law of Diffusion. Fick’s First Law states that the flux of molecules across a barrier is proportional to the permeability ($P$) of the molecules times the transfer surface area ($A$) over which diffusion can occur times the concentration gradient for the molecules ($\Delta C$; Flux = $PA\Delta C$). For this form of Fick’s Law, permeability is actually the diffusion coefficient ($D$) of the molecules in the membrane (their mobility once they are dissolved) times the partition coefficient ($B$ — the partition coefficient, which represents how easily the molecules dissolve in the lipid bilayer membrane) divided by the thickness of the membrane ($X$) or $[P = (D \times B)/X]$. Solely on the basis of molecular size, larger molecules will have smaller diffusion coefficients than smaller molecules. On the basis of ease of dissolving in the lipid bilayer membranes, molecules that are more lipid soluble (higher $B$) will diffuse faster than those that are less lipid soluble.

For the two gases of primary importance for the respiratory system, oxygen is smaller than carbon dioxide and thus would have a tendency to have larger diffusive fluxes across the barrier based solely on molecular size (Fig. 15). However, carbon dioxide is much more soluble in liquid than oxygen. The combination of these two factors leads to a permeability of carbon dioxide molecules across the blood-gas barrier that is 20 times higher than the comparable permeability of oxygen molecules. The transfer surface area of the blood-gas barrier is the extensive alveolar capillary membrane that is about 100 m$^2$ (at least the size of a tennis court) in a healthy adult human lung. Using Fick’s First Law of Diffusion for gas exchange (Fig. 16), one can see that the concentra-

---

**Fig. 14.** Imbalances of ventilation and perfusion regionally in the lungs are common causes of poor gas exchange.
tion-flux relationships facilitate the rapid equilibration of oxygen and carbon dioxide between the previously deoxygenated blood and air in the alveolar spaces. Thus in normal healthy individuals, both oxygen and carbon dioxide concentrations equilibrate across the blood-gas barrier in about one-third the time that it takes for the blood to flow through the pulmonary capillaries. However, at very high levels of exercise (particularly in patients with already compromised gas exchange function), equilibration of gases may not occur before the more rapidly flowing blood leaves the lungs. This is one of the bases for using exercise testing for evaluating the cardiopulmonary function of patients.

How does water cross the blood-gas barrier? The P-flow or concentration-flux relationship for the movement of water across the blood-gas barrier (particularly the capillary wall) is based on Starling’s hypothesis for fluid exchange across capillary walls (Fig. 17). This hypothesis states that the flux of water is determined by two components—the hydrostatic pressure gradient (ΔP) and the osmotic pressure gradient (Δπ) across the capillary wall. Thus volume flux equals a constant times ΔP minus Δπ [flux = Lp(ΔP - Δπ)]. The normal ΔP favors filtration of water out of the capillary into the interstitial space. The hydrostatic P difference equals the capillary blood P minus the P of fluid in the interstitial space. The Δπ favors the retention of water inside the capillary. The osmotic P difference equals the osmotic P due to plasma proteins (colloid osmotic P) minus the osmotic P due to proteins in the interstitial space. Thus Starling’s hypothesis with all of the variables known can be used to estimate whether water at any given point along the capillary will have a tendency to leave the capillary or to enter the capillary. In many capillaries, the answer will differ between the arterial end and the venous end as the capillary hydrostatic blood P changes due to blood flow from one end of the capillary to the other. These concentration-flux factors are important in understanding water balance across capillary walls throughout the body but are particularly important for the formation of pulmonary edema fluid in the lungs and of tubular fluid in the kidneys. Pulmonary edema fluid begins as increased
interstitial water that left the pulmonary capillaries either due to increased capillary blood P (increasing ΔP) or increased leak of proteins into the interstitium (decreasing Δτ). The most life-threatening form of pulmonary edema is the subsequent alveolar pulmonary edema (too much water in the alveolar airspaces). Generally, once an alveolus begins to fill with water, it will completely fill with water and thus it will become totally useless for gas exchange. Neighboring alveoli may still be air-filled, but as the total number of ventilated alveoli decreases, the patient will develop very low levels of oxygen in the blood. Thus, when there is water in the alveolar airspaces, normal gas exchange is greatly compromised.

THE KEY CONCEPTS OF PRESSURE-FLOW RESISTANCE IN THE RENAL SYSTEM

This section will look at some of the P-flow-R relationships important in renal physiology. First, we will look at the importance of the P-flow-R and concentration-flux relationships for blood flow and filtration during the formation of tubular fluid in the kidneys. Second, we will look at the importance of concentration-flux relationships for the reabsorption and secretion of solutes and water across the tubular walls and the ultimate excretion of solutes and water in the urine.

Activity 7: you might want to open this section with an activity having the students in small groups discuss how the blood to tubular fluid flow in the renal system is the same as or differs from the cardiovascular and respiratory blood flows (7).

P-Flow and Concentration-Flux Relationships Involved in Renal Blood Flow

The primary function of the kidneys is to homeostatically regulate the water and electrolyte content of the blood. The kidneys accomplish this function by regulating the extracellular fluid volume, the osmolarity, numerous ions including those involved in determining the body’s pH, and the blood levels of certain wastes and foreign substances. This primary function is facilitated by the unique anatomy of the blood vessels and tubules in the kidneys. Blood enters the kidneys through arteries and eventually ends up in arterioles. However, at the tubule level in the kidney, blood enters arterioles (the afferent ones—leading to), goes through a capillary network (the glomerular capillaries), and then leaves via arterioles (the efferent ones—leading away from) where blood then enters a new series of capillaries (peritubular capillaries that loop around the tubules) before going into venules and eventually veins (Fig. 18) (6). This anatomy is key to the ability of the kidneys to vary the volume and composition of the urine.

Filtration (blood to tubular lumen) across the glomerular capillary wall into Bowman’s capsule of the tubule in the nephron occurs by the same concentration-flux principles as water balance across other capillary walls (Starling’s hypothesis). The hydraulic or hydrostatic ΔP favors filtration of water into the tubule. The Δτ favors the retention of water inside the glomerular capillaries. When water is filtered into the space of Bowman’s capsule, a fluid pressure can be created that would oppose further water movement into the space.

The regulation of filtration from the glomerular capillaries into the tubules is by either an autoregulatory mechanism or by reflex control. The myogenic response is an example of an intrinsic autoregulatory...

![Diagram of renal blood flow](http://advan.physiology.org.org)
mechanism. When the smooth muscle in the wall of the arteriole is stretched by increased blood P, the muscle cells contract. This vasoconstriction increases the R to flow, and then by a negative feedback loop, the blood flow through the arteriole will decrease. The opposite response occurs when the wall of the arteriole is less stretched by decreased blood P. Another autoregulatory response is that of tubuloglomerular feedback. When fluid flow into a distal tubule increases, specialized cells there send a chemical message to its contributing afferent arteriole causing it to constrict. As R to flow increases, less water enters its glomerular capillary network to be filtered into that tubule. This is also a negative feedback loop.

Reflex control of filtration out of the glomerular capillaries is also important for kidney regulation of extracellular fluid volume. For example, sympathetic nerves and certain hormones cause constriction of the afferent arterioles (Fig. 19) (6). When afferent arterioles are constricted and R to flow in them increases, less water enters the glomerular capillaries thereby decreasing the hydrostatic P in the glomerulus and decreasing filtration into the tubule. Sympathetic nerves also constrict efferent arterioles but to a slightly lesser extent than afferent arterioles. On the other hand, efferent arterioles are more sensitive to the circulating vasoactive chemical angiotensin II (see renin-angiotensin-aldosterone system) than afferent arterioles and will constrict more forcefully. When efferent arterioles constrict, R to flow in them increases and more water stays in the glomerular capillaries, thereby increasing the hydrostatic P in the glomerulus and increasing filtration into the tubule (Fig. 20) (7).

**P-Flow and Concentration-Flux Relationships Involved in Modification of Tubular Fluid and the Formation of Urine**

The various segments of the nephron—the proximal tubules, the loops of Henle, the distal tubules, and the collecting ducts—then handle water and small solutes that are filtered into the nephron from the glomerular capillaries. Throughout the rest of the nephron, certain solutes are reabsorbed and transport proteins located in the membranes of the epithelial cells lining the segments secrete certain solutes. The end result of the reabsorption (tubular lumen to blood) and secretion (blood to tubular lumen downstream from the glomerulus) of salts and other solutes is the urine that is excreted (lumen to outside of body) after storage in the urinary bladder.

**Activity 9: what would happen to urine flow if the glomerular filtration rate remained normal but the reabsorption of solutes and water in the nephron dropped to one-half normal? (7)**

This section will look at how water moves into and out of the tubular lumen and how the kidneys can produce both concentrated and dilute urine. Most of
the active transport of solutes out of the tubular lumen and back into the blood occurs in the proximal convoluted tubules (the initial segment of the tubules). Every day, the proximal tubules are capable of reabsorbing 100% of the filtered sugar (D-glucose) and 99.5% of the filtered salt. The reabsorption of sugars, amino acids, and other organic nutrients is by secondary active transport coupled to sodium, with water following passively by osmosis. Thus, of the filtered water, 80% is reabsorbed in the proximal tubules and loops of Henle by accompanying the simultaneous active solute transport. Varying amounts of the remaining 20% of the filtered water are reabsorbed in the distal and collecting tubules. The **regulation of water reabsorption** in the distal and collecting tubules is by hormonal influences on transport proteins in the tubular cells. For example, when the osmolarity center in the brain detects dehydration of the body, secretion of the hormone **vasopressin** (antidiuretic hormone) by the cells of the hypothalamus is stimulated. Vasopressin reaching the kidneys via the blood interacts with the tubular cells, inserting special water channels (proteins known as **aquaporin 2**) into the cell membranes on the luminal side (Fig. 21). With more open water channels there, cells reabsorb water more readily, and the potential urine becomes more concentrated. Therefore, this is a negative feedback control for conserving water by preparing lower volume of more concentrated urine for excretion when the body water level becomes low.

Water reabsorption from the distal and collecting tubules occurs passively through these water channels by osmosis. Osmosis is facilitated in the deep portions of the kidney (the medulla) by a buildup of solutes in the tissue surrounding the tubules. This medullary vertical osmotic gradient is set up by the special anatomy of the loops of the kidney tubules and the peritubular capillaries leading to the tendency to trap salt (NaCl) and urea molecules in the tissue. Thus, when the body needs more water and after the insertion of water channels, many water molecules move by osmosis out of the tubular fluid, through the cells, and into the interstitium to eventually be reabsorbed into the blood. As water molecules enter the interstitium, they dilute the high osmolarity in the tissue, thereby removing some of the gradient contributing to reabsorption. Conversely when the body is well hydrated, water channels in the cells of the tubule become stored again in vesicles inside the cell and less water can move out of the tubule and eventually into the blood. This regulation of the concentration-flux of water in the kidneys, based on the principles of osmosis, allows the body to form both concentrated and dilute urine to appropriately regulate extracellular fluid volume. Diuretics are drugs used clinically to increase urine volume to remove excess water from the body. There are several types of diuretics that work via direct effects on the basic physiology and/or transport properties of various segments of the nephrons. Many diuretics directly inhibit the reabsorption of sodium out of the tubular fluid (and thus less water is reabsorbed by osmosis). Some diuretics actually create a tubular fluid with high osmolarity so that salts and water stay inside the lumen to become urine.

There is one other major hormonal system—the renin-angiotensin-aldosterone system—that is involved in regulating solute and water excretion via the kidneys. The kidneys secrete the hormone renin in response to local reductions in NaCl or extracellular fluid volume or blood P. Renin activates angiotensinogen (from the liver) in the blood into becoming angiotensin I. Angiotensin I is converted to angiotensin II by angiotensin-converting enzyme produced in the lungs. Angiotensin II stimulates the adrenal cortex to secrete the hormone aldosterone into the blood. Aldosterone stimulates sodium reabsorption and potassium secretion by the distal and collecting tubules in the kid-
ney's. More sodium is reabsorbed than potassium is secreted. Thus, when water reabsorption has also been stimulated by vasopressin, water accompanies the sodium by moving passively out of the tubular fluid into the blood. Both of these highly regulated transport processes help to replenish the extracellular fluid volume. This is another example of a basic concentration-flux movement of water molecules that determines the ultimate volume of urine excreted by the body.

SUMMARY

This presentation has tried to briefly develop some of the P-flow-R and concentration-flux relationships that are vital to the normal functioning of the respiratory and renal systems. There are at least 13 different variations on these 2 systems that incorporate some aspects of the general physiological model of gradients and conductance. With care to demystify these concepts for the students by using consistent terminology, the joy of having universally applicable general models should greatly enhance student learning. Even the exercise of preparing this presentation in a logical fashion has been enlightening to the author who never quite realized the universality of these concepts. Physiology can surely be more exciting when students (and faculty) see the commonalities of the big picture!

Address for reprint requests and other correspondence: B. E. Goodman, Physiology and Pharmacology Group, Div. of Basic Biomedical Sciences, School of Medicine, 414 E. Clark St., Vermillion, SD 57069 (Email: bgoodman@usd.edu).

Received 12 March 2001; accepted in final form 27 March 2001

REFERENCES