19EIRIPC21 / 19PEIRIPC21	MODELLING AND CONTROL OF BIOLOGICAL SYSTEMS

UNIT-IV

HUMAN THERMAL REGULATION

Humans are classified as a homeotherms, organisms that have nearly constant body temperature that is largely independent of the temperature of their surroundings. Human oral core body temperature is 37 o C with a diurnal variation of only about 0.5–0.8 o C. Lower values occur in the early morning and higher values in the late afternoon. Rectal core temperatures are slightly higher than oral core temperatures with an average of 37.5 °C and exhibit similar diurnal variation. Exertion that increases the metabolic rate increases core temperature. Major factors affecting human thermal regulation in a gaseous environment are shown in Table 1

Environment	Physiology
1. Temperature 2. Humidity 3. Air Movement 4. Radiant Exchange 5. Barometric Pressure 6. Gas Composition	1. Circadian Rhythm 2. Metabolic Rate (absolute) 3. Metabolic Rate (percent capacity) 4. External Work 5. Hydration 6. Acclimation/ Acclimatization 7. Body Temperature (skin and core) 8. Ventilation Rate 9. Sweat Rate 10. Skin Wetness

Thermoregulation is the process by which the body maintains its nominal core temperature given changes in external temperature and metabolic loading. Increases or decreases in metabolic rate respectively increases or decreases the production of heat. Factors that affect the metabolic rate include exercise, hormone levels, stress, and ingestion of food, age, and gender. Heat is transferred from or to the surface of the body and lungs by radiation, evaporation, conduction, and convection. Thus, the balance between heat production and loss is derived from the first law of thermodynamics

$$\dot{Q}_m = \dot{Q}_e + \dot{Q}_r + \dot{Q}_k + \dot{Q}_c + \dot{Q}_{st} + W \quad (1)$$

where

$\dot{Q}_m$ = metabolic heat rate
$\dot{Q}_e$ = evaporative heat loss positive, gain negative
$\dot{Q}_r$ = radiative heat loss positive, gain negative
$\dot{Q}_k$ = conductive heat loss positive, gain negative
$\dot{Q}_c$ = convective heat loss positive, gain negative
$\dot{Q}_{st}$ = heat storage rate
W = mechanical work

Body temperature is controlled by negative feedback that requires sensors, a controller, and actuators. In addition to the hypothalamus itself that also acts as a sensor, cold and warm sensitive temperature receptors are located throughout the body. The body temperature receptors are located in the skin and in the interior of the body, specifically in the spinal cord, abdomen, larger veins, and thorax. The hypothalamus, primarily neurons in the anterior hypothalamic-preoptic region, is generally recognized as the body's temperature controller or thermostat. The hypothalamic thermostat works in conjunction with other hypothalamic, autonomic, and higher nervous thermoregulatory centres to keep core body temperature constant. Temperature sensitive neurons in the hypothalamus are stimulated by the temperature receptors. Warm sensitive neurons in the hypothalamus increase their firing rate in response to an increase in body temperature to promote heat loss. Cold sensitive neurons in the hypothalamus increase their firing rate in response to a decrease in body temperature to promote heat conservation and increase heat production. Additional thermoregulatory responses are involuntary, mediated by the autonomic nervous system, some neurohormonal, and others semi-voluntary or voluntary behavioral responses.

SUBSYSTEMS OF HUMAN BODY - SKIN, CORE.

If the core body temperature decreases below the set point, cold sensitive neurons, primarily in the anterior hypothalamic-preoptic region, initiate the following hyper thermic responses:

Cutaneous Vasoconstriction – Stimulation from the posterior hypothalamic preoptic sympathetic centers constricts smooth muscles in the arterioles near the body's surface. As a result, warm blood is moved deeper within the body so that heat loss is reduced. Maximal vasoconstriction can decrease cutaneous blood flow to 30 mL min-1 from a nominal flow of 300-500 mL min-1.

Piloerection – Piloerection as a response to cold is vestigial in humans. Since humans retain only very little body hair, the reflex does not serve a useful purpose. The sympathetic nervous system causes small muscles at the base of each hair, the arrectores pilorum, to contract and pull the hair erect resulting in goose bumps in humans. While not important for humans, piloerection in animals allow the entrapment of a thicker layer of insulated air to reduce heat transfer.

Chemical Thermogenesis – Production of Thyrotropin Releasing Hormone stimulates the anterior pituitary gland to increase secretion of Thyroid Stimulating Hormone that in turn promotes production of Thyroxin (T4) by the thyroid that increases cellular metabolism that produces heat. In addition, an increase in sympathetic stimulation and release of epinephrine and norepinephrine from the adrenal medulla also increases cellular metabolism.

Shivering – The primary shivering motor centre, located in the dorsomedial region of the posterior hypothalamus, is stimulated by signals from the cold sensitive receptors in the skin and spinal cord. When activated, the shivering motor centre transmits signals to the anterior motor neurons that increase the tone of the skeletal muscles. When the tone increases above a critical level, shivering is initiated. Shivering can increase surface heat production by 500%. However, this effect is limited to a few hours because of depletion of muscle glucose and the onset of fatigue.

If the core body temperature increases above the set point, the warm sensitive neurons, primarily in the anterior hypothalamic-preoptic region, initiate the following hypothalamic responses:

Skin Vasodilation – Inhibition of the adrenergic activity of the sympathetic centres in the posterior hypothalamus causes the smooth muscles of the arterioles to relax resulting in dilation of blood vessels in the skin. This increases skin blood flow and therefore temperature, promoting heat transfer out of the body. Maximal vasodilation can increase cutaneous blood flow to 3000 mL min-1 from a nominal flow of 300-500 mL min-1.

Decrease in Metabolic Rate – Reduction in the metabolic rate decreases the production of heat by the body. This is realized by inhibiting the mechanisms that produce heat by chemical thermogenesis and shivering as discussed above.

Sweating – If the heat is sufficiently high, the cholinergic sympathetic fibres that innervate the sweat glands release Acetylcholine that stimulates sweat. This activation of the sweat glands produces sweat that results in heat loss through evaporation. By this mechanism, many times the basal metabolic heat rate can be removed.

A schematic of the thermoregulatory system is illustrated in Figure 1.

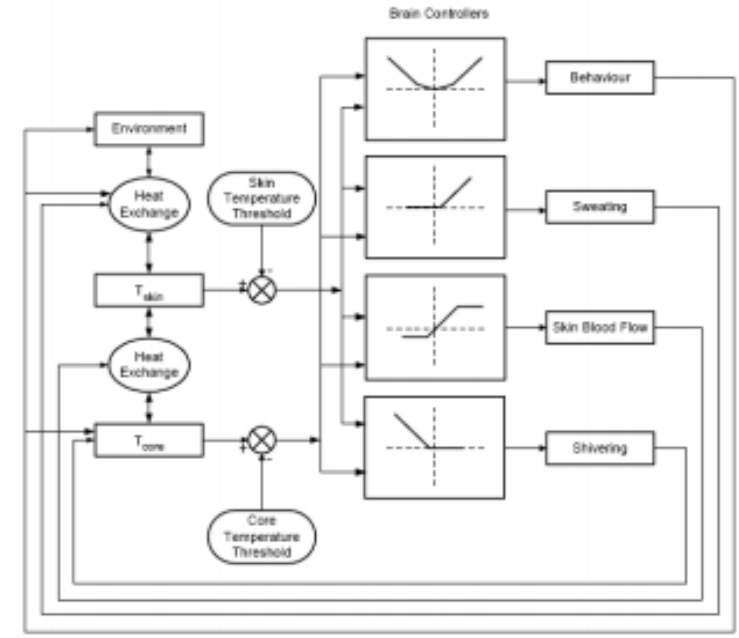


Figure 1 Thermoregulation Feedback Control, from (5)

HEAT TRANSFER MODEL

A major problem in thermal physiology modelling is the mathematical description of the thermal state of the organism. From the mathematical point of view, the human organism can be separated into two interacting systems of thermoregulation: the *controlling active system* and the *controlled passive system*. Mathematical modelling of these systems are called active model and passive model, respectively.

The active system is simulated by active modelling, which predicts regulatory responses such as shivering, vasomotion, and sweating. The main purpose of the active model is that it regulates the passive heat transfer model and it is responsible for the maintenance of the human body's temperature.

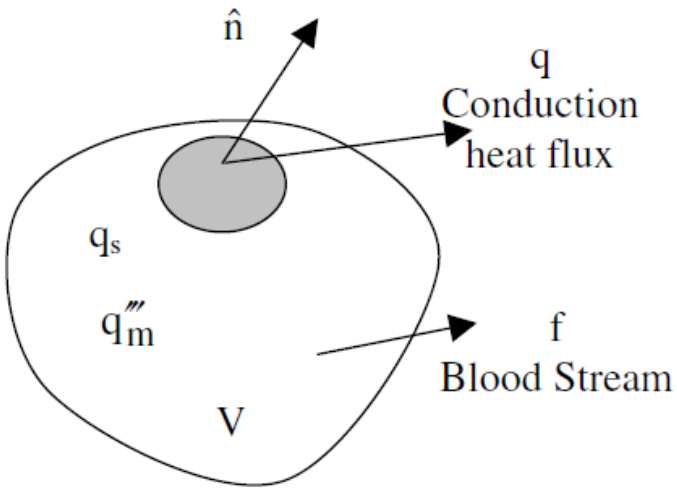
The passive system is modelled by passive modelling, which simulates the physical human body and the heat transfer phenomena occurring in human body and at its surface. For example,

the metabolic heat produced within the body, is distributed over body regions by blood circulation and is carried by conduction to the body surface, where, insulated by clothing. In order to loose the heat to the surroundings, the body uses four mechanisms of heat transfer; radiation, conduction, convection, evaporation and respiration. All of these heat transfer phenomena given above are modelled by the passive modelling.

All thermoregulation models use the same general equations to describe the heat transfer. Heat is transferred from core to shell and hence to skin surface by conduction and blood convection.

Heat Transfer Within the Tıssue

Consider a representative control volume of tissue. This basic element is in continuous thermal communication with surrounding tissues. To maintain equilibrium, thermal energy which is generated inside the element (q'_m'') is conducted to adjacent elements, transported (convicted) by the blood stream or stored inside the element.



As illustrated in Figure. 3.3, energy-balance equation for this small control volume of tissue is summarized as:

$$\left[\begin{array}{c}\text{Rate of heat}\\ \text{entering}\\ \text{through the bounding}\\ \text{surface of V}\end{array}\right]+\left[\begin{array}{c}\text{Rate of energy}\\ \text{generation}\\ \text{in V}\end{array}\right]+\left[\begin{array}{c}\text{Rate of energy}\\ \text{trasported by}\\ \text{blood stream}\\ \text{in V}\end{array}\right]=\left[\begin{array}{c}\text{Rate of storage}\\ \text{of energy}\\ \text{in V}\end{array}\right] \qquad (3.1)$$

Conduction

The fundamentals law of heat conduction was developed by Fourier and the conductive heat flux vector is assumed to obey Fourier's law of conduction. Accordingly,

q(r,f,z, t) = -k(r) ÑT(r,f,z, t) W/m2

where the temperature gradient is a vector normal to the isothermal surface, the heat flux vector q(r,f, z, t) represents heat flow per unit time, per unit area of the isothermal surface in the direction of the decreasing temperature and k (r) is referred as the thermal conductivity of mammalian tissue which is dependent upon tissue temperature and location. Since the heat flux vector q(r,f, z, t) points in the direction of decreasing temperature, the minus sign is included in Equation to make heat flow a positive quantity.

Metabolic Heat Generatıon

The rate of energy generation within an organism is defined as the rate of transformation of chemical energy into heat and mechanical work by aerobic and anaerobic metabolic activities. These activities are the sum of the biochemical processes by which food is broken down into simpler compounds with the exchange of energy. The factors which influence the metabolic heat generation include surface area, age, gender, stress, and hormones. Although metabolic heat generation is related to overall body weight and size, the critical factor is surface area rather than weight itself. This reflects the fact that as the ratio of body surface area to body volume increases, heat loss to the environment increases and the metabolic heat generation must be higher to replace the lost heat. Hence, if two people weight the same, the taller or thinner person will have a higher metabolic heat generation than the shorter or fatter person. According to above information, the total amount of heat generated in the control volume is given by:

$$q_m = \int_V q'''_m \, dV$$

where q¢m¢¢ is the specific rate of heat production which may generally be a function of tissue temperature and location.

The amount of heat produced is determined by energy metabolism. At rest, approximately 56% of total heat production occurs in the internal organs and about 18% in the muscle and skin.

During physical exercise, heat production increases several-fold and the percentage of heat produced by muscular work can raise to as much as 90%.

Convection by the Circulatory System

Heat produced in the body should be absorbed by the bloodstream and conveyed to the body surface. Because all body tissues are poor conductors of heat. If the heat transfer in the body depended on conduction, very large temperature gradients would be needed, and the ability to adapt to varying environmental conditions would be poor. Therefore, the convective flow of blood throughout the body is very important in internal heat transfer

When there is a significant difference between the temperature of the blood and the tissue through which it flows, convective heat transfer will occur, altering the temperature of both the blood and the tissue.

The effects of the blood circulation to the internal heat distribution within the body can be summarized in three major ways

1. It minimizes temperature differences within the body. Tissues having high metabolic rates are more highly perfused, and thus are kept at nearly same temperature as less active tissues. Cooler tissues are warmed by blood coming from active organs.

2. It controls effective body insulation in the body skin region. When the body wishes to reject heat, how warm blood flow to the neighbourhood of the skin is increased by “vasodilation”, and how the blood is bypassed from arteries to veins via deeper channels through “vasoconstriction”, when conservation of body heat is vital. These automatic mechanisms either raise or lower the temperature gradient for heat transfer by conduction in the sub skin layers

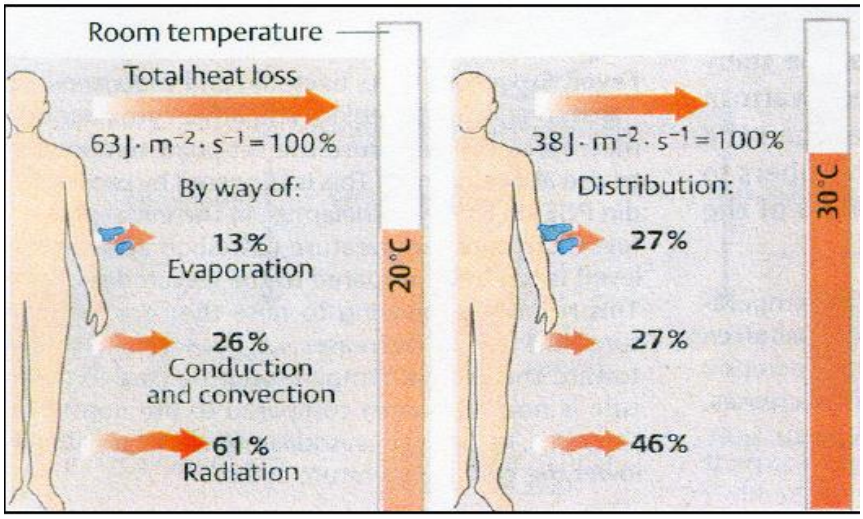
3. Counter current heat exchange between major arteries and veins often occurs to a significant extent. If heat conservation is necessary, arterial blood flowing along the body’s extremities is precooled by loss of heat to adjacent venous streams. This reduces the temperature of the limbs and lowers heat losses. Since most arteries lie deep, while veins occur both in superficial and deep regions, the extent of the arteriovenous heat exchange depends on the route taken back to the body trunk by the venous blood. This is automatically regulated by the vasodilation-vasoconstriction mechanisms.

Storage of Thermal Energy

When the body temperature is constant the rate of heat storage in the tissue is zero, in practice it is negligible over long time periods. However, over short periods and severe environments, heat storage in the tissue, which can be an important component of the heat balance, determines the tolerance time for work.

Heat Exchange With Environment

Heat flow inside the human body occurs when the temperature of the body surface is lower than that of the body interior. The body supply to the skin is the chief determinant of heat transport to the skin. Heat loss occurs by the physical processes of radiation, conduction, convection, and evaporation



Radiation

Radiation is the loss of heat in the form of infrared waves. When the surrounding is cooler than the body, net radiative heat loss occurs. Under normal conditions, close to half of body heat loss occurs by radiation. In contrast, when one's surrounding is hotter than the one's body, a net heat gain via radiation occurs

Convection

When the body shell transfers heat to the surrounding air, convection also comes into play. Because warm air tends to extend and rise and cool air falls, the warmed air enveloping the body is continually replaced by cooler air molecules. This process, called convection, substantially enhances heat exchange from the body surface to the air.

Evaporation

Heat loss by radiation and heat loss by convection alone are unable to maintain adequate temperature homeostasis at high environmental temperatures or during strenuous physical activity. Because water absorbs a great deal of heat before vaporizing, its evaporation from the body surfaces removes large amount of body heat. The water lost by evaporation reaches the skin surface by diffusion and by neuron activated sweat glands. At temperatures above 36°C or so, heat loss occurs by evaporation only.

TYPES OF HEAT LOSS

Heat can be lost through the processes of conduction, convection, radiation, and evaporation. Conduction is the process of losing heat through physical contact with another object or body. For example, if you were to sit on a metal chair, the heat from your body would transfer to the cold metal chair.

Radiation

Radiation is the loss of heat in the form of infrared waves. All objects continually radiate energy in accordance with the Stefan-Boltzmann law, i.e., proportionately with the surface area, emissivity, and the fourth power of the absolute temperature. When the surrounding is cooler than the body, net radiative heat loss occurs. Under normal conditions, close to half of body heat loss occurs by radiation. In contrast, when one's surrounding is hotter than the one's body, a net heat gain via radiation occurs.

The amount of incident radiation that is captured by a body depends on its area, the incident flux, and the body's absorptivity. It is common to estimate the absorptivity of a body as equal to its emissivity at the temperature of the surroundings, although this is strictly true only when the body is in radiative equilibrium with the surroundings.

The net rate of heat exchange by radiation between an organism and its environment, usually expressed in terms of unit area of the total body surface.

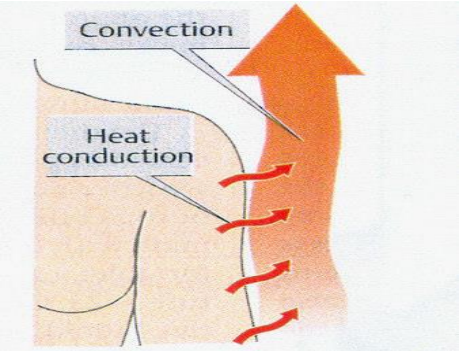
$$q_r = \varepsilon * \sigma * (T^4{}_s - T^4{}_a) \quad (W/m^2)$$

where _ is the emissivity which is approximately equal to the absorptivity. For incident infrared radiation, the absorptivity of human skin is very high, about 0.97, and is dependent of colour. For visible light, the skin has an absorptivity of about 0.65- 0.82, depending on whether it is white or dark, respectively (Cooney, 1976). Stefan-Boltzmann Constant, s , is 5.67051×10-8 (W/m2K4). Ts is the surface temperature of the body or clothes and Ta is the temperature of surroundings.

Convection

When the body shell transfers heat to the surrounding air, convection also comes into play. Because warm air tends to extend and rise and cool air falls, the warmed air enveloping the body is continually replaced by cooler air molecules. This process, called convection,

substantially enhances heat exchange from the body surface to the air, because the cooler air absorbs heat by conduction more rapidly than the already warmed air.



The movements of fluid which carry heat away from the body surface may be driven by two mechanisms: “free convection” due to density differences in the fluid associated with temperature gradients; or “forced convection”, due to external forces such as wind Pure free convection occurs under stagnant conditions when the velocity of the ambient toward the person is zero. Forced convection heat transfer occurs when the ambient is approaching the body with a definite (and usually steady) velocity

Convective heat losses from the body are strongly dependent on air velocity. The simplest equation for characterizing convective losses is

$$q_c = h_c * (T_s - T_a) \qquad (W/m^2)$$

Ts is the surface temperature of the body or clothes and Ta is the temperature of surroundings. And hc is the convective heat transfer coefficient.

The calculation of heat loss due to convection requires the estimation of convection heat transfer coefficient h_c, which is calculated from the equation given below

$$Nu = \frac{h_c \times D_{limb}}{k_a}$$

where Nu is the Nusselt Number, Dlimb is the external diameter of the limb (m), hc is the convection heat transfer coefficient and ka is the thermal conductivity of the air (W/mK).

a) Free Convection

In the situation of density gradients, the body force acts on a fluid. The net effect is the bouncy force, which induces free convection currents. In the most common case, the density gradient

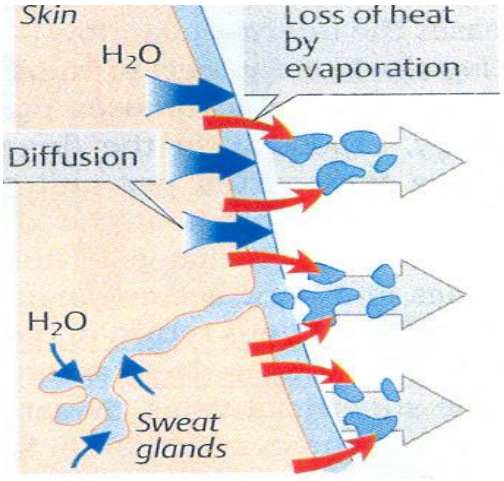
is due to a temperature gradient, and body force is due to the gravitational field. For a subject with a mean skin temperature lower than air temperature, the air adjacent to the skin surface will become heated by conduction and will rise due to buoyancy. This is the mechanism by which heat is lost from the body by free convection.

b) Forced Convection

When the body is exposed to a wind or is moving through the air, the natural convective boundary-layer flow is displaced and the body losses heat by forced convection. The variables that influenced forced convection are the mean air velocity, the flow direction and the nature of the flow whether it is laminar or turbulent. The degree of turbulence and its scale can have a profound effect upon the heat loss.

Evaporation

Heat loss by radiation and heat loss by convection alone are unable to maintain adequate temperature homeostasis at high environmental temperatures or during strenuous physical activity. Because water absorbs a great deal of heat before vaporizing, its evaporation from the body surfaces removes large amount of body heat. The water lost by evaporation reaches the skin surface by diffusion and by neuron activated sweat glands. At temperatures above 36°C or so, heat loss occurs by evaporation only. In addition to this, the surrounding air must be relatively dry in order for heat loss by evaporation to occur. Humid air restricts evaporation. When the air is extremely humid (e.g. in a tropical rain forest), the average person can not tolerate temperatures above 33°C, even under resting conditions.



In human body, evaporative heat losses occur by several mechanisms:

a) Heat losses by diffusion of water through the skin

b) Heat losses by sweat secretion

c) Heat losses by evaporation of water into inspired air.

a) Heat Losses by Diffusion of Water Through The Skin

Water diffusion through the human skin is part of the "insensible" perspiration. This diffusion totals about 350 ml/day in an average person and is assumed to be proportional to the difference between the vapor pressure of water at the skin temperature and the partial pressure of water vapor in the ambient air. Inouye (Cooney, 1976) gave the correlation about the diffusional heat loss per unit area.

b) Heat Losses By Sweat Secretion

When the heat loss amount is not ample to maintain the core temperature in a suitable range, an automatic mechanism of the body appears. This mechanism for increasing the heat loss is the sweating response, which provides secretion of a dilute electrolyte solution from numerous glands to the skin surface. Then, evaporation from the wetted surface then occurs.

c) Heat losses by evaporation of water into inspired air.

When air is inspired into the lungs, heat and water vapor are transferred to the air by convection and evaporation from the surface lining the respiratory tract. By the time the air has reached the deepest parts of the lungs, the air is at deep body temperature (37°C) and saturated with water vapour (47 mm Hg partial pressure). As the air moves outward through the respiratory tract during expiration, some heat is transferred back to the body and some water is condensed. However, the inspired air still contains significantly more heat and water than the inspired air. Respiration results in a latent heat loss and a sensible heat loss.

Heat-Loss Mechanisms

Heat-loss mechanisms protect the body from excessively high temperatures, which can be damaging to the body. Most heat loss occurs through the skin via the physical mechanisms of the heat exchange, such as radiation, conduction, convection, and evaporation. When the core temperature arises above normal, the hypothalamic heat-producing centre is inhibited. At the same time, the heat-loss centre is activated and so triggers one or both of the following mechanisms.

a) Vasodilation of cutaneous blood vessels: Inhibiting the vasomotor fibres serving blood vessels of the skin allows the vessels to dilate. As the skin vasculature swells with warm blood, heat is lost from the shell by radiation, conduction and convection.

b) Sweating: If the body is overheated or if the environment is so hot that heat condition not be lost by other, heat loss by evaporation becomes necessary. The sweat glands are strongly

activated by sympathetic fibres and spew out large amounts of perspiration. When the relative humidity is high, evaporation occurs much more slowly. In such cases, the heat-liberating mechanisms cannot work well, and we feel miserable and irritable.

UNIT-V

MASS BALANCING OF LUNGS

The human external respiratory system (lungs) is a mass transfer device with the vital purpose of continually exchanging the metabolic gases, oxygen and carbon dioxide, between man and his environment.

Pulmonary Function

BREATHING is the process of inspiration (air flows into the lung) and exhalation (air flows out of the lung).

Inspiration begins when the diaphragm and the intercostal muscles of the chest wall contract in response to neural impulses from the brain stem (Fig. 3). Contraction of the diaphragm causes it to descend and contraction of the intercostal muscles raises the ribs; the chest cavity expands. Because the lungs are functionally connected to the chest wall by the pleural sac, the lungs also expand (Fig. 3). This increase in lung volume reduces the air pressure in the alveolar ducts and alveoli. When the pressure in the alveoli (PA) becomes less than the pressure at the mouth, which is ordinarily atmospheric pressure (Patm), air flows in until PA = Patm

Exhalation occurs when the muscles of inspiration relax. The lung returns ***passively*** to its pre-inspiratory volume due to its elastic properties. This reduction in volume raises the pressure in the lung causing air to flow out.

VENTILATION CYCLE is one inspiration and exhalation. Ventilation rate (*f)* is in the range of 10-18 breaths per min. Both the rate and depth can be changed by output from the respiratory centers in the brain stem (medulla oblongata). During heavy exercise air flow can increase 20-fold and blood flow 3-fold. To expel such increased volumes, active exhalation is required in which abdominal muscles and internal intercostal muscles contract. These actions actively decrease the size of the thorax (chest cavity).

Lung volumes play a major role in gas exchange and in the work of breathing. They are measured under dynamic and static conditions. Dynamic volumes refer to measurements made when volumes are changing, i.e., during gas flow. Static volumes can be measured between two points where there is no flow, for example before and after inspiration.

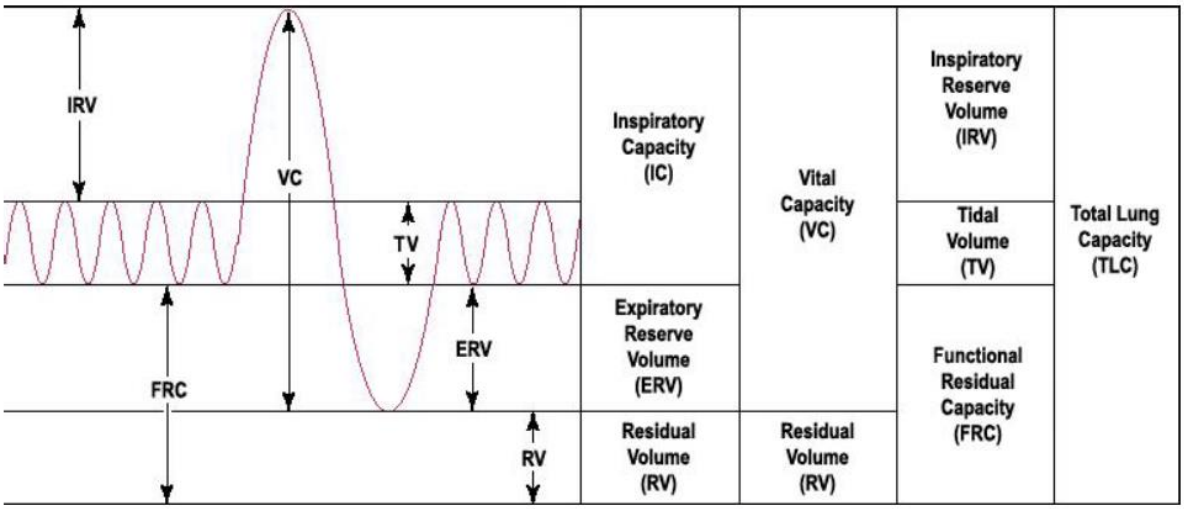


Figure 4. Lung volumes and capacities. image by Vihsadas (modified),

Residual volume (RV): Amount of air in the lungs at the end of maximal exhalation (~ 1.5 L young men).

Tidal volume (TV): Volume of air inhaled or exhaled with each breath (in adult males ~ 0.5L; in females usually about 20- 25% less).

Inspiratory reserve volume (IRV): Volume of air that can be inspired after a normal inspiration (~ 3.0 L in males).

Expiratory reserve volume (ERV): Maximal volume of air that can be expired (exhaled) from resting expiratory level (~1.0 L in males).

Inspiratory capacity (IC=TV+IRV): Maximal volume of air that can be inspired from resting expiratory level (~3.5 L in males).

Functional residual capacity: (FRC=RV+ERV): Volume of air in lungs at end of a normal exhalation. (~2.5 L in males) (see Fig. 4).

Vital capacity (VC=ERV+TV+IRV): Volume of air that can be exhaled after maximal inspiration (~ 4.5 L)

Total lung capacity (TLC=RV+ERV+TV+IRV): Volume in lungs at end of maximal inspiration (~6 L).

The functional units of the lung are the alveoli where the alveolo-capillary membranes introduce environmental air to pulmonary blood. These alveoli are outpouchings near the terminal portions of the gas distribution system and an estimated 300 million alveoli participate

in the normal lung (pair implied). An elaborate system of conductive airways connects the alveolated regions to the environment. Functionally, the conductive airways do not contribute significantly to membrane mass transfer and this (typically) 150 millilitres of volume is known as an anatomic dead space. In contrast, the alveoli and the alveolated transition regions of airways provide the active mass transfer area, an estimated 70 square meters in a resting volume of (typically) 2500 millilitres.

As pulmonary gas is expired in tidal volumes of (typically) 500 millilitres, alveolar gas displaces the expiring anatomic dead space gas. Then, upon inspiration, the "previous" alveolar gas is rein spired from the (approximately) constant volume dead space and "fresh air" follows until the tidal volume requirements of the alveolar regions are satisfied. Pulmonary gas distribution is then primarily convective and temporal, with many potential anomalies:

1. Tidal volumes, respiration frequencies, and ventilation patterns may alter time constants and influence the ventilator distributions

2. Dead space volume y and the distribution of this volume relative to local alveolar groups, influences "fresh air" ventilation and interalveolar mixing characteristics

3. Resistance in these same conductive airways, and the compliance of the alveolar region tissues, combine to determine both global and local (distributions) convection patterns.

4. Resistance and compliance characteristics may also promote the asynchronous ventilation of alveolar groups and, in turn, modify the respiratory responses that define certain convective maldistributions or dead space parameters

5. Alveolar volumes and the distribution of alveolar volumes alter transient responses

. Pulmonary blood distribution is likewise complicated in structure (38) and potential anomalies;

1. Cardiac output and pulsatile blood flow are definite parameters of gas uptake.

2. Portions of venous (deoxygenated) blood are shunted around the mass transfer surfaces and mix with arterial (oxygenated) blood without being conditioned by pulmonary gas .

3. Hydrostatic pressures, and variations in capillarity or vasoconstriction, combine to induce a preferential perfusion of local lung tissues

4. Capillary volumes influence blood-gas exposure time

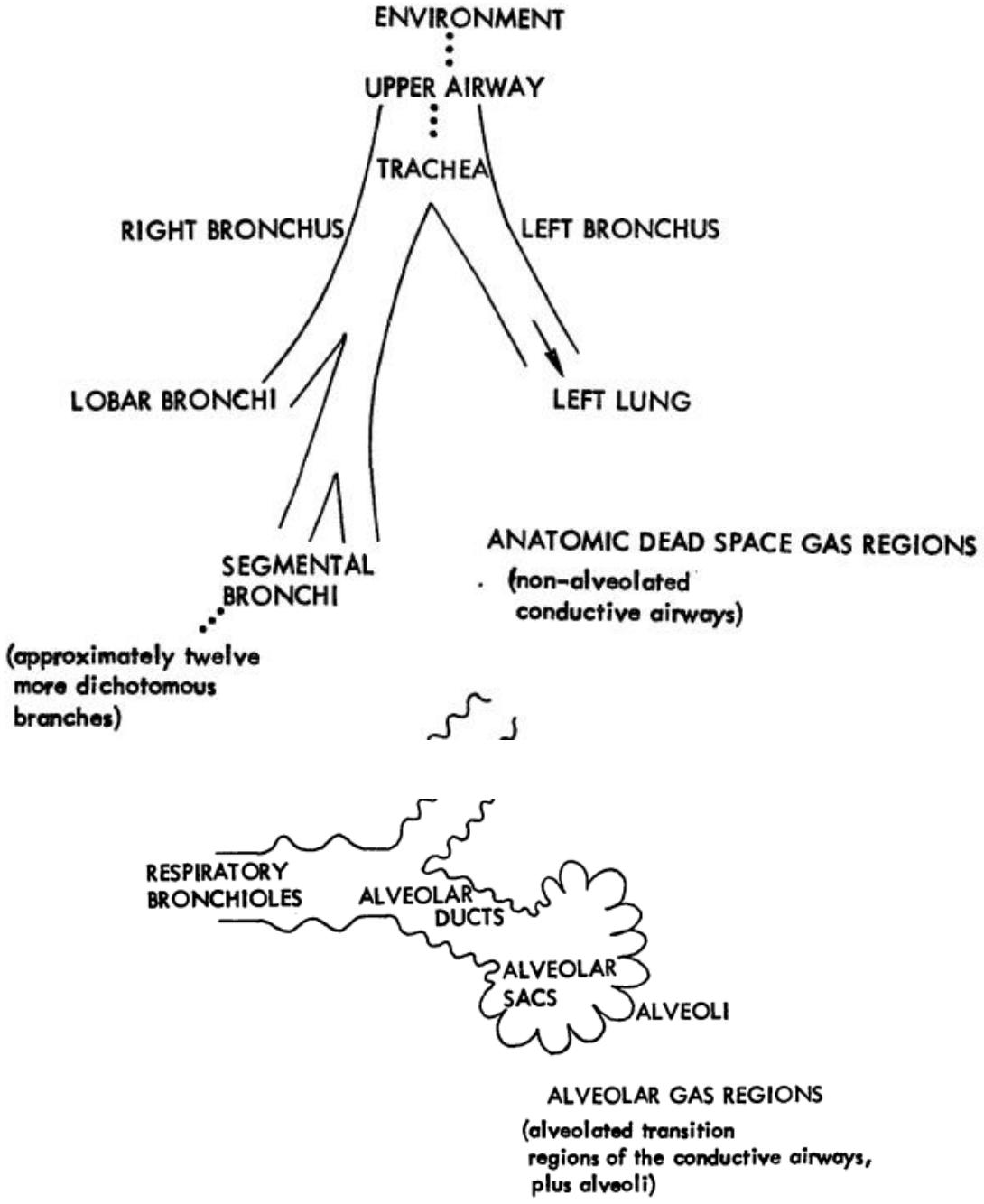


Figure A-1. Functional gas regions of the lung

Ventilation and perfusion parameters are essential specifications of the local mass transfer units, but to these must be added the characteristics of the gas-membrane-blood diffusion barrier. Often, an assumption of alveolar gas - end capillary blood equilibration was invoked while some of the remaining parameters of respiration were investigated. However, mass transfer coefficients are certainly finite and, although measurements are made by inference and are difficult to isolate, an impaired membrane diffusion process can contribute significantly to overall gas uptake limitations. The mass transfer coefficients (per unit volume) are numerically distributed over the entire lung transport surface and have a temporal aspect due principally to the periodic inflations of the alveoli with respiration.

The remaining parameters of pulmonary gas uptake are the metabolic requirements of the body, the quality of "fresh air", and the (respiratory) gas capacity of the blood. There are, then, four primary areas of interest; gas distributions, blood distributions, diffusion limitations, and "external" respiratory parameters.

TRANSPORT OF OXYGEN AND CARBON DIOXIDE IN BLOOD AND TISSUES

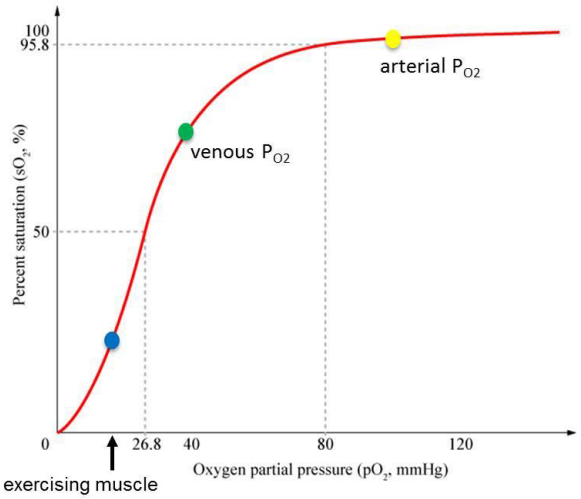


Figure 12. Hemoglobin dissociation curve. image by Diberri (modified),

To enhance delivery and transport of O2 and CO2 to and from tissues, specialized mechanisms (O2-hemoglobin and bicarbonate transport of CO2) have evolved.

OXYGEN TRANSPORT

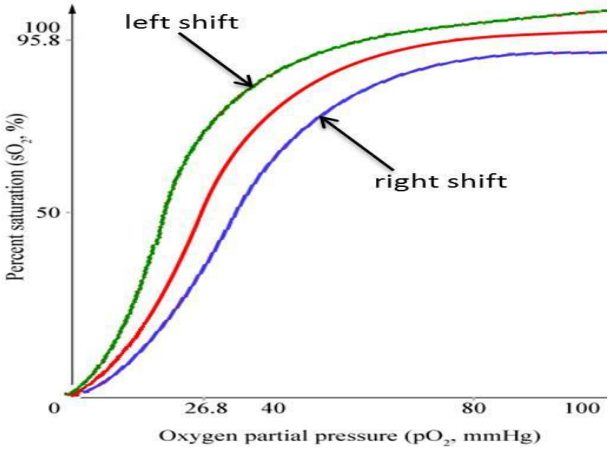


Figure 13. Shifted hemoglobin dissociation curve. image by Diberri (modified),

Oxygen is not very soluble in water and therefore requires the carrier, haemoglobin (Hb), for transport in blood. Blood normally contains about 15 g of Hb per 100 ml. This effectively raises the solubility of O2 from 3ml/L of plasma (blood minus the red blood cells) to 200 ml/L plasma. Since oxygen consumption ranges from 250 to 1500 L/min, this extra O2 carrying capacity of Hb enables the heart and lungs to provide for the O2 needs of the body.

Hemoglobin binds up to 4 molecules of O2 tightly, cooperatively, and reversibly. Normally Hb is almost completely saturated (96%) when exposed to room air (FiO2 = 21%). This occurs because of the transit time (0.75 seconds) for the red blood cell through the alveolus-capillary unit and the rapid equilibration (0.3 seconds) for both carbon dioxide and oxygen within this region of the lung.

This rapid equilibration reflects the driving pressure for diffusion and the solubility of the gas. The driving pressure for diffusion of CO2 in the alveolus-capillary unit is lower (PMVCO2-PaCO2 = 46 mm Hg - 40mm Hg = 6 mm Hg) than that for O2 (PaO2 - PMVO2 = 100 - 40 = 60 mm Hg), but the solubility of CO2 in plasma is much greater. The net result is that the rates of diffusion for CO2 and O2 are approximately equal in the alveolus-capillary unit. This means that in normal lungs **there is ALWAYS adequate time to saturate Hb with O2 regardless of ventilator rate.**

Oxygen concentration in the blood is dependent on the **Hb concentration** in the red blood cells, the number of red blood cells (**haematocrit**), and on the adequacy of **perfusion** of the lungs rather than on diffusion rate itself.
Not all of the O2 bound to Hb is released in the tissues. At rest only about 25% of the O2 in blood is released (Fig. 12). This provides a large driving force for diffusion and a large reservoir of O2 to be called upon when needed as in exercise.

The Hb-O2 dissociation curve (Fig. 12) is **S-shaped** because the interaction of oxygen with haemoglobin is **cooperative**. That is, when one oxygen molecule binds, it increases the affinity of the haemoglobin for the next oxygen molecule. Each haemoglobin molecule can bind four oxygen molecules.

The plateau of the Hb-O2 dissociation curve is called the "**association part"** of the curve, because oxygen is loaded in the lungs at relatively high partial pressures. Increasing the partial pressure above 100 or down to about 80 mm Hg, ***does not result*** in a large change in the % saturation. This tends to stabilize arterial O2 content, making it relatively insensitive to moderate changes in breathing or altitude.
The "**dissociation part"** of the curve is the steep part of the curve (Fig. 12). In this region a small change in PO2 results in a large change in % saturation which allows for large quantities of oxygen to be dumped in the tissues.

The P50 is the partial pressure of oxygen required to saturate 50% of the haemoglobin. A normal P50 is about 26-27 mm Hg. This value is a useful measure of the affinity of haemoglobin for O2.

Oxygen-Hb binding and association is affected by a number of parameters including temperature, the red blood cell metabolite 2,3 phosphoglycerate (DPG), and pH. Elevated temperature, low pH and increased 2,3 DPG shift the curve to the right (**decrease affinity**) which **enhances unloading of O2 from Hb** (Fig. 13). Note that these are conditions found within the interstitial tissue surrounding actively contracting muscle. Hypoxic conditions also result in increased formation of 2,3-DPG by the red blood cells.

Conversely, a decrease in temperature, high pH and a decrease in 2,3, DPG shifts the O2-Hb dissociation curve to the left (**increase affinity**) which **promotes loading of O2 onto Hb** (Fig. 13).

CO2 transport

Carbon dioxide is a product of oxidative metabolism. Unlike O2, CO2 is very **soluble in water** and does not need a carrier for transport in the blood. Most (60%) of the carbon dioxide in blood is transported as **bicarbonate (HCO3-)**. The conversion of CO2 to bicarbonate is catalysed by the enzyme carbonic anhydrase located inside red blood cells.

CO2 + H2O = H2CO3 = HCO3- + H+

Once formed, the HCO3- is transported out of the RBC into the plasma in exchange for Cl-.
About 10% of the total CO2 in blood is transported as dissolved CO2. The amount dissolved is proportional to the PCO2, and to the solubility coefficient for CO2. At PaCO2 = 40 mm Hg, there would be approximately 26.8 ml CO2/L of plasma.
The remaining 30% of the CO2 combines with Hb to form carbamino-hemoglobin compounds.

Because **CO2 diffuses 20X more rapidly than O2,** a rise in blood CO2 can be compensated by an increase in ventilator rate. **Hyperventilation increases the amount of CO2 removed from the body and increases the unloading of CO2 from the blood in the lung.**

CONTROL OF RESPIRATION

Breathing is essentially automatic and can only be altered temporarily by voluntary efforts. You cannot consciously stop breathing for long. You breathe when you are asleep, awake, or even anesthetized. Breathing is finely tuned to meet metabolic demands, such that during exercise ventilation increases to maintain arterial PO2, PCO2 and pH within a narrow range. To achieve this tight regulation, peripheral receptors send information to a CNS respiratory center whose output adjusts initiation, duration, depth, and rate of breathing.
The intercostal muscles and diaphragm are skeletal muscles that will not contract unless stimulated. Thus breathing depends on cyclical excitation of the motor neurons that innervate these muscles. Destruction of these nerves by the polio virus for example results in paralysis and death if the individual is not ventilated.

The underlying respiratory rhythm is established by **respiratory centres** in the **medulla of the brain stem**. The general term for this integration centre is the **respiratory rhythm generator**. Inspiratory neurons located in the respiratory centre initiate respiratory rhythm by sending signals to the motor neurons that innervate the effector skeletal muscles (intercostal and

diaphragm). This rhythm is modified by input from **peripheral sensors** (**chemoreceptors and mechanoreceptors)** located in blood vessel walls and by central receptors (chemoreceptors) in the brain.

Inspiration is limited by several inputs including stretch of the lungs and innate rhythm generators within the brain stem (medulla). The medullary inspiratory neurons are quite sensitive to drugs such as barbiturates and morphine. Death from an overdose of these drugs is often due to cessation of breathing.

Inspiratory receptors in the lung include:

1. Pulmonary stretch receptors located in the smooth muscle of the large and small airways of the lung are mechanoreceptors that fire with the inflation of the lung. These receptors **stop inspiration** as part of the **Hering-Breuer reflex**. In the adult this reflex is evoked only under conditions of large tidal volumes as in rigorous exercise.

2. J Receptors located in the walls of the pulmonary capillaries which are stimulated by pulmonary vascular congestion, edema, air emboli (air in the blood), and low lung volumes. Stimulation of these receptors can result in **rapid breathing** (**hyperpnea)**, and or laboured breathing (**dyspnea).**

3. Pulmonary irritant receptors located in airway epithelium and the nasal mucosa. Mechanical or chemical irritation elicits a **cough reflex** and **bronchoconstriction**.

Ventilation is Regulated by Chemoreceptors

Respiratory rate and tidal volume can increase or decrease over a wide range. At rest, chemoreceptors located in the periphery and centrally within the CNS provide feedback to regulate these two factors.

Peripheral chemoreceptors are the carotid receptors and aortic bodies. They are stimulated by:

a. decrease in PaO_2 (hypoxia)

b. increase in $PaCO_2$ (respiratory acidosis)

c. decrease in pH within the arterial blood (metabolic acidosis).

Of the two, the **carotid receptor is the predominate input** in controlling respiration.

Central chemoreceptors are widely distributed throughout the brain stem. They **respond to an increase in blood PCO2. These receptors actually sense H+ concentration in the interstitial fluid of the brain.** They are not affected by changes in arterial pH because the blood brain-barrier is not permeable to H+ or HCO3-. Instead, CO2 equilibrates across this barrier, causing a change in the interstitial fluid pH. Because the interstitial fluid and the adjoining cerebrospinal fluid contain little protein, they are not well buffered. Hence **small changes in PCO2 produce large changes in pH in this area**.

Ventilatory Response to Oxygen

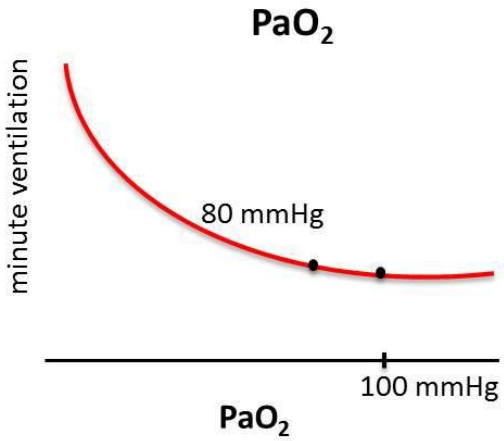


Figure 15. Effect of low arterial O2 pressures on ventilation

The ventilator response to hypoxia is shown in the graph below (Fig.15). PaO2 must decrease to about 50-60 mm Hg before respiration is increased. It has been suggested that the carotid chemoreceptors (which respond to changes in PaO2), are designed to protect the organism against hypoxia rather than to regulate respiration. Note that the stimulation to hypoxia is **arterial PO2 not arterial O2 content**. That means that individuals **with anaemia do not have increased ventilation** because their PaO2 is normal

Ventilatory Response to Carbon Dioxide

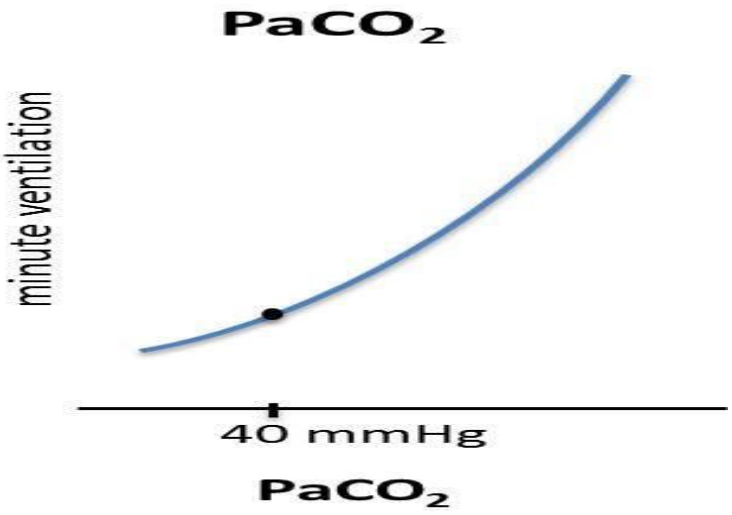


Figure 16. Effects of arterial PCO2 on minute ventilation

A very small increase in PaCO2 (2-4 mm Hg) provides a powerful stimulus to increase respiration (doubles alveolar ventilation) (Fig. 16). What is the physiologic role of this response? Recall that changes in PaCO2 have profound effects on pH. Thus this tight regulation of PaCO2 allows for tight control of acid-base balance. For example, in emphysema patients retention of CO2 occurs because of the decrease in the elastic recoil. This raises their PaCO2 leading to increased minute ventilation (i.e, "blowing down" the CO2 in the blood). Of the two sets of receptors involved in this reflex response to elevated PaCO2, the central chemoreceptors are more important accounting for ~70% of the increased ventilation.
Hypoxia (low PO2) potentiates the effects of CO2. The response curve is shifted to the left and has a steeper slope. Thus a lower PaO2 will result in a stronger ventilator response for the same arterial PCO2.

Very high levels of carbon dioxide (greater than 70-80 mm Hg) can depress respiration, cause headaches, restlessness, faintness, and even unconsciousness or coma.

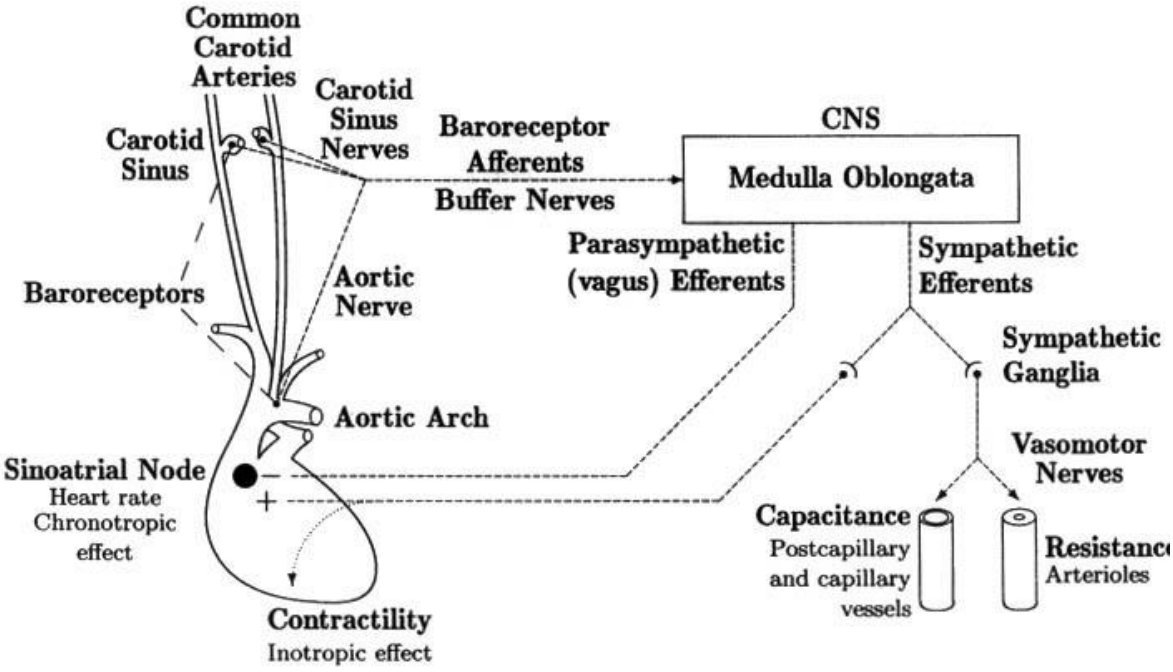
CONTROL OF CARDIAC FRATE AND BLOOD PRESSURE

Control Mechanisms in the Human Circulatory System

Control of the human cardiovascular system involves a manifold of mechanisms whose explicit functions are not fully understood. However, we can roughly divide this complex

environment into two types of control: the long- and short= term control of human circulation. *Long-term control* operates mainly via renal and humoral activities. The kidneys increase the output of water and salt in response to an enhanced arterial pressure. This action decreases blood volume and thus cardiac output. The net effect is a decline in arterial pressure. A drop in the arterial pressure promotes secretion of renin from the kidneys. Renin promotes the formation of the hormone angiotensin II, which enhances vessel constriction and thus increases arterial pressure. *Short-term regulation* is mainly mediated by the CNS and involves baroreceptors, mechanoreceptors, and chemoreceptors The overall goal of neural control is to redistribute blood flow to the different areas of the body by innervating the heart and the vessels. The nervous activity from the CNS modifies the heart rate, the cardiac contractility, and the state of vessel constrictions. Chemoreceptors are sensitive to chemicals in blood and react to alterations in the concentration of oxygen, carbon dioxide, or hydrogen ions. A drop in arterial pressure may decrease the concentration of oxygen. The chemoreceptors respond by increasing cardiac strength and vessel constriction. Baroreceptors are stretch receptors that are sensitive to pressure alterations. The most important receptors are located in high pressure regions such as the carotid sinus and the aortic arch. Mechanoreceptors (or low pressure receptors) are located in the low pressure areas such as the atria and the pulmonary veins. Mechanoreceptors are also stretch receptors and provide arterial pressure control by combating alterations in venous volume. Baroreceptors are the best known and most easily accessible receptors; consequently they have been investigated extensively. The phenomenon of *autoregulation* is a local control mechanism independent of the CNS. Local tissues can control blood flow in response to moderate changes in cardiac output and arterial pressure via dilation or contraction of vessels . This may be due to a contractile response by the smooth muscles surrounding the vessels when blood vessels are stretched.

Baroreceptor Mechanism



The baroreceptor mechanism demands the lion's share of our interest since this mechanism is believed to play the largest role in short-term pressure control. The baroreceptor mechanism provides rapid negative feedback control of arterial blood pressure. An instantaneous drop in arterial pressure is sensed by the baroreceptors, starting a chain of events leading to an increase in heart rate and cardiac contractility. This drop also stimulates the contraction of the vessels. These responses tend to alter the arterial pressure toward its previous value. The baroreceptor mechanism has no long-term regulatory functions. An instantaneous step increase in the carotid sinus pressure is followed by enhanced firing activity in the baroreceptor nerves themselves. This firing activity declines significantly for the first few seconds and then decays more slowly. The decay continues and the time it takes the firing rate *n* to reach the pre stimulation value can be 1 to 3 days

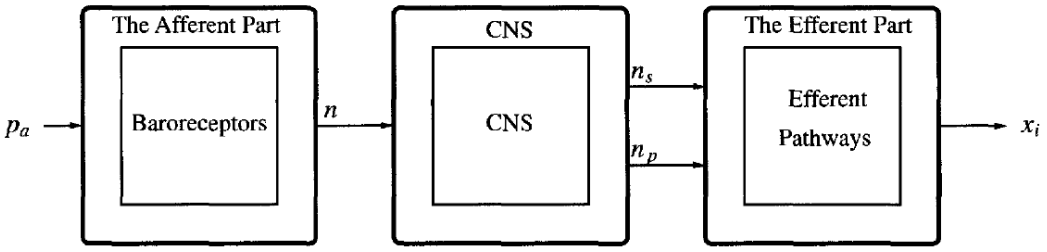


Figure 7.1. *The complete baroreceptor mechanism divided into three components: an afferent component, the central nervous system (CNS), and an efferent component. Alterations in the arterial pressure p_a generate the firing rates n in the afferent part. From the CNS the sympathetic n_s and the parasympathetic n_p nervous activities are transmitted via the efferent pathways to modify the heart and the vasculature x_i.*

Afferent Part

As mentioned in the previous section, the baroreceptors are stretch receptors located in the vessel walls. The most accessible of these receptors are located in the carotid sinus and in the aortic arch. The carotid sinus baroreceptors are located in a distinctive part of the two common carotid sinus arteries, as shown in Figure 7.2. The aortic arch baroreceptors are located in the walls of .the aortic arch. The carotid sinus receptors are the most studied, whereas the aortic arch baroreceptors have received less attention. But the aortic arch and the carotid sinus receptors are believed to be functionally equal, except that the aortic arch receptors operate at a higher pressure (Ganong, 1975). We restrict our studies to the carotid sinus baroreceptors.

Baroreceptors are nerve endings that respond to deformations in vessel Nerve activity arises from two components: a pressure mechanical component and a mechanical-electrical one (Brown, 1980). Baroreceptors react to deformations in the vessel walls by a pressure-mechanical mechanism. It is not known exactly how this mechanism is mediated. One suggestion is that the pressure alterations may cause changes in the cross-sectional areas of the vessels and thus deformations. The second component generates the nerve activity of the receptors via a mechanical-electrical mechanism within the receptors. We call this nerve activity from the carotid sinus receptors *the firing rates,* which are denoted by *n.* Signals from the carotid sinus and the aortic arch are transmitted from the receptors via the glossopharyngeal nerve and the vagus nerve, respectively. The two nerves are joined in the so-called buffer nerves, which direct the impulses to the CNS.

CNS and the Efferent Part

The signal from the receptors arrives at the CNS via the buffer nerves. The information is then processed in the medulla oblongata of the CNS. Subsequently, the cardio inhibitory centre and the vasomotor centre of the medulla oblongata generate sympathetic *ns* and parasympathetic *np* nerve activities, respectively. An enhanced firing rate *n* excites the cardio inhibitory centre and inhibits stimulation of the vasomotor centre. The net effect is an enhanced parasympathetic activity and a diminished sympathetic activity. The efferent pathways transmit the two nervous signals to the various parts of the cardiovascular system. (The sympathetic nerve fibres innervate most of the cardiovascular system, whereas the parasympathetic nerve fibres are restricted to the heart.) In summary, we have the following.

Enhanced sympathetic activity

• stimulates the heart rate and improves cardiac contractility,

• stimulates vessel constriction in the arteries, arterioles, and veins (Ganong, 1975; Guyton, 1991).

Enhanced parasympathetic activity

• decreases heart rate,

• has little effect on cardiac contractility and vessel constriction