REFRACTORY HYPOXIA

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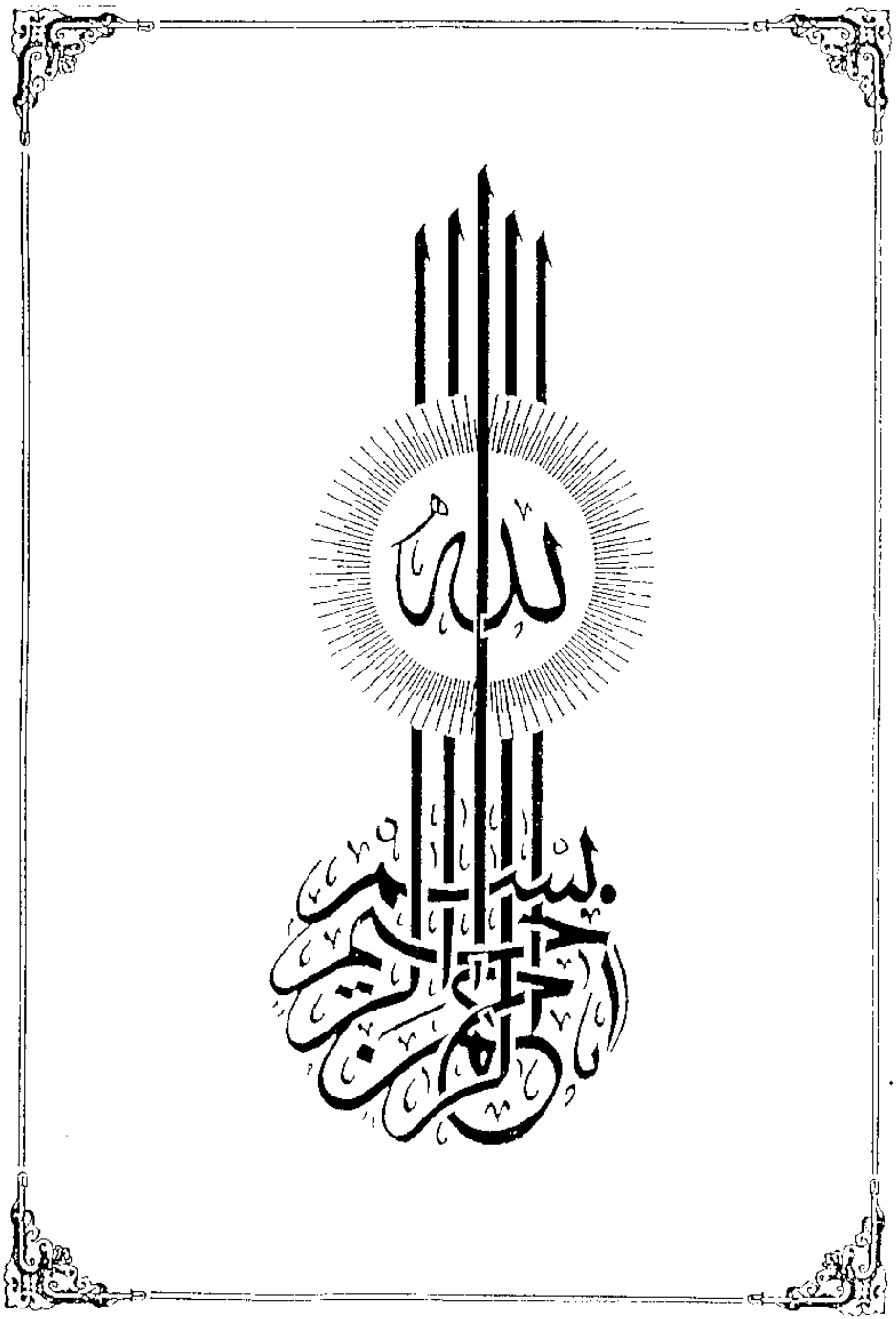

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INTRODUCTION

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Refractory hypoxia is one of the most difficult situations, which is being faced, in the field of anesthesia and intensive care .

Refractory hypoxia, is usually present at 30 % true shunt of cardiac output, and not responding to increase in fractional inspired oxygen (FIO_2) . Refractory hypoxia may be due to cardiac causes or pulmonary causes, one of the pulmonary causes is adult respiratory distress syndrome (ARDS), which is the severe form of acute lung injury (Shapiro (a), 1985) .

So, refractory hypoxia, is also present in the situations that cause ARDS, as in shock lung, fat embolism, aspiration pneumonitis,cardiopulmonary bypass, and in other causes of ARDS .

Thus, refractory hypoxia, represents a challenging situation for the anesthesiologist to maintain arterial oxygen concentration at a good level, to ensure cardiopulmonary stability, to detect, and to deal with the complications as early as possible .

Normal And Abnormal Pulmonary Oxygenation

Regulation of respiration

The neural control of breathing

There are two independent respiratory control mechanisms, one related to the voluntary control of breathing, which may be termed the behavioural system, and the other, the metabolic or automatic system, without conscious control, driving respiration in response to metabolic and other afferent stimuli .

The behavioural system :

Voluntary movements are subserved by the corticospinal tracts, the signals arising in the motor cortex and passing down the fibers of the internal capsule to decussate in the pons and thence, via the corticospinal tracts in the laterlal part of the spinal cord, to synapse with the anterior horn cells of the motor neurons supplying voluntary muscles . Voluntary control of breathing movements uses these same corticospinal pathways (Fig. 1) . In general, it overrides the respiratory drive

from the metabolic system . It should be noted that respiratory function tests requiring voluntary maneuvers, for example vital capacity, peak expiratory flow, maximum breathing capacity and voluntary cough, are only tests of the behavioural system and do not tell us anything about the integrity of the metabolic system (Loh, 1986) .

The metabolic system :

Groups of neurons forming longitudinal columns of cells in the medulla, connected in the region of nucleus tractus solitarii (NTS) just beneath the fourth ventricle, and also nucleus retro ambigualis (NRA) deeper in the medulla (Fig. 1), cross in the medulla and project down the antro-lateral part of the spinal cord to synapse with the anterior horn cells of respiratory muscles, probably via an inter nuncial neurone . The neurons of NTS and NRA project to both respiratory and expiratory msucles, although those of NTS are largely inspiratory to the diaphragm . They also receive projections from various other neurons in the pons and medulla . The generation of a rhythmical pattern of breathing is a highly complex interaction between the pontine and medullary respiratory nuclei and has not been defined clearly in experimental animals, let alone in man . There is probably a pontine rhythm generator which inhibits tonic inspiratoy and expiratory medullary neurone activity, which are themselves mutually inhibitory (Sears et al., 1982) .

These pontine cneters can be divided into two centers; **apneustic center,** which is located in the area of caudal pons, is responsible for stimulation of inspiratory neurons in the medulla; and **pneumotoxic center**, which is located in nucleus parabrachialis and the Kolliker Fuse nucles, which is responsible for stimulation of expiratory neurons in the medulla . The function of medullary neurons is also modulated by mpulses from stretch receptors in the lung parenchyma, that relay to the medulla via afferents in the vagi, and rapid inflation of the lung inhibits inspiratory discharge (Hering-Breuer inflation rreflex) . This stretching of the lung during inspiration reflexly inhibits inspiratory drive, reinforcing the action of the pneumotoxic center in producing intermittency of respiratory neurons discharge . When all the pontine tissue is separated from the medulla, respiration continue whether or not the vagi are intact . This respiration is somewhat irregular and gasping, but it is rhythmic, its occurrence demonstrates that the respiratory center neurons are capable of spontaneous rhythmic discharge. So from that, the respiratory centers in the pons apparently make the rhythmic discharge of the medullary neurons smooth and regular . It appears that there are tonically discharging neurons in the apneustic center which dirve inspiratory neurons in the medulla, and these neurons are intermittetntly inhibited by impulses in afferents from the pneumotoxic center and vagal afferents (Ganong, 1987) .

The chemical control of breathing :

The ultimate goal of respiration is to maintain proper concentrations of oxygen, carbon dioxide, and hydrogen ions in body fluids . It is fortunate, therefore, that respiratory activity is highly responsive to changes in any of these concentrtions . Excess carbon dioxide or hydrogen ions affect respiration mainly by direct excitatory effects on the medullary chemoreceptors, they are near to the respiratory center but separate from it . These receptors monitor the H^+ concentration of the cerebrospinal fluid, including the brain interstitial fluid . CO_2 readily penetrates membranes, but H^+ and HCO_3^- penetrate slowly . The CO_2 that enters the brain and CSF is promptly hydrated . The H_2CO_3 dissociates, so that the local H^+ concentrations rises . From that, H^+ concentration in the brain interstitial fluid parallels the arterial PCO_2, stimulation of medullary chemoreceptors resulting in increase ventilation, thereby increases elimination of carbon dioxide from the blood and this also removes hydrogen ions from blood because decreased blood carbonic acid (Guyton, 1982) . On the other hand, oxygen does not have a significant direct effect on the respiratory center . Instead, it acts almost entirely on the peripheral chemoreceptors located in the carotid and aortic chemoreceptors, and this in turn transmit approptriate neuronal signals to the respiratory center for the control of respiration . The carotid and aortic bodies are peripherally locate

chemoreceptors, they are composed of islands of two types of cells, type I and type II cells, surrounded by fenestrated sinusoidal capillaries . Unmyelinated nerve fibers are located at intervals between those two types of cells . There is some evidence that those nerve fibers are the chemoreceptors, which sense O_2 tension . Because the blood supply per unit of tissue is so enormous (blood flow in each 2 mg carotid body is about 0.04 ml/m, or 2000 ml/100 g tissue per minute), the O_2 needs of thecells can be met largely by dissolved O_2 alone . Therefore the receptors are stimulated only by dissolved O_2 but not combined O_2 . Type I cells contain dopamine, which inhibits discharge inthe carotid body nerves, but despite this, there is evidence thatthe carotid or aortic body cells type II (glomus cells) in someway condition the nerve endings to make them sensitive tooxygen . Afferents from the carotid bodies reach the medullavia the glosspharyngeal nerve, while those from the the aortic bodies via the vagi (Ganong, 1987) .

Non chemical influences on respiration :

Afferents from proprioceptors :

The active and passive movements of joints stimulate respiration, persumably because impulses in afferent pathways from proprioceptors in muscles, tendons, and joints stimulate the respiratory center .

Afferents from high centers :

Pain and emotional stimuli affect respiration, so there must also be afferents from the limbic system and hypothalamus to the respiratory neurons in the brain stem . The pathways for voluntary control pass from the neocortex to the motor neurons innervating the respiratory musles, by passing the medullary neurons . Automatic or metabolic control is sometimes disrupted without loss of voluntary control . The clinical condition that results has been called Ondine's Curse . Patients with this itriguing conditin generally have disease processes that compress the medulla or bulbar poliomyelitis . The condition has also been inadvertently produced in patients who have been subjected to bilateral anterolateral cervical cordotomy for pain . This cuts the pathways that bring about automatic respiraton while leaving the voluntary afferent pathways in the corticospinal and rubrospinal tracts intact (Sugar, 1978) .

Oxygen Transpot

The total amount of oxygen delivered to the systemic circulation is the product of two factors : The cardiac output and the cotent of oxygen per unit of arterial blood (CaO_2) . The CaO_2 is determined by the concentration and characteristics of hemoglobin and the arterial oxygen saturation (SaO_2), as indicated by the following equation :

CaO_2 = Hgb (g/dl) X SaO_2 (%) X 1.39 ml O_2/g Hb

The last term in the equation reflects the amount of oxygen that is normally bound to fully saturated hemoglobin, the so-called carrying capacity of normal hemoglobin . The arterial oxygen saturation refer to the percentage of the total oxygen binding sites on hemoglobin that is actually occupied by oxygen . The SaO_2 is in turn determined by the PaO_2 and the physiochemical properties of hemoglobin, as reflected by the oxygen-hemoglobin dissociation curve (Ingram and Fanta, 1988) .

The oxyhemoglobin (Oxy-Hb) dissociation curve relates the saturation of hemoglobin to the PaO_2 . Hemoglobin is fully saturated (100 %) by a PO_2 of 700 mm Hg . The normal arterial saturation of hemoglobin is 95 to 98 percent at PaO_2 of about 90 to 100 mm Hg . Mixed venous blood has a PO_2 (PVO_2) of about 70 mm Hg and is approximately 75 % saturated . The oxy-Hb curve can also relate O_2 content (CO_2) to the PO_2 . The oxy-Hb curve can also relate the O_2 transport (L/min) to the peripheral tissues to the PO_2 . This is obtained by multiplying O_2 content by the cardiac output (Q_t), [O_2 transport = Q_t X Cao_2] . Thus if Q_t = 5 L/min and CaO_2 = 20.4 ml O_2/0.1 L, then the arterial point corresponds to 1.02 L/min going to the periphery and the venous point corresponds to 0.75 L/min returning to the lungs, from that the oxygen consumption (VO_2) will be 0.26 L/min . The oxy-Hb

curve can also relate the O_2 actually available to the tissues, as a function of PO_2 . Of the 1.0 L of O_2 normally going to the periphery 0.2 L/min of O_2 cannot be extracted because it would lower the PO_2 below the level at which the organs such as the brain can survive; the O_2 available to the tissues is, therefore, 0.8 L/min . The position of Oxy-Hb curve is best described by the PO_2 level at which Hb is 50 percent saturated (P50) . The normal P_{50} is 26.7 mm Hg . A value of P_{50} < 25 mm Hg describes a left shifted Oxy-Hb curve, meaning that at any given PO_2 Hb has a higher affinity for O_2 and, therefore, is more saturated than normal . This may require a higher tissue perfusion than normal to produce the normal amount of tissue oxygenation . A value of P_{50} > 27 mm Hg describes a right-shifted Oxy-Hb curve, meaning that at any given PO_2 Hb has a low affinity for O_2 and is, therefore, less saturated than normal . This may allow a lower tissue perfusion than normal to produce the normal amount of O_2 delivered to the tissues (Benumof, 1986) .

Oxygen Cascade

The oxygen tesion gradient from atmosphere into mitochondrion has been called the oxygen cascade and comprises alterating stages of mass transport (pulmonary ventilation and blood flow) and diffusion within the alveoli, across the alveolar/capillary membrane and between the systemic capillary

and the site of utilization within the mitochondrion . A summary of the factors influence oxygenation at different levels in the cascade is shown in (Fig. 4) .

Factors affecting the affinity of hemoglobin for oxygen

Effect of Temperature and pH :

A rise in temperature or a fall in pH shifts the curve to the right (Fig. 5), when the curve is shifted in this direction, a higher PO_2 is required for hemoglobin to bind a given amount of O_2 . Conversely, a fall in temperature or a rise in pH shifts the curve to the left, and a lower PO_2 is required to bind a given amount of O_2 . The decrease in O_2 affinity of hemoglobin when the pH of blood falls is called Bohr effect and is closely related to the fact that deoxyhemoglobin binds H^+ more actively than dose oxyhemoglobin .

The effect of 2,3- Diphosphoglycerate (2,3 DPG)

The effect of 2,3-DPG leads to reduce the affinity of