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The effects of acid-base disturbances on cardiovascular and pulmonary function

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Disturbances in acid-base balance are commonly met problems in clinical medicine and decisions about their treatment are of great importance in patients with cardiopulmonary problems, in whom acid-base disturbances may be especially critical. Similarly, cardiopulmonary function may be significantly compromised even in patients with no intrinsic heart or lung disease, in the face of acid-base disturbances. It is essential, therefore, to understand the physiological consequences of these disturbances on the cardiovascular and pulmonary system.

Of major importance is the effect of acid-base disturbances on the delivery of oxygen to the various tissue cells of the body. In order to understand all the pathophysiological mechanisms involved it is necessary to review the effects of acid-base changes on the heart, the peripheral vessels, the lungs, and the diffusion of oxygen between air, blood, and tissues.

The requirement for oxygen by the various tissue cells of the body is met by the combined cardiovascular and pulmonary systems, which function as a unit termed the "oxygen transport system" of the body. The movement of oxygen from the ambient air to the tissue cells involves ventilation, pulmonary perfusion, diffusion, oxygen-carrying capacity of hemoglobin, cardiac output (including cardiac muscle performance), systemic distribution of flow, and finally the oxygen delivery capacity of hemoglobin. It is important to understand the effects of changes in pH on each of these steps in the chain.

Effects of acid-base disturbances on cardiovascular function

Heart. The action potential of cardiac muscle is not altered to any significant degree by acid-base derangements [1], but contractile force may vary considerably as pH changes. Acidosis (pH 6.8 to 7.2) causes depression of the contractile state [1–10]. Alkalosis, which has been studied much less extensively, has an opposite action, although the positive inotropic effect of an elevated pH is relatively modest in comparison with the marked depression that can occur during severe acidosis [1, 2, 5, 7, 10–12].

Although these conclusions are generally accepted now, there had been extensive debates in the past concerning whether acid-base disturbances had any significant effect on the heart. Early workers reported cardiac depression following the onset of acidosis [13–16], but several investigations during the past decade were interpreted as demonstrating no significant change in myocardial contractility, even at pH levels as low as 6.8 [17–20]. The apparent conflict has been resolved recently, and it is now clear that failure to demonstrate cardiac depression at a low pH in some experiments has been due to masking of the direct myocardial effect of acidosis by the action of catecholamines [9, 20, 21].

Isolated cardiac muscle and heart preparations *in vitro* invariably exhibit decreased contractile force during either metabolic or respiratory acidosis [1, 3, 6, 8, 10]. The hearts of intact animals with normal sympathoadrenal responses, on the other hand, may display an increase, a decrease, or no change in contractile force, depending on the rapidity with which acidosis develops, the time at which measurements are made, presence and type of anesthesia, etc. [9]. The characteristic response to a rapid infusion of lactic acid in anesthetized dogs with constant heart rate, aortic pressure, and venous return is a transient (< 5 minute) increase in the maximal rate of left ventricular pressure rise (max dp/dt) and in stroke power and a simultaneous decrease in end-diastolic pressure, indicating an increase in the contractile state of the left ventricle. If the pH does not fall below 7.2 to 7.3, most intact animals stabilize at this new level of increased contractile strength, and if cardiac output is not controlled, it too tends to rise. However, if the pH falls low enough or fast enough, the

positive inotropic response disappears and end-diastolic pressure rises while stroke power and maximum dp/dt fall below control values; thus, the final contractile state of the left ventricle in severe acidosis is significantly depressed (Fig. 1).

The differences between the responses of isolated hearts and intact animals are due primarily to sympathoadrenal factors. If adrenergic responses are blocked with propranolol, no positive inotropic effects are seen, even transiently and even at pH 7.2 to 7.3. The final myocardial depression in the absence of beta-stimulation is much more severe than in normal animals [9, 21].

The heart rate, like the inotropic state, may be higher, lower, or unchanged after the onset of acidosis in an intact animal [9]. In isolated hearts or in beta-blocked animals, though, a fall in pH is always accompanied by a decrease in the rate of beating. In the absence of hypoxia or marked changes in K^+, little or no effect on the rhythm of the heart has been observed in most studies when pH is altered [1, 7, 9, 22].

It is apparent, then, that the sympathoadrenal system constitutes an important aspect of the heart's response to acidosis. Beta-receptor stimulation during acidosis results from increased release of norepinephrine from cardiac nerve endings and epinephrine and norepinephrine from the adrenal medulla [23–27]. Part of the release may be initiated by reflex stimulation of the carotid body with secondary hyperpnea [28], and an even more potent factor is the direct stimulation of the cardiac centers in the brain as a result of perfusion with hypercarbic blood [29, 30]. Even if the central and reflex drives to catecholamine release are eliminated, however, acidosis can still cause significant increases in catecholamine release, since exposure of the adrenal gland or sympathetic nerve endings to a low pH stimulates release of stored catecholamines directly [9, 23, 25, 27].

In addition to its effects on cardiac function through direct action and through release of catecholamines, acidosis has been thought to influence the heart by a third mechanism: depression of myocardial responsiveness to catecholamines. Opinion is divided on this issue [18, 31], but most experiments have suggested that increases in heart rate and contractile force are less marked at a pH below 7.1 than at 7.4, when cardiac sympathetic nerves are stimulated either directly or reflexly and when catecholamines are infused intravenously [4, 9, 32–36]. Interpretation of such findings on a cellular level is difficult, of course, because an apparent depression in reactivity might be observed if endogenous release of norepinephrine had caused partial "saturation" of receptor sites before infusion or nerve stimulation was begun [9, 37, 38]. Whatever the cellular mechanism, most data suggest that increases in rate and strength of beating are less at acidotic pH's than at pH 7.4, following a controlled increment in sympathetic stimulation.

In contrast, the effects of vagal stimulation are markedly enhanced at pH levels below 7.1, probably as a consequence of inhibition of acetylcholinesterase [39]. The resulting tendency for a given quantity of acetylcholine to have a protracted duration of action leads to an increased danger of vagally-mediated bradycardia or arrest during acidosis.

The exact mechanisms by which the pH influences the inotropic state of the heart remain uncertain, but at least two mechanisms may play important roles. First, as discussed in detail by Katz [40], hydrogen ions compete with calcium for binding to the myocardial protein troponin. In order for crossbridges between actin and myosin to be formed, ATP to be broken down, and contraction to occur, the inhibitory action of troponin on actin-myosin interaction must be overcome. Calcium ions, which are released from the sarcoplasmic reticulum with each action potential,

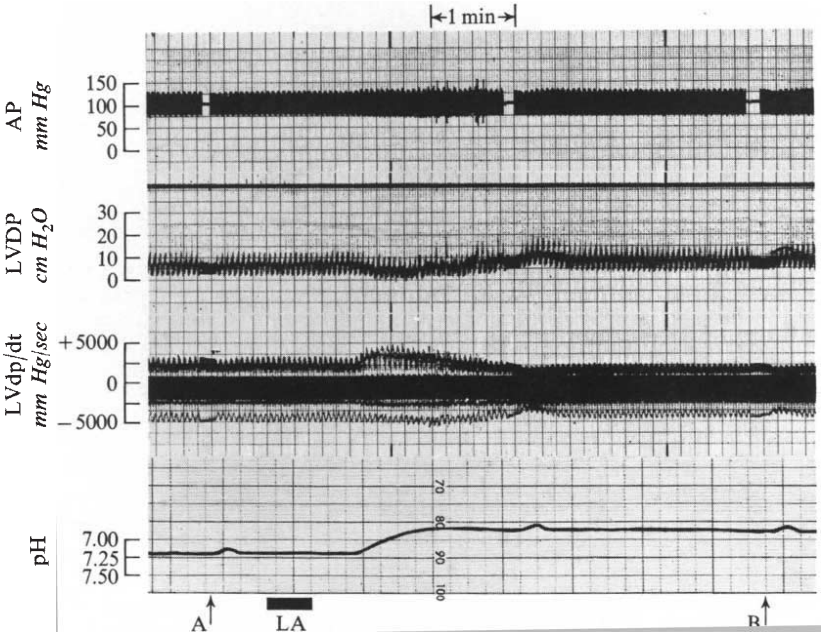

Fig. 1. *Effect of an infusion of lactic acid on left ventricular function in an anesthetized dog with normal innervation.* AP = aortic pressure; LVDP = left ventricular pressure at high gain to emphasize diastole; LV dp/dt = the first derivative of left ventricular pressure; pH = arterial pH measured in femoral artery; LA = period of infusion of isotonic lactic acid; A and B = points at which the respirator was cut off to eliminate ventilation-mediated variations in venous return. Aortic pressure, flow, and heart rate were held constant throughout the experiment. As pH fell from 7.4 to 7.1, max LV dp/dt rose and LV end-diastolic pressure fell, indicating that a positive inotropic effect had occurred. Within a few minutes max LV dp/dt fell and LV end-diastolic pressure rose, and the final steady state level of function indicated that depression of left ventricular function had occurred. (Reprinted from ref. [9], with permission from the Am. J. Physiol.)

stimulate mechanical contraction by binding with troponin and negating its inhibitory influence. In the presence of elevated concentrations of intracellular H^+, a smaller percentage of the available Ca^{++} is able to react with troponin, fewer actin-myosin interactions occur, and the strength of contraction is reduced.

A second mechanism by which contractile force may be lowered during acidosis involves the binding and release of calcium to sarcoplasmic reticulum in the cardiac cell [41]. Calcium is normally sequestered in the sarcoplasmic reticulum during diastole. After it has been released into the cytoplasm to initiate contraction, it is actively taken up again to induce relaxation. The ability of the sarcoplasmic reticulum to release Ca^{++} readily can affect the strength of contraction by controlling the amount of Ca^{++} that is potentially available for binding to troponin. Sarcoplasmic reticulum that has been isolated from heart tissue releases less Ca^{++} when the pH of the medium is low [41]. Thus, if such results can be extrapolated to the intact animal, acidosis may cause a reduction in the amount of Ca^{++} released during each beat, resulting in a diminished force of contraction.

Acidosis causes a rise in extracellular K^+, and hyperkalemia may influence the contractility as well as the rhythm of the heart [42]. The relative importance of K^+ shifts versus pH changes *per se* has not been tested satisfactorily, but it is clear that acidosis depresses the heart even in the absence of hyperkalemia.

Peripheral vessels. Like changes in the heart, changes in the peripheral vasculature during acid-base disturbances represent a combination of the direct influence of pH on the vessels plus indirect actions mediated by the sympathoadrenal system. The direct action of respiratory or metabolic acidosis on most systemic arterial vessels is to induce relaxation, resulting in a fall in peripheral resistance [9, 43–47]. Simultaneously, the increased sympathoadrenal activity that is caused by acidosis tends to counteract the direct vascular effect [43, 46, 47]. Finally, the response of the peripheral vessels to both alpha and beta-adrenergic stimulation is usually reduced in the presence of a low pH [32, 37, 44, 48]. The net effect of these various factors may be variable, depending on the degree of acidosis, the rate at which it develops, and the state of the animal in the control condition.

Generally, metabolic or respiratory alkalosis has been observed to cause an over-all decrease in peripheral vascular resistance, and the direct vasodilatory action is thought to be counteracted in part by sympathetically-mediated constriction [43]. If these findings are true, it is apparent that the average intrinsic arteriolar tone is maximal at pH 7.4 and that a variation in either direction from normal tends to decrease the over-all systemic resistance, an effect that may be opposed by the sympathoadrenal system.

The veins represent a special case in the response of the peripheral vasculature to acid-base disturbances. Acidosis is associated with venoconstriction, and the constriction may be present, though reduced, even in the absence of sympathetic stimulation [49–51]. Because the capacity of the venous bed is so vast, constriction can cause a marked displacement of blood into the central circulation, leading toward elevated pulmonary vascular volume and pressure and, potentially, cardiac overload. The response of the veins to alkalosis has not been elucidated satisfactorily.

Distribution of flow. The response of special vascular beds may differ from the overall response of the total peripheral vascular system. Cerebral circulation has been studied most extensively in this regard. Vascular resistance in the brain is exquisitely sensitive to interstitial pH, and since cerebral vessels are affected very little by sympathoadrenal factors the direct effect of the acid-base state is of overwhelming importance. As discussed elsewhere in this symposium [52], the blood-brain barrier retards diffusion of ions between the vascular space and cerebrospinal fluid but allows CO_2 to diffuse readily into the cerebral tissue. Accordingly, the P_{CO_2} of the blood determines the pH of the cerebral tissue, at least during short-term acid-base alterations, and cerebral flow increases with an acute rise in P_{CO_2} and decreases with an acute fall, whatever the pH of the blood [53, 54]. With chronic acid-base derangements, on the other hand, interstitial pH may gradually approach that of the blood, whatever the P_{CO_2}; thus, chronic metabolic acidosis may be associated with decreased cerebral vascular resistance, even though P_{CO_2} is low [55, 56].

The observation that cerebral vessels are more sensitive to changes in P_{CO_2} and tissue pH than are other arterial systems implies that a redistribution of regional blood flow should occur during systemic acid-base disturbances. Experimental results support such a conclusion [57].

It has been suggested that renal and mesenteric vessels may also react somewhat differently than most other vascular beds by consistently increasing their resistance during acidosis [58, 59]. Other studies have demonstrated renal and mesenteric vasodilatation as pH falls [60–63], however, and it seems likely that in those beds as in the general circulation, the interplay of direct dilatation and sympathetic constriction may yield a variety of results, depending on the experimental conditions.

Variable and confusing changes may also occur in coronary resistance during acid-base derangements. The predominant determinant of myocardial flow is the requirement of the heart for O_2, which in turn is determined by the characteristics of mechanical contraction [64]. Thus, whatever the influence on the coronary vasculature of pH itself, or of secondary sympathoadrenal factors, it would be expected that myocardial flow might vary widely and unpredictably during pH derangements, depending on the changes that occur in heart rate, blood pressure, cardiac contractile force, etc.

Except for its influence on the cerebral vascular bed, where low P_{CO_2} and tissue alkalosis cause severe vasoconstriction, the actions of alkalosis on specific peripheral vessels have not been completely studied. Difficulties arise

in part because of technical problems. If pH is raised by hyperventilation, some of the responses observed may be due to the reflex effects of hyperventilation *per se* rather than alkalosis. Infusions of alkalotic solutions should avoid this problem, but unfortunately, experiments involving this procedure have often employed sodium bicarbonate solutions that were hypertonic, and hypertonicity of itself exerts a profound influence on both peripheral resistance and cardiac function [65]. The few results that are available suggest that regional responses of peripheral beds to alkalosis may be rather complex. When acidotic solutions are infused into the dog hind limb, resistance decreases in both skin and muscle beds; alkalotic solutions, on the other hand, dilate the muscle vasculature but constrict the flow to the skin [66]. Again, use of hypertonic solutions complicates analysis of these interesting observations.

It should be emphasized that the overall changes in total peripheral resistance that are observed during acid-base derangements may mask complex and divergent responses in various organs. There may be selective alterations not only in various beds but also in discrete anatomical sites in one bed. For instance, Fleishman, Scott, and Haddy [49] suggest that although resistance of small arterioles in the dog foreleg falls with acidosis, large arteries may simultaneously constrict and offset the vasodilatory action.

Effects of acid-base disturbances on pulmonary function

Ventilation

Ventilatory drive. The level of ventilation is controlled by negative feedback from blood P_{O_2}, P_{CO_2}, and pH. The receptor sites that react to acidosis, hypercapnia, and hypoxia are in the arterial chemoreceptors (carotid and aortic bodies) and in the medulla oblongata of the brain. It seems probable that of these factors, pH of both the blood and the brain provides the major chemical mechanism for ventilatory control. Confusion has arisen, however, because changes in blood pH are a poor index of pH in the brain or cerebrospinal fluid. Gray [67], in developing his multifactorial theory of ventilatory control, looked only at the blood changes and showed that separate gain factors had to be assigned for the ventilatory stimulus caused by changes in blood P_{CO_2}, pH, and P_{O_2} in order to describe satisfactorily the chemical control at rest. For instance, acidosis caused by an acute elevation of blood P_{CO_2} was found to cause a greater increase of ventilation than the same decrease in pH caused after mineral acid infusion; thus changes in blood pH alone are inadequate to explain chemical feedback control and either blood P_{CO_2} or CNS tissue pH must be invoked.

Rapid equilibration occurs between cerebral spinal fluid and blood P_{CO_2} so that acidosis caused by elevation of arterial P_{CO_2} is rapidly reflected by a corresponding acidosis in the cerebrospinal fluid. Returning the intraarterial pH to normal by infusion of sodium bicarbonate eliminates only about 45% of the acute ventilatory response to an increase in arterial P_{CO_2} [68]. The infused bicarbonate does not alter cerebrospinal fluid bicarbonate acutely [52]; hence, the cerebrospinal fluid acidosis caused by the elevated P_{CO_2} persists in spite of the bicarbonate infusion and continues to stimulate ventilation even though blood pH is normal. It is this type of disparity between changes in blood and CSF pH that makes it necessary to assume that changes in blood pH and P_{CO_2} act as independent stimuli to ventilation.

Along similar lines of interpretation an acute metabolic acidosis caused by infusion of HCl may cause respiratory alkalosis in the CSF; the infused acid does not rapidly cross the blood-brain barrier but the secondary respiratory alkalosis is rapidly reflected by a similar hypocapnic alkalosis in the CSF [68, 69]. In acute respiratory acidosis or alkalosis blood hydrogen ion concentration (H^+) and cerebrospinal fluid (H^+) change in the same direction and augment each other to produce a greater ventilatory response. In acute metabolic acid-base disturbances the changes in blood and cerebrospinal fluid (H^+) may be in opposite directions thereby opposing one another to yield a smaller net ventilatory response. The (H^+) at the pH sensitive medullary centers probably lies somewhere between that in the blood and CSF.

When an acid-base disturbance persists for more than 24 hours active transport at the blood-brain barrier returns the (H^+) in the CSF toward normal. According to Mitchell et al [69] the compensatory pH shift in the CSF during chronic acid-base disturbances in the blood is complete. Thus according to this view when a steady state is reached a pH error no longer exists in the cerebrospinal fluid or brain tissue to drive ventilation; only the (H^+) change in blood persists to sustain chronic changes in ventilation by action on peripheral chemoreceptors. On the other hand, Fencl, Miller, and Pappenheimer [70] find in an experimental animal model that once a steady state is achieved a small pH error persists in the CSF and brain tissue which is always in the same direction but of less magnitude than that which persists in blood; thus the latter investigators suggest that medullary chemoreceptors still provide a significant part of the remaining ventilatory response to chronic acid-base disturbances. Fencl et al [70] also postulate that the pH sensitive regions of the brain medulla are located within brain tissue nearer the blood-brain barrier than the ventricular surface; consequently, cerebrospinal fluid pH may not accurately reflect brain tissue pH when a steady state does not exist. In either case, however, the delayed adjustments of cerebrospinal fluid and brain tissue pH back toward normal after an acute change in acid-base balance create a period of acclimatization during which the ventilatory response is modified gradually to a new steady state level [69]. Thus the ventilatory response to an acute metabolic acidosis should gradually increase to a

new steady state level as the initial opposing respiratory alkalosis in the cerebrospinal fluid is eliminated and (H^+) in the medullary centers increases.

Conversely ventilatory drive in response to an acute respiratory acidosis should gradually decline with time to a new steady state as the (H^+) of the brain and cerebrospinal fluid is readjusted toward normal by the ion pump at the blood-brain barrier. Respiratory depression from acute metabolic alkalosis should be more evident after the opposing respiratory acidosis in the brain is eliminated by active transport at the blood-brain barrier. Conversely hypoxic stimulation to ventilation should gradually approach a maximum as the opposing hypocapneic alkalosis in the brain is eliminated by active transport.

Ventilatory mechanics. Acute respiratory acidosis can significantly increase nonelastic resistance in the lungs by a central effect mediated through the vagus nerves [71]; thus, nonelastic resistance in dogs almost doubles when arterial P_{CO_2} is raised acutely from 40 to 100 mm Hg [72]. On the other hand, acute metabolic acidosis caused by infusions of mineral acids does not alter mechanical properties of the lung [72]. If the increase in nonelastic work caused by hypercapnia is mediated by reductions in intracerebral pH rather than by the increase in molecular CO_2 then this effect likely would be eliminated or greatly modified if respiratory acidosis became chronic.

Pulmonary perfusion

Acidosis affects pulmonary vascular pressures in two ways. Acidosis tends to increase pulmonary vascular resistance and thereby raise pulmonary artery pressure [73] but in man [74–76] this response is probably small. Normally this mechanism may help to redistribute flow from poorly ventilated regions of lung to better ventilated regions but the response to acidosis or hypercarbia is probably not as effective in this regard as the vasoconstriction due to regional hypoxia [77, 78].

Acidosis tends to redistribute blood from peripheral venous beds into the lung thereby elevating pressures in the left atrium, pulmonary veins, and capillaries as well as in the pulmonary arteries [50, 51, 74, 75, 79]. During exercise this type of redistribution [50] may be beneficial by keeping the left ventricle primed with enough blood to sustain a high cardiac output. In a patient with metabolic or respiratory acidosis this mechanism may greatly reduce the rate at which blood or saline may be infused intravenously without causing pulmonary edema [51].

Oxygen diffusion between air, blood, and tissues

Acute acid-base disturbances and the position of the oxyhemoglobin dissociation curve. Acute changes in blood pH cause the so-called "Bohr shift" in the position of the oxyhemoglobin dissociation curve [80]. Any point on this dissociation curve represents a point of equilibrium between the rate of association between oxygen and reduced hemoglobin and the rate of dissociation of oxyhemoglobin [81]. The position of the curve is determined not by the absolute rates of these two processes but by the ratio of the rate constants for association and dissociation. If the ratio of association to dissociation increases then the position of the curve shifts to the left and the P_{O_2} required to maintain a given oxygen saturation of hemoglobin decreases; if this ratio decreases the curve shifts to the right and the P_{O_2} required to sustain a given oxygen saturation increases. Changes in pH of the blood between 7.0 and 8.0 at 37°C predominantly alter the *rate* constant for dissociation of oxyhemoglobin, the rate of association remaining relatively unchanged [82, 83]. Thus acidosis by increasing the rate of dissociation of oxyhemoglobin shifts the dissociation curve to the right; alkalosis by decreasing the rate of dissociation shifts the curve to the left.

These shifts in position of the O_2 dissociation curve do not change the intrinsic shape over most of the curve; the curve is simply magnified (right shift) or attenuated (left shift) along the P_{O_2} axis. Thus a decrease of pH from 7.4 to 7.2 increases the P_{O_2} at every level of O_2 saturation by a factor of 1.2; a rise of pH from 7.4 to 7.6 decreases the P_{O_2} at any given O_2 saturation by a factor of approximately 0.8. In view of these facts it is possible and often convenient to define the position of the curve by a single measurement, the oxygen tension at 50% oxyhemoglobin saturation (P_{50}). Normally at rest the P_{50} is 26.5; the P_{50} increases above this value for a right shift of the O_2 dissociation curve and decreases for a left shift.

Chronic acid-base disturbances and the oxyhemoglobin dissociation curve. The position of the oxyhemoglobin dissociation curve is sensitive not only to changes in pH but also to changes in the intracorpuscular concentration of 2,3-diphosphoglycerate (2,3-DPG) [84]. This molecule by binding to reduced hemoglobin increases the rate of oxyhemoglobin dissociation and may also slow the rate of association so that the oxyhemoglobin dissociation curve shifts to the right [85]. In addition 2,3-DPG exerts a secondary action by its tendency to reduce intracorpuscular pH through an effect on the Donnan equilibrium [86]. Chronic hypoxia causes the 2,3-DPG concentration in the red cell to increase tending to shift the O_2 dissociation curve right [87, 88]. Acidosis, perhaps through its inhibition of red cell glycolysis, causes the intracorpuscular concentration of 2,3-DPG to fall [86, 89]; this shifts the oxyhemoglobin dissociation curve to the left, a direction opposite to that of the Bohr shift caused by acidosis. Alkalosis, perhaps by stimulating red cell glycolysis, causes the 2,3-DPG concentration to increase [86] and shifts the dissociation curve to the left, again a direction opposite to that of the Bohr shift in response to alkalosis. It apparently takes six to eight hours after an acute change in blood pH for red cell concentrations of 2,3-DPG to show significant

changes but if acid-base disturbances persist for longer than this the subsequent changes in 2,3-DPG concentration will oppose the Bohr shift and return the dissociation curve back toward its normal position.

Effect of the position of the oxyhemoglobin dissociation curve on oxygen transport. At the tissue level an increased rate constant for O_2 dissociation (i.e., a shift of the dissociation curve to the right) is reflected kinetically by an increased pressure head driving oxygen into tissues at any given oxyhemoglobin saturation; on the other hand in the lung the same increase in rate constant reduces the pressure head driving oxygen into blood and also reduces the final oxygen saturation in equilibrium with a given alveolar O_2 tension. Thus a given shift in the oxyhemoglobin dissociation curve has opposing effects on O_2 transport in lungs and tissues. These opposing effects are shown diagrammatically in Fig. 2.

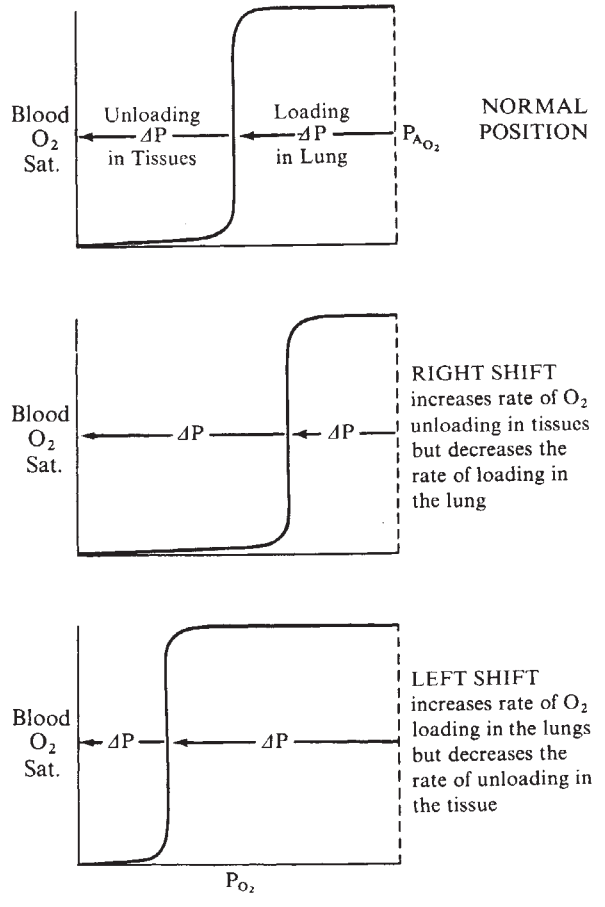

Fig. 2. *Exaggeration of the S-shaped oxyhemoglobin dissociation curve illustrating the importance of the position of this curve in optimizing oxygen transport.* Optimally the curve should be positioned so that pressure gradients available for loading oxygen in the lung and for unloading oxygen into tissues accurately reflects the relative resistances to oxygen transfer in the lungs and tissues. If the curve is shifted too far to the left, the rate of tissue oxygen extraction will begin to curtail oxygen transport. If the curve is shifted too far to the right oxygen transport will be curtailed by incomplete oxygenation of blood.

As illustrated in Fig. 2 the position of the oxyhemoglobin dissociation curve helps to determine the relative magnitude of the mean pressure gradients for loading oxygen onto hemoglobin in the lung and for unloading oxygen from hemoglobin into tissues. A shift of the curve to the right as in acidosis favors unloading oxygen from hemoglobin into tissues but is unfavorable for loading oxygen onto hemoglobin in the lung. A shift of the curve to the left as in alkalosis favors loading of oxygen onto hemoglobin in the lung but is unfavorable for unloading of oxygen from hemoglobin into tissues. Thus, depending on the circumstances, the effects of a given shift in the oxyhemoglobin dissociation curve may be beneficial or detrimental to the organism depending on the relative resistance offered to oxygen transfer in tissues and in the lung, the tissue oxygen tension which is required to sustain adequate aerobic metabolism, and the adequacy of compensatory redistribution of blood flow preferentially to tissues which require higher oxygen tension. For a given set of circumstances there probably exists an optimal position of the oxyhemoglobin dissociation curve which would reflect the relative resistance to gas transfer in the lungs and in the tissues (see Appendix).

Physiological variations in acid-base balance

Muscular exercise. Marked changes in acid-base balance occur during muscular exercise and these changes are directly related to the severity of the exercise [90–92]. The changes are greater in venous blood than they are in arterial. The changes that occur in arterial and femoral venous blood during upright leg exercise are shown in Fig. 3. At rest arterial pH is 7.40 and femoral venous 7.37. As exercise loads are progressively increased arterial pH falls progressively to about 7.36 at 50% of maximal oxygen uptake and to 7.20 at maximal oxygen uptake. At the same exercise levels femoral venous pH falls to 7.30 and 7.10, respectively. Thus, the pH difference between arterial and femoral venous blood increases from 0.03 at rest to 0.06

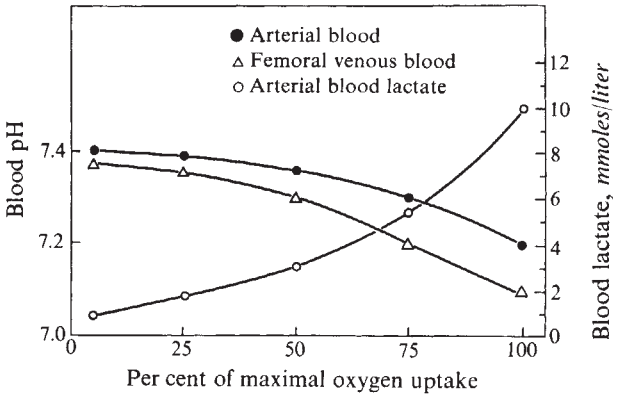

Fig. 3. *Changes in pH of both arterial and femoral venous blood* and *changes in arterial blood lactate from rest to exercise at the maximal oxygen uptake level.* (For description see text.)

at 50% of maximal oxygen uptake and to 0.10 at maximal oxygen uptake. The changes in brachial venous blood are less marked than those in femoral venous blood. Arterial blood lactate levels with increasing work loads are also plotted in Fig. 3. With progressive exercise loads arterial blood lactate increases from 0.8 mmoles/liter at rest to approximately three mmoles/liter at 50% of maximal oxygen uptake and to about ten mmoles/liter at maximal oxygen uptake.

The acidosis that accompanies muscular exercise stimulates ventilation. However, this stimulation is inadequate alone to explain the increase in ventilation that occurs during muscular exercise.

Oxygen dissociation curves in both arterial and femoral venous blood during rest and exercise at the maximal oxygen uptake level are shown in Fig. 4. At rest the arterial and femoral venous curves lie very close together so that the pickup of oxygen by hemoglobin in the pulmonary capillary and the delivery of oxygen by hemoglobin in the skeletal muscle capillary occur from approximately the same position. However, during heavy exercise there is a separation of the arterial and femoral venous oxygen dissociation curves. Because CO_2 diffusion is so rapid, the pickup of oxygen in the pulmonary capillary occurs from a curve near that of arterial blood and the delivery of oxygen in the skeletal muscle capillary in the leg occurs from a curve near that of femoral venous blood. Such a separation makes the relative positions of the curve slightly more favorable both to pick up and to deliver oxygen.

The pH changes that occur during muscular exercise probably do not affect cardiovascular performance to a great degree. The direct depressant effect on the myocardium of pH 7.2 is fairly small and normally is more than offset by increased sympathoadrenal activity. Obviously, a patient in whom beta-receptor responsiveness was blocked by propranolol treatment might be in a less favorable position. If acidosis inhibits peripheral responsiveness to norepinephrine during exercise as it seems to do in controlled experimental preparations, it seems likely that local buildup of H^+ in the exercising muscles will serve to insure that blood flow will be maximal to them. In contrast, nonexercising muscle will feel the full effect of the increased sympathetic activity that accompanies exercise.

It is of special interest in analyzing the response to exercise to recall that acidosis causes venous constriction. The increase of venous return seen during muscular exercise may be due not only to muscular contractions acting as a pump in concert with the venous valves but also to active venous constriction secondary to the acidotic blood from exercising muscles.

Altitude. The ascent to high altitude causes both acute and chronic changes in acid-base balance at rest and also alters the changes in acid-base balance that occur during muscular exercise. At high altitude arterial hypoxia stimulates ventilation through the peripheral chemoreceptors but initially this stimulus is opposed by the hypocapnia in the medullary center and blood caused by the hyperventilation. The hypocapnic central restriction imposed on the hypoxic drive is gradually removed as active transport mechanisms bring the cerebrospinal and brain tissue (H^+) back to normal within 24 hours [93]; thus ventilation is allowed to increase to near its final steady state value within this same period.

Renal compensation for the respiratory alkalosis in blood occurs more slowly than in the CSF [89]; in well-trained subjects studied after two weeks at 14,000 feet [89] the resting arterial blood pH was still 7.50. The arterial pH in these same subjects fell to an average value of 7.40 during maximal exercise, whereas arterial blood pH normally falls to about 7.20 during peak exercise at sea level. Even in long-term residents at 10,000 feet arterial blood pH falls to only about 7.30 at maximal work loads. Theoretically a relative alkalosis may be beneficial for oxygen transport during heavy exercise at high altitudes by lowering

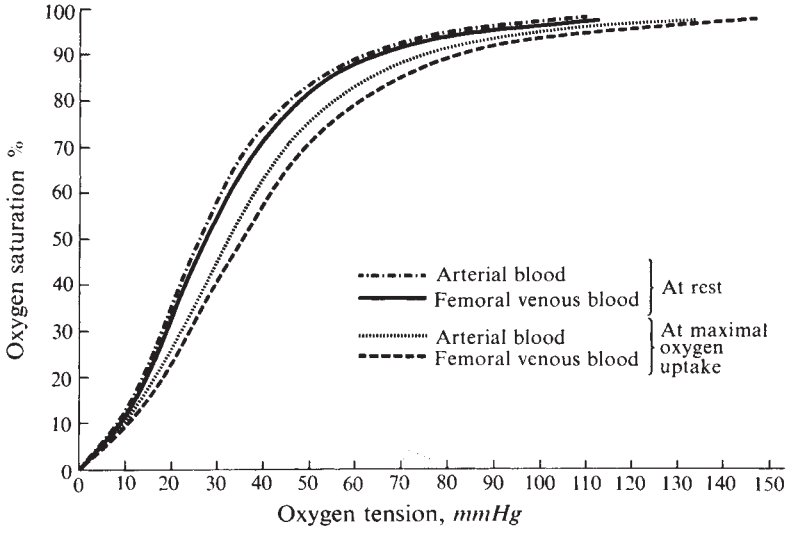

Fig. 4. *Oxyhemoglobin dissociation curves of both arterial and femoral venous blood at rest and at exercise at the maximal oxygen uptake level.* (For description see text.)

the P_{50} of blood and enhancing oxygen uptake in the lungs.

Even though a lower P_{50} might enhance the efficiency of O_2 transport during heavy exercise at high altitude, there is a tendency for the P_{50} of blood to increase at high altitude owing to an increase in red cell 2,3-DPG. The magnitude of the increase in P_{50} that occurs at high altitude varies in different studies, the largest increase (4 mm Hg at 4,530 m) being reported recently by Lenfant, Torrance, English, and their associates [95]. On the other hand, the decrease in P_{50} caused by the relative alkalosis during heavy exercise at high altitude should more than offset the increase in P_{50} due to 2,3-DPG. Further investigation is needed to clarify under what conditions the changes in P_{50} that occur at altitude during rest and exercise might be beneficial or harmful. The P_{50} which is optimal for oxygen transport at rest may not be optimal at heavy exercise.

Pathological variations in acid-base balance

Respiratory and metabolic alkalosis. Respiratory alkalosis may be caused by hyperventilation of a patient on assisted ventilation, as a consequence of some primary central nervous system disorder or secondary to hypoxic stimulation of arterial chemoreceptors. This condition causes very little effect on cardiac function. With the marked decrease in arterial P_{CO_2} there will be constriction of cerebral vessels and a diminution in cerebral flow. Also alkalosis impairs oxygen unloading in the tissues as a consequence of the left shift of the oxyhemoglobin dissociation curve. The combination of lowered cerebral perfusion and of impaired unloading of oxygen from oxyhemoglobin may cause cerebral hypoxia even though blood oxygenation seems adequate (Fig. 5). This situation might be particularly detrimental in patients with cerebral vascular disease or with a poor cardiac output secondary to either heart failure or hypovolemic shock.

The most appropriate treatment of hyperventilation due to hypoxia is correction of the hypoxia either with an oxygen-enriched atmosphere or by correcting the primary reason for a disturbed gas exchange in the lungs. It has been suggested that some of the manifestations of acute mountain sickness may be consequent to the respiratory alkalosis caused by the hypoxic ventilatory drive not only in blood but also in the brain tissue where alkalosis may partially inhibit a compensatory increase in cerebral blood flow thereby impairing cerebral O_2 transport.

In the presence of central hyperventilation due to central nervous system disease it is often tempting to correct the respiratory alkalosis in the blood by increasing the CO_2 concentration in the inspired air but this procedure is dangerous unless the physician is certain that the hyperventilation is not caused by a low pH in the brain; a low CSF pH has been reported in association with central hyperventilation (and a high blood pH) in a variety of CNS lesions [96–98].

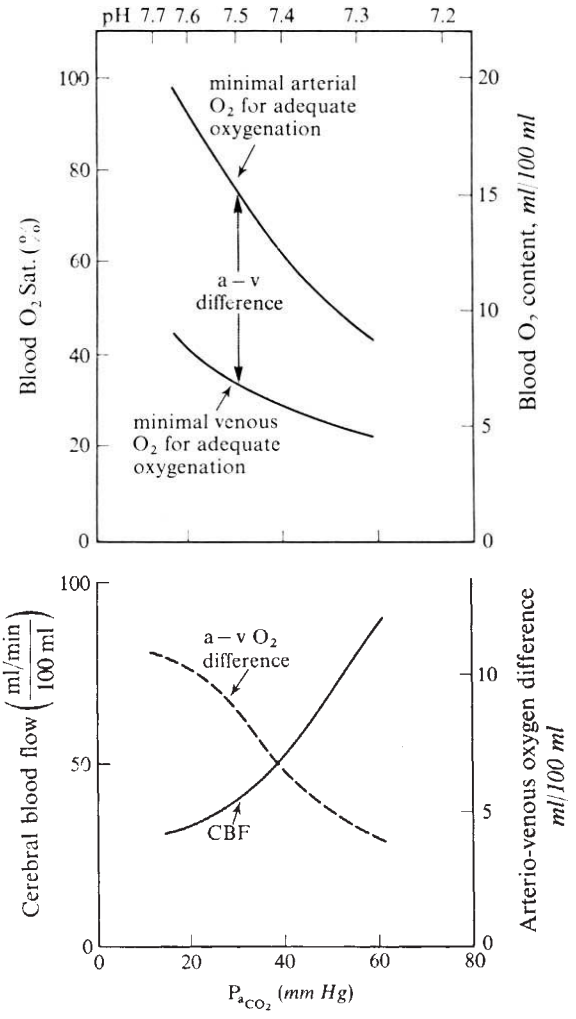

Fig. 5. *Interrelationships among cerebral blood flow, arterial CO_2 tension ($P_{a_{CO_2}}$), A-V O_2 difference required to sustain a normal cerebral oxygen consumption (lower panel) and the minimal O_2 saturation and content required to maintain venous return from the brain above a critical P_{O_2} of 17 mm Hg (upper panel).* An acute reduction of arterial P_{CO_2} to 15 mm Hg by hyperventilation theoretically would reduce the cerebral blood flow and widen the A-V O_2 difference across the brain; the associated left shift in the position of the oxygen dissociation curve owing to the respiratory alkalosis will raise the minimum oxygen saturation required to maintain P_{O_2} of cerebral venous blood above the critical level which is required to maintain consciousness. Because the A-V O_2 difference required to maintain a normal cerebral O_2 consumption is also much larger during hyperventilation (shaded area) the arterial oxygen saturation required to keep the brain adequately oxygenated rises above 97%. Mild sustained hypoxia under such circumstances might cause hypoxic brain damage.

In metabolic alkalosis, the changes are similar except that hypocarbia and the cerebrovascular constriction that accompanies it are not important factors. If alkalosis persists for more than a day a progressive rise of 2,3-DGP in red cells may raise the P_{50} of blood back to its normal level thereby improving tissue oxygenation [86]; but in the

interim between the onset of alkalosis and the compensatory rise in 2,3-DPG hypoxic tissue damage may result. Thus it would be particularly important to avoid transients of metabolic alkalosis caused by diuretics in patients with impaired circulation; in this sense the rapid "contraction" alkalosis which can occur with ethacrynic acid may significantly impair oxygen transport One advantage of mercurial diuretics is that their effectiveness diminishes as the pH of the blood increases.

Respiratory and metabolic acidosis. Both respiratory and metabolic acidosis, when severe, depress cardiovascular function. The direct effects include a decrease in the contractile state of the heart, relaxation of systemic arterioles resulting in a fall in peripheral resistance, and a decrease in blood pressure. All of these effects are counteracted in the normal subject by increased sympathetic neuronal activity and release of catecholamines from the adrenal medulla. Even though the response to catecholamine effect is attenuated by the acidosis the compensatory increased release of catecholamines is usually adequate to maintain adequate circulation. However, if the acidosis becomes severe enough the compensatory mechanism may become inadequate and circulatory collapse may occur. In patients with compromised sympathetic responses or with cardiac function that is already depressed the cardiovascular effects of acidosis may be much more severe. Thus patients with congestive heart failure, who have a depletion of cardiovascular sympathetic stores [99], as well as depressed cardiac muscle function, are especially susceptible to the detrimental effect of acidosis. Similarly, patients who are being treated with beta-adrenergic blocking drugs lack the compensatory mechanisms required to maintain circulatory integrity in the face of acidosis. In addition, parasympathetic activity is enhanced during severe acidosis. Even though parasympathetic activity is attenuated in patients with congestive heart failure [100], the effect of acidosis in enhancing the action of acetylcholine may contribute to the general circulatory collapse.

With acute acidosis the oxyhemoglobin dissociation curve shifts to the right (P_{50} is elevated) which favors the unloading of oxygen in the tissues but depresses the ability to load oxygen in the lungs. When no lung disease is present this latter effect is unimportant. However, whenever pulmonary diffusing capacity imposes an important limitation to oxygenation of blood in the lung capillaries, the acidosis may actually impair net oxygen transport.

With chronic acidosis, a decrease in 2,3-DPG [82] in the red cell tends to compensate for the initial Bohr shift and move the curve back to the left. Too vigorous treatment of a chronic respiratory or metabolic acidosis may impair oxygen transport in tissues by causing an easily overlooked shift of the oxyhemoglobin dissociation curve to the left. The possible detrimental effects on oxygen transport to the brain caused by applying too vigorous artificial ventilation to a patient with chronic respiratory acidosis are illustrated in Fig. 6 and may in part explain the convulsive CNS

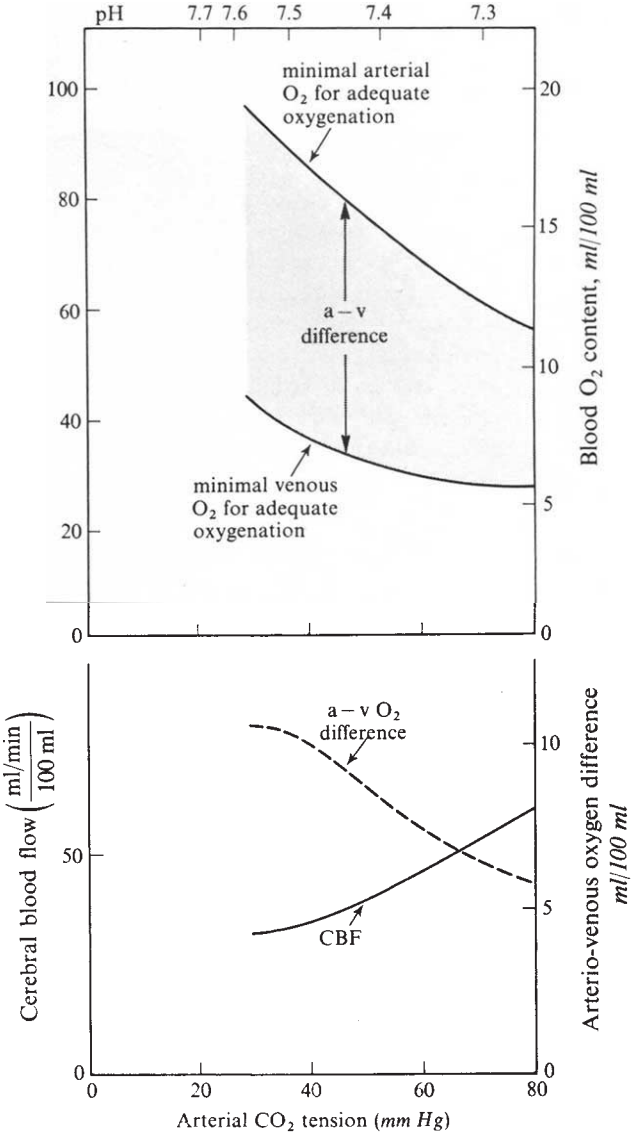

Fig. 6. *A recalculation of the relationships in Fig. 5 for a patient with chronic respiratory acidosis in whom the arterial P_{CO_2} is normally 70 mm Hg and arterial pH is 7.30.* The assumption is made that the normal Bohr shift of hemoglobin due to the acidosis has been eliminated by a reduction of red cell 2–3 DPG. A rapid reduction in the arterial P_{CO_2} to only 30 mm Hg by artificial ventilation might so impair cerebral O_2 transport that the minimal O_2 saturation of blood required to maintain adequate cerebral oxygenation would be greater than 97% in such a patient. If cerebrovascular disease were present or the arterial blood could not be fully saturated owing to the intrinsic lung disease cerebral hypoxia might occur at higher levels of arterial P_{CO_2}.

disorders described by Rotherman, Safar, and Robin [101] in patients treated for respiratory failure with mechanical ventilators.

One can in general predict that it is more dangerous to repair a chronic or subacute acidosis rapidly than slowly, and more dangerous to repair it through a respiratory

pathway than through intravenous infusions of alkali. The infusion of bicarbonate solutions will not be rapidly reflected in brain tissue so that cerebral alkalosis and vasoconstriction are less likely to occur than if alkalinization is achieved by rapidly lowering arterial P_{CO_2} with hyperventilation.

In spite of the dangers accompanying rapid changes of blood pH, there are clinical situations in which rapid alkalinization is required. In the acidotic patient in whom replacement of salt depletion is urgent, failure to treat the acidosis increases the risk of precipitating pulmonary edema with infused salt loads [51]. Also a patient with progressive cardiogenic shock and severe acidosis may require rapid correction of the pH before cardiac function can be improved and death of the patient prevented. When rapid alkalinization is necessary disturbances in oxygen transport should be minimized by insuring adequate oxygenation of the blood with an oxygen-enriched atmosphere.

Appendix A

Effect of the position of the oxyhemoglobin dissociation curve on the final equilibrium between alveolar oxygen tension and oxygen saturation of blood leaving the lung. For a given ratio of ventilation to perfusion in the lung the following linear relationship exists between alveolar oxygen tension and oxygen saturation of blood leaving the lung:

$$P_{A_{O_2}} = F_{I_{O_2}}(P_B - 47) - P_{A_{CO_2}} F_{I_{O_2}} - 863 \frac{\dot{Q}_C}{\dot{V}_A} F_{I_{N_2}} \quad \text{Cap}\,(S_{c'_{O_2}} - S_{\bar{v}_{O_2}}) \tag{1}$$

where

$P_{A_{O_2}}$ = alveolar oxygen tension in mm Hg;

$F_{I_{O_2}}$ = fraction of oxygen in inspired air;

P_B = barometric pressure;

47 = water vapor tension in air saturated with water vapor at 37° C;

$P_{A_{CO_2}}$ = alveolar CO_2 tension;

$\dot{Q}_C$ = pulmonary capillary blood flow (L/min);

$\dot{V}_A$ = alveolar ventilation (L/min STPD);

$F_{I_{N_2}}$ = fraction of nitrogen in inspired air;

Cap = oxygen capacity of blood in ml O_2 per ml blood;

$S_{c'_{O_2}}$ = fractional oxygen saturation of blood leaving lung capillaries;

$S_{\bar{v}_{O_2}}$ = fractional oxygen saturation of mixed venous blod.

Given the inspired oxygen fraction ($F_{I_{O_2}}$), the alveolar CO_2 tension ($P_{A_{O_2}}$), and the ratio of blood flow to ventilation ($\dot{Q}_C/\dot{V}_A$) this equation describes all the possible values of alveolar oxygen tension ($P_{A_{O_2}}$) with respect to oxygen saturation of blood leaving lung capillaries ($S_{c'_{O_2}}$) (Fig. 7). If the oxyhemoglobin dissociation curve is plotted on the same graph the point of intersection between the line representing Eq. (3) and the dissociation curve indicates the final equilibrium which will be achieved between alveolar oxygen tension and oxygen saturation of blood (i.e., if the blood remains in lung capillaries long enough for equilibrium to be reached). With this graphical representation it is possible at a glance to see what a given shift in the oxyhemoglobin dissociation curve will do to this final equilibrium. Alkalosis will tend to increase the saturation and decrease the oxygen tension of arterial blood, whereas acidosis will lower the saturation but increase the oxygen tension. The effect is small in a normal person at sea level in whom the ratio of $\dot{V}_A/\dot{Q}_C$ is high but the effect will become significantly greater in a normal person at high altitude or in a patient with ventilatory failure due to lung disease who has a low ratio of $\dot{V}_A/\dot{Q}_C$ (Fig. 7). Whether such changes are beneficial or detrimental depends upon the relative importance of the opposing changes in oxygen tension and oxygen saturation in delivering oxygen to tissues and perhaps upon the compensatory mechanisms which are available.

Appendix B.

Effect of the position of the oxyhemoglobin dissociation curve on the rate of oxygen diffusion into blood. The time required for the oxygen saturation of lung capillary blood to rise from the mixed venous level ($S_{\bar{v}_{O_2}}$) to any given saturation ($S_{c_{O_2}}$) is given by the following equation [102]:

$$\Delta t = 60\left[(\text{Cap})\frac{V_c}{D_{M_{O_2}}}\int_{S_{\bar{v}}}^{S_c}\frac{dS_c}{P_A - kP_c} + \int_{S_{\bar{v}}}^{S_c}\frac{dS_c}{\theta(P_A - kP_c)}\right] \tag{2}$$

where

Δt = time in seconds for oxygen saturation to rise from $S_{\bar{v}_{O_2}}$ to $S_{c_{O_2}}$;

Cap = O_2 capacity of the blood in ml O_2/ml blood;

V_C = pulmonary capillary blood volume in ml;

$D_{M_{O_2}}$ = diffusing capacity of the pulmonary membrane for oxygen in ml/min/mm Hg;

$P_{A_{O_2}}$ = alveolar oxygen tesnion;

$P_{c_{O_2}}$ = blood oxygen tension in equilibrium at pH 7.4 with the mean intracorpuscular oxygen saturation ($S_{c_{O_2}}$) as the blood traverses lung capillaries;

k = P_{O_2} multiplication factor which takes into acount shifts in position of the O_2 dissociation curve away from its normal resting position (i.e., employing P_{50} to denote the position of the O_2dissociation curve $k = P_{50}/26.5$);

θ = rate at which red cells in one ml of while blood will take up oxygen from plasma in ml/min.

The formula indicates that when the O_2 dissociation curve is shifted to the left (i.e., when $P_{50} < 26.5$) k is less than 1.0. Consequently, at any given alveolar oxygen tension ($P_{A_{O_2}}$) the time (Δt) required for the oxygen saturation to rise from $S_{\bar{v}_{O_2}}$ to some specified value $S_{c_{O_2}}$ is less than would be required if the dissociation curve were in its normal position (i.e., when $P_{50} = 26.5$ and $k = 1.0$); conversely, when the

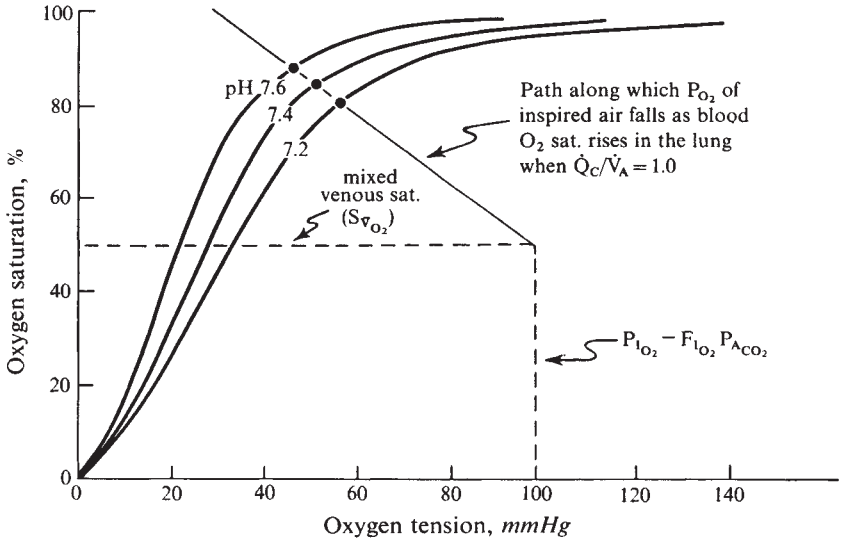

Fig. 7. *Effect of shifts in the position of the O_2 dissociation curve on the final equilibrium between alveolar air and blood leaving lung capillaries breathing air at an altitude of about 10,000 feet.* An alveolar P_{CO_2} of 40 mm Hg and a mixed venous O_2 saturation of 50% were assumed. The curved lines represent the oxyhemoglobin dissociation curves at pH 7.2, 7.4, and 7.6. The straight diagonal line is a graphic representation of Equation (1) in Appendix A. The intersections (solid circles) between the solid straight line and the O_2 dissociation curves represent the oxygen saturation and P_{O_2} of blood leaving the lung equilibrated with the alveolar oxygen tension at different levels of blood pH. Alkalosis (pH 7.6) increases the O_2 saturation and decreases the P_{O_2} of blood leaving the lung. Acidosis lowers the O_2 saturation but raises the P_{O_2} of blood leaving the lung.

O_2 dissociation curve is shifted to the right k is greater than 1.0 and the time (Δt) required for oxygen saturation to rise to a specified level will be longer than normal.

In general then a shift of the O_2 dissociation curve to the right by acidosis tends to impair oxygenation of blood leaving the lung in two ways: 1) by reducing the oxygen saturation in equilibrium with a given alveolar oxygen tension, and 2) by reducing the rate at which equilibrium between alveolar and capillary blood oxygen tension can occur. Alkalosis has opposing effects on oxygen transport in the lungs.

Appendix C.

Effect of acid-base shifts on tissue unloading of oxygen. Krogh developed the concept that oxygen tension of blood leaving tissue capillaries cannot fall below some critical lower limit without curtailing tissue oxygen consumption; this critical blood oxygen tension should set an effective lower limit to oxygen saturation of blood leaving tissue capillaries. Krogh with the help of Danish mathematician Erlang [103] derived a formula showing that the maximal oxygen tension difference (ΔP) between capillary blood and intervening tissue should vary directly with metabolic rate and indirectly with the capillary density of the tissues. Their original formula can be rearranged into the following approximation:

$$\Delta P = \frac{1.9 \times 10^{-2}\, Mr^2}{k} \left| \left(1 + \frac{1}{\phi}\right) \ln\left(1 + \frac{1}{\phi}\right) - \frac{1}{\phi} \right| \quad (3)$$

where ΔP is in mm Hg;

ϕ = is capillary density expressed as the ratio of capillary blood volume to tissue volume;

M = metabolic rate of tissue in ml of O_2 utilized per min per ml of tissue;

r = capillary radius in μ;

k = diffusion coefficient of tissue in ml/min per cm^2 per unit pressure gradient in atmospheres per μ.

Thus at a given tissue metabolic rate the oxygen consumption of the tissue will not be limited by oxygen delivery as long as the difference between oxygen tension of blood leaving the tissue capillaries and the value of ΔP in Eq. (3) are high enough to maintain a tissue oxygen tension between capillaries greater than that which is critical for sustaining mitochondrial function (1 to 4 mm Hg).

The critical P_{O_2} in capillary blood of a given tissue can vary not only as a consequence of the level of tissue metabolic activity in accordance with Eq. (5) but also as a consequence of the fraction of total tissue capillaries which is being perfused at any given moment. Stainsby and Otis found that the critical P_{O_2} in capillary blood perfusing the resting gastrocnemius-gracilis muscle group in dogs was higher at rest than when contracting, presumably because a greater fraction of the total capillary bed of the muscle was being perfused during muscle stimulation: when a greater fraction of the potential capillary bed is perfused the effective capillary density (ϕ in Eq. (3)) increases.

An optimal P_{50} for oxygen transport. The upper limit for the relationship between oxygen consumption and end-capillary blood oxygen saturation ($S_{c'O_2}$) in the lung for a given mixed venous O_2 saturation ($S_{\bar{v}}$) is given by the following modification of the Fick equation.

$$\dot{V}_{O_2} = (60\, V_C/\Delta t)\,(S_{c'O_2} - S_{\bar{v}O_2})\,Cap \quad (4)$$

where

V_{O_2} = oxygen consumption in ml/min;

V_C = pulmonary capillary blood volume in ml;

Δt = time required for oxygen saturation of blood in lung capillaries to rise from $S_{\bar{v}}$ to $S_{c'O_2}$ (Eq. (2));

Cap = oxygen capacity of blood in ml/ml;

$S_{\bar{v}O_2}$ and $S_{c'O_2}$ are expressed as fractions of the O_2 cap.

Equation (2) is used to calculate Δt. Theoretical relationships between $S_{c'O_2}$ and V_{O_2} have been constructed in Fig. 8 for different levels of P_{50} assuming that mixed venous oxygen

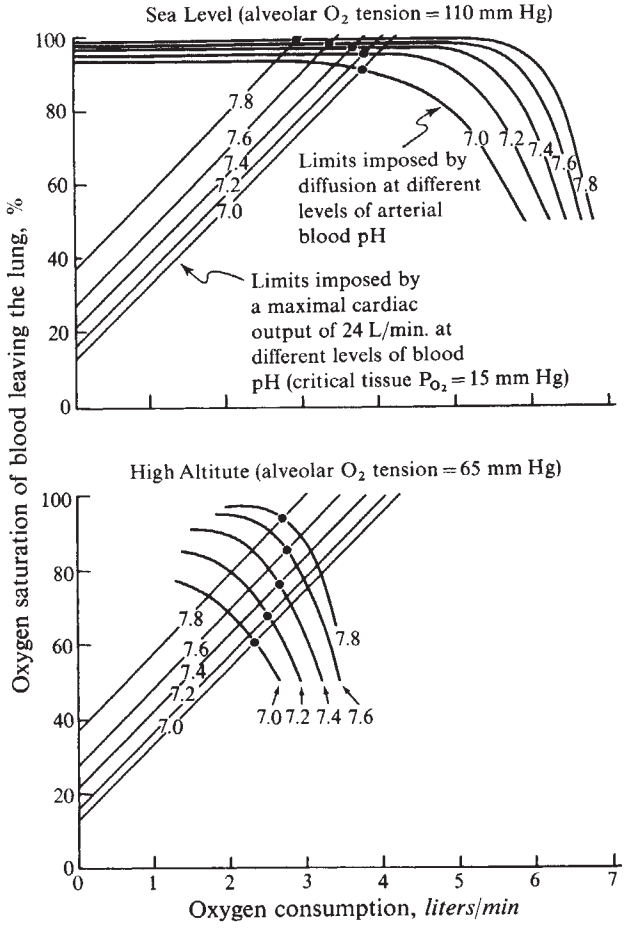

Fig. 8. *Theoretical limits (closed circles) to oxygen consumption imposed by a normal alveolar capillary membrane and by a maximal cardiac output of 24 liters/min at different levels of arterial blood pH at sea level (upper panel) and at high altitude (lower panel).* The upper limits imposed on oxygen saturation by a normal pulmonary membrane diffusing capacity for oxygen at different levels of pH (curved lines) were calculated from Equations (2) (Appendix B) and (4) (Appendix C) assuming an average critical P_{O_2} in mixed venous blood of 15 mm Hg. The limits imposed on maximal O_2 consumption at different levels of arterial O_2 saturation and pH (straight diagonal lines) were estimated from Equation (5) (Appendix C). The intersections between the diagonal straight line and curved line representing the same pH indicate the theoretical maximal O_2 consumption at that pH. The optimal pH appears to be about 7.20 at sea level and 7.60 at high altitude.

saturation ($S_{\bar{v}_{O_2}}$) is set by a critical P_{O_2} of 15 mm Hg for mixed venous blood. Normal values were assumed for $D_{M_{O_2}}$ and V_C at heavy exercise and the measurements of θ_{O_2} obtained by Staub, Bishop, and Forster [104] were employed.

In the same figure the upper limit for oxygen consumption ($\dot{V}_{O_2max}$) for any given $S_{c'_{O_2}}$ has been calculated for the same levels of P_{50} assuming a maximal cardiac output ($\dot{Q}_{max}$) of 24 liters/min and employing the standard Fick

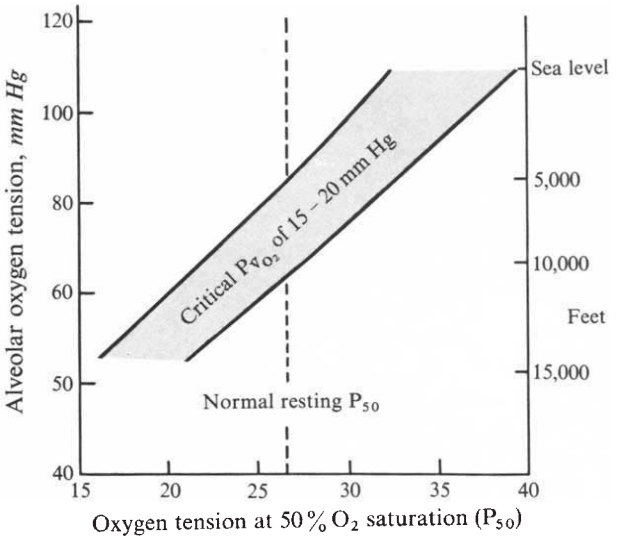

Fig. 9. *Theoretical range of optimal P_{50} for achieving maximal O_2 consumption during acute exposure to different altitudes or to corresponding alveolar oxygen tensions.* The calculations were made as indicated in Fig. 8 assuming that the critical P_{O_2} of mixed venous blood lies between 15 and 20 mm Hg.

equation:

$$\dot{V}_{O_2max} = \dot{Q}_{max} (S_{c'_{O_2}} - S_{\bar{v}_{O_2}}) \text{ Cap.} \qquad (5)$$

The points of intersection of the relationships described by Eqs. (4) and (5) for different levels of P_{50} indicate the maximal O_2 consumptions which theoretically could be sustained at different positions of the O_2 dissociation curve. The analysis suggests that a theoretical optimal position of the O_2 dissociation curve exists which will provide maximal O_2 delivery for a given cardiac output. This optimal position theoretically should vary from sea level to high altitude (i.e., with alveolar oxygen tension) as shown in Fig. 9.

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