

# Alpha-Stat and pH-Stat Management Techniques in Artificial Blood Oxygenators

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## Abstract

This clinical observation relates blood pCO<sub>2</sub>, solubility, total CO<sub>2</sub> content, oxygenator FiCO<sub>2</sub> and ventilation rate, CO<sub>2</sub> transfer, and respiratory quotient during hypothermic cardiopulmonary bypass.

Techniques employed to obtain the above parameters include blood gas analysis, temperature correction, gas and blood flow settings, mass spectrometry, Kelman's algorithm of the Singer-Hasting nomogram, and O<sub>2</sub> and CO<sub>2</sub> transfer calculations.

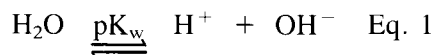
Membrane lung O<sub>2</sub> and CO<sub>2</sub> transfer curves demonstrate the following respiratory quotient (RQ) and CO<sub>2</sub> blood content requirements for two common hypothermic pCO<sub>2</sub> management techniques:

TECHNIQUE	COOLING	WARMING
pH-Stat	CO <sub>2</sub> content increase, RQ lower than normal	CO <sub>2</sub> content decrease, RQ much greater than normal
Alpha-Stat	CO <sub>2</sub> content constant, RQ normal	CO <sub>2</sub> content constant, RQ normal

Oxygen, carbon dioxide transfer versus patient temperature plots from hypothermic CPB demonstrate the perfusionist's complete control of blood CO<sub>2</sub> content and blood pCO<sub>2</sub>.

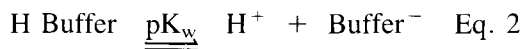
## Introduction

The pH of a solution is indirectly proportional to the hydrogen ion concentration in that medium. In the body the primary source of free hydrogen ions is from the dissociation of water.



This reaction is governed by the dissociation constant (pK<sub>w</sub>) of water. As temperature decreases the pK<sub>w</sub> parallels this decline resulting in fewer free hydrogen ions and a resulting higher pH. The intracellular hydroxyl/hydrogen ion concentration (OH<sup>-</sup>/H<sup>+</sup>) remains constant at a ratio of 1.0 ± .3 at any temperature as the result of chemical and electrical equilibrium.<sup>1</sup> Therefore the intracellular pH may be said to remain constant with changing temperature.

A buffer may be defined as any substance capable of donating or receiving a proton in an attempt to maintain a constant pH.



Three primary buffer systems found in humans are the bicarbonate, phosphate, and protein systems. In order to receive a proton (free hydrogen ion), a buffer must be in the dissociated or proper charge state. The ability of a buffer to dissociate or be in the proper charge state during hypothermia is dependent upon the pK for that buffer system.

As temperature decreases and the pK<sub>w</sub> of water decreases, the pk of a buffer system must parallel this change in order to remain effective. It has been shown that during hypothermia the major normothermic buffer system, bicarbonate, is inadequate.<sup>1</sup>

A protein buffer system, specifically the imida-

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zole portion of histidine found in plasma and red blood cells, has a pK which parallels the pK of neutrality (pK<sub>w</sub>) and is therefore the primary hypothermic buffer system.<sup>1</sup> Like all buffers, imidazole must lose a proton during dissociation and be in the proper charge state in order to be effective. The imidazole protein minus a proton is identified as alpha imidazole.

As the solubility increases with decreasing temperature, a constant CO<sub>2</sub> content will result at a lower pCO<sub>2</sub>. In order to maintain hypothermic biological neutrality, and the OH<sup>-</sup>/H<sup>+</sup> ratio, the imidazole protein buffer charge state, and total CO<sub>2</sub> content must remain constant. This strategy is defined as alpha-stat. The end result is a decrease in the pCO<sub>2</sub> due to increased carbon dioxide solubility and will result in a concomitantly high actual blood pH.

During cardiopulmonary bypass (CPB) the easiest method of controlling the acid-base status is through manipulation of the respiratory component. Normothermic blood pH is proportional to the metabolic and respiratory components.

$$\text{pH} \propto \frac{\text{Metabolic}}{\text{Respiratory}} \propto \frac{\text{Base Excess}}{\text{pCO}_2} \quad \text{Eq. 3}$$

Alteration in the acid-base status by manipulating the carbon dioxide content may be illustrated with the Henderson-Hasselback equation as shown in Equation 3.

Carbon dioxide is carried primarily as bicarbonate and dissolved in solution. Dissolved carbon dioxide content is related to the partial pressure of the gas and the solubility as follows in Equation 4.

$$\text{CO}_2 \text{ volumes } \% = \text{pCO}_2 \text{ (mmHg)} \times \text{Solubility (mlCO}_2\text{/mmHg/100 ml blood)} \quad \text{Eq. 4}$$

During CPB the perfusionist regulates the respiratory acid-base component by selecting an artificial lung ventilation rate adequate to alter CO<sub>2</sub> content yielding a desired blood pCO<sub>2</sub>. In order to adequately quantitate the physiological results of a specific acid-base management technique, the perfusionist must know the actual (temperature corrected) pCO<sub>2</sub> and pH values to determine CO<sub>2</sub> gas content, CO<sub>2</sub> transfer ( $\dot{V}_{\text{CO}_2}$ ) and determine the proper oxygenator ventilation rate.

Carbon dioxide transfer across a membrane may be represented by the Fick Formula:

$$\dot{V}_{\text{CO}_2} = \frac{D_{\text{CO}_2} \times (C_1 - C_2)_{\text{CO}_2}}{\Delta X} \quad \text{Eq. 5}$$

Where:  $\dot{V}_{\text{CO}_2}$  = ml CO<sub>2</sub>/min.  
 $D_{\text{CO}_2}$  = Diffusion coefficient  
 (ml CO<sub>2</sub> × cm/minute)

$(C_1 - C_2)_{\text{CO}_2}$  = CO<sub>2</sub> concentration gradient

$X$  = CO<sub>2</sub> diffusion distance (cm)

Assuming the temperature and solubility are constant, the above equation may be rewritten as:

$$\dot{V}_{\text{CO}_2} = D_{\text{CO}_2} \times \frac{(\text{pCO}_{2,1} - \text{pCO}_{2,2})}{\Delta X} \quad \text{Eq. 6}$$

In a parallel channel gas transfer device such as a membrane blood oxygenator, the amount of CO<sub>2</sub> transferred per unit time is a function of the mean driving force, the partial pressure difference for CO<sub>2</sub>.

The mean driving force for CO<sub>2</sub> between the gas and blood streams is determined by the CO<sub>2</sub> partial pressure gradients between the arterial and venous blood and the inspired and expired gases\*. Carbon dioxide transfer is linearly proportional to the CO<sub>2</sub> driving force under constant ventilation, blood flow, and membrane boundary layer conditions.<sup>2</sup> The venous blood pCO<sub>2</sub> is a major determinant of CO<sub>2</sub> transfer in a fixed oxygenator design.

Oxygen transfer approximation by measuring blood oxygen content is common in the study of artificial oxygenating devices. The direct measurement of CO<sub>2</sub> transfer in artificial lungs was not reported until 1974 (Snider et al.). Early investigators estimated  $\dot{V}_{\text{CO}_2}$  by the Fick Formula. Carbon dioxide content determination by the VanSlyke apparatus was cumbersome, and less accurate predictions were made employing pCO<sub>2</sub>, pH and % O<sub>2</sub> saturation of hemoglobin using a nomogram.<sup>4</sup>

Clinical calculation of carbon dioxide transfer can be determined by measuring the artificial lung inlet and outlet ventilating gas % CO<sub>2</sub> and multiplying the difference by the total gas sweep rate.<sup>2,4,6</sup> Correlation between the outlet ventilating gas pCO<sub>2</sub> and outlet blood pCO<sub>2</sub> (PaCO<sub>2</sub>) has been demonstrated with some success.<sup>3,4</sup> However, few

\*LMΔPCO<sub>2</sub> is the log mean driving force for CO<sub>2</sub>. It is calculated as follows:

$$\text{LM}\Delta\text{PCO}_2 = \frac{\Delta P_1 - \Delta P_2}{\ln(\Delta P_1 - \Delta P_2)} \quad \text{where } \Delta P_1 = (\text{PvCO}_2 - \text{PinCO}_2) \quad \Delta P_2 = (\text{PaCO}_2 - \text{PexCO}_2)$$

**TABLE 1**  
**Group I and Group II control characteristics for the pH-stat and alpha-stat management techniques.**

	ACID BASE STATUS	TEMPERATURE CORRECTED AT 28°C	NOT TEMPERATURE CORRECTED AT 37°C
Group I	pH-Stat	pCO <sub>2</sub> 35-45 mmHg pH 7.35-7.45	pCO <sub>2</sub> 58-67 mmHg pH 7.25-7.33
Group II	Alpha-Stat	pCO <sub>2</sub> 25-35 mmHg pH 7.45-7.58  "Actual blood values"	pCO <sub>2</sub> 35-45 mmHg pH 7.35-7.45  "False blood gas analyzer values"

reports exist illustrating the CO<sub>2</sub> transfer requirements to maintain a specific acid-base status during hypothermic CPB.<sup>5</sup> The CO<sub>2</sub> transfer rate is determined by the CO<sub>2</sub> driving force regulated by the venous blood pCO<sub>2</sub>, ventilating gas pCO<sub>2</sub> and sweep rate, as well as the artificial lung design and gas path boundary phenomena. The perfusionist may select the oxygenator CO<sub>2</sub> driving force to achieve the oxygenator respiratory quotient (RQ), which is the ratio of carbon dioxide transfer to oxygen transfer ( $\dot{V}_{CO_2}/\dot{V}_{O_2}$ ), to achieve a desired blood CO<sub>2</sub> content and pCO<sub>2</sub>.

The CO<sub>2</sub> transfer requirements to maintain two different acid-base management strategies are presented in this paper. Both strategies are related to different temperature control mechanisms. A "pH-stat" management technique is presented in which actual blood pH and pCO<sub>2</sub> are maintained at 37° C temperature corrected normal values. This technique is commonly associated with homeotherms such as man. Poikilotherms however exhibit an "alpha-stat" strategy during hypothermia in which the pCO<sub>2</sub> is allowed to decrease, resulting in a high pH, normal OH<sup>-</sup>/H<sup>+</sup> ratio, constant CO<sub>2</sub> content, and biological neutrality. The pCO<sub>2</sub> and pH requirements for each technique are presented in Table One.

## Methods

Cardiopulmonary bypass was initiated using a Cobe CML membrane oxygenator<sup>a</sup> on 22 adult patients undergoing open-heart surgery. Fourteen were randomly chosen to be managed by pH-stat and 8 by alpha-stat. Arterial and venous blood gas

data were collected at every degree centigrade change in nasopharyngeal temperature during the cooling and warming phases. Oxygen transfer in ml O<sub>2</sub>/minute/m<sup>2</sup> body surface area was calculated as previously reported.<sup>4,6,7</sup> The oxygenator was ventilated at a constant gas sweep rate of 10 L/min. as recommended by the manufacturer. The arterial pO<sub>2</sub> and pCO<sub>2</sub> were controlled by varying the ventilating gas FiCO<sub>2</sub> and FiO<sub>2</sub>.

Carbon dioxide transfer was estimated from calculated gas inlet and outlet CO<sub>2</sub> concentrations using the calibrated 100% O<sub>2</sub>/room air and 100% CO<sub>2</sub> gas flow meter settings and exit gas mass spectrometer pCO<sub>2</sub> measurements.<sup>4</sup>  $\dot{V}_{CO_2}$  is reported as ml CO<sub>2</sub>/min/m<sup>2</sup> body surface area.

Blood gas and pH measurements were taken at the initiation and termination of each cooling and warming phase. Mixed venous samples were "temperature corrected" to the venous blood temperature and arterial samples to the nasopharyngeal temperature.

The arterial pCO<sub>2</sub> and pH values were maintained within the limits for each technique outlined in Table One. The oxygen and carbon dioxide transfer were plotted with respect to temperature. The best fit curves were constructed using the least squares method.

## Results

Figure One illustrates the carbon dioxide and oxygen transfers versus nasopharyngeal temperature for the pH-stat methodology. The pH, blood gas, and oxygenator ventilation parameters are listed at the beginning and end of each phase. The pH-stat blood CO<sub>2</sub> content increased dramatically to prevent a change in the arterial pCO<sub>2</sub> during the

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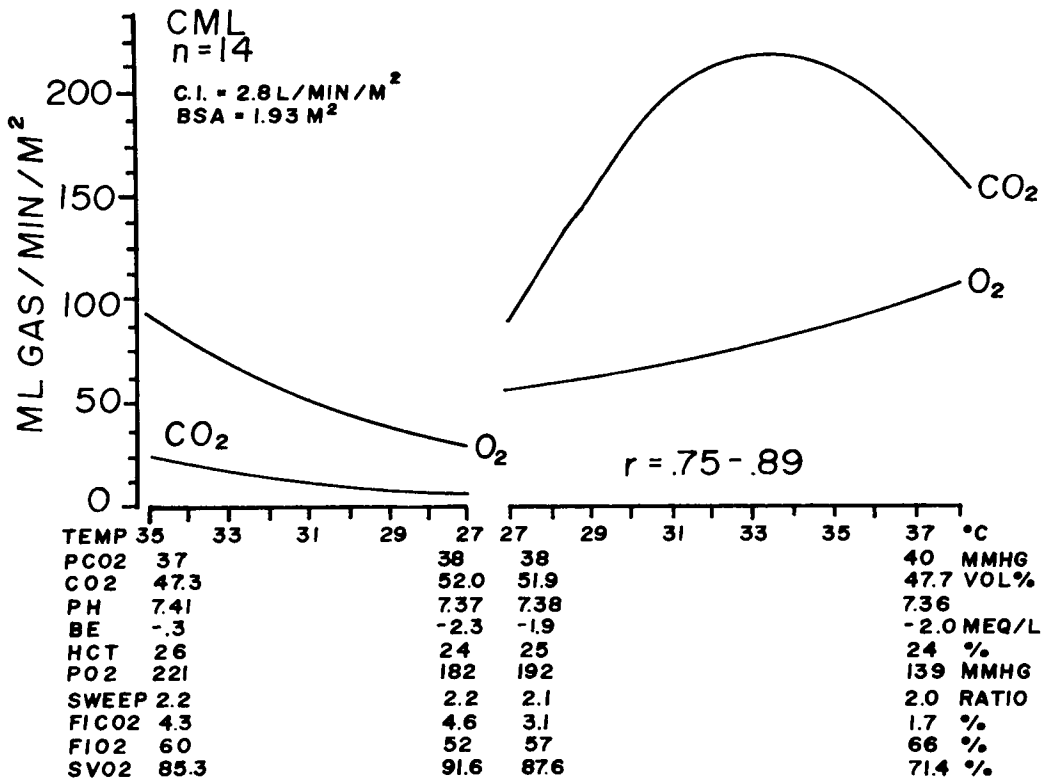


FIGURE 1. Group I O<sub>2</sub> and CO<sub>2</sub> transfer rates during CPB cooling and warming phases, Cobe Membrane Lung (CML) ventilation settings are included.

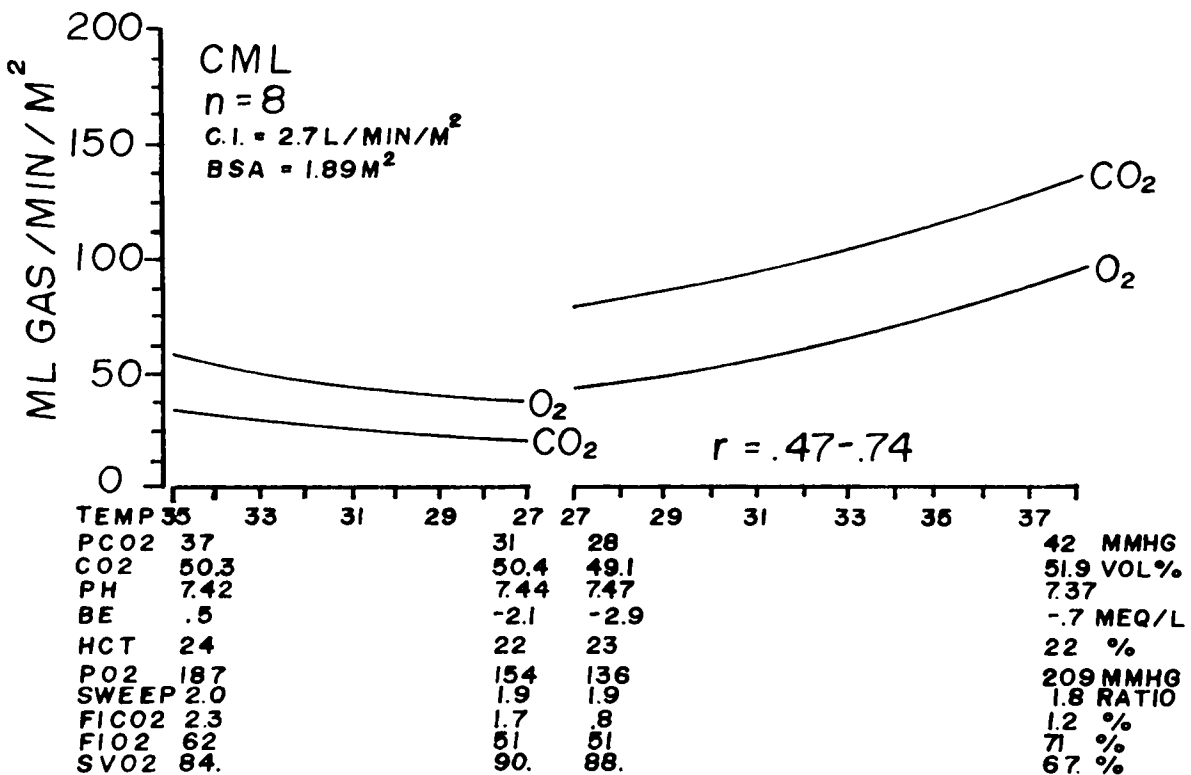


FIGURE 2. Group II O<sub>2</sub> and CO<sub>2</sub> transfer rates during CPB cooling and warming phases. Cobe Membrane Lung (CML) ventilation settings are included.

cooling phase. The oxygenator RQ was less than .35 during this period. Upon the initiation of the warming phase, an oxygenator RQ greater than 1.5 was required to eliminate the CO<sub>2</sub> retained during the cooling phase and CO<sub>2</sub> produced as a result of increased patient metabolism.

Figure Two represents the alpha-stat management technique's CO<sub>2</sub> and O<sub>2</sub> transfer with respect to temperature. An average oxygenator RQ of .7 was maintained during cooling to yield 37°C non-temperature corrected "normal values." During cooling, the CO<sub>2</sub> content is maintained and actual blood pCO<sub>2</sub> falls and pH rises. During the warming phase, a higher RQ was necessary to arrive at 37°C "normal" blood pCO<sub>2</sub> and pH at the end of the warming phase.

## Discussion

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When following the pH-stat acid-base management scheme, the actual (temperature corrected) arterial pH and blood gases are maintained at 37°C normal (pH = 7.35-7.45mmHg, pCO<sub>2</sub> = 35-40) values. In order to remain within the limits defined by this technique, the perfusionist must decrease the CO<sub>2</sub> driving force either by decreasing the oxygenator's gas sweep rate or increasing the ventilating gas FiCO<sub>2</sub>. These perfusionist management actions will raise the CO<sub>2</sub> content and maintain the partial pressure in the face of increasing solubility (Figure One). During the warming phase, it becomes necessary to utilize a high oxygenator RQ in order to remove the CO<sub>2</sub> retained during cooling as well as the CO<sub>2</sub> produced by the patient tissue in order to achieve normal pCO<sub>2</sub> and pH values at 37°C.

In the alpha-stat technique, an oxygenator euthermic RQ may be established at the initiation of normothermic CPB which results in normal 37°C non-temperature corrected values.<sup>1,10</sup> Maintenance of uncorrected 37°C normal pH and pCO<sub>2</sub> values during the cooling phase will result in a constant CO<sub>2</sub> content, intracellular OH<sup>-</sup>/H<sup>+</sup> ratio, and proper imidazole charge state.<sup>1,8,9</sup> Figure Two illustrates a nearly constant oxygenator RQ during the cooling phase to maintain the non-temperature corrected normal values. During the warming phase a higher yet consistent RQ is required to remove the carbon dioxide produced by the patient

tissue. Hyperventilation of the artificial lung to remove CO<sub>2</sub> retained in the cooling phase is not necessary as found with the pH-stat strategy.

When utilizing an alpha-stat technique, blood pH and pCO<sub>2</sub> should be analyzed at 37°C and not temperature corrected. Temperature correction of blood gases may be misleading due to the inability to accurately select a true core temperature as the result of internal gradients.<sup>1</sup> A constant blood CO<sub>2</sub> content, intracellular OH<sup>-</sup>/H<sup>+</sup> ratio and alpha imidazole charge state may be assured during rapid cooling by maintaining 37°C non-temperature corrected normal values.<sup>2</sup> However, in order to accurately calculate O<sub>2</sub> and CO<sub>2</sub> transfer rates and monitor patient oxygenation (pO<sub>2</sub>), actual temperature corrected blood values must be determined.

The arterial blood pCO<sub>2</sub> and CO<sub>2</sub> content during hypothermia are determined by the CO<sub>2</sub> transfer rate at the initiation of CPB and during rapid cooling. The CO<sub>2</sub> transfer rate is determined by the perfusionist selection of CO<sub>2</sub> driving force by varying the gas sweep rate and ventilating gas inlet pCO<sub>2</sub>.

The proper ventilating gas sweep rate and FiCO<sub>2</sub> must be selected by the perfusionist to achieve a desired CO<sub>2</sub> transfer rate to alter CO<sub>2</sub> content and achieve the desired arterial pCO<sub>2</sub> at a given temperature. Both ventilation techniques require knowledge of the patient's blood gas status immediately prior to initiation of CPB and during the cooling phase either through frequent sampling or continuous monitoring.

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