

[CHAPTER 29]

The Perioperative Period

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29.1 INTRODUCTION

Current medical and anesthesia textbooks state that abnormal $[H^+]$ impairs every single organ system. This is caused by alterations in protein, enzyme and cell function. While this is a physiological truth, it is not very useful in daily clinical practice of perioperative medicine.

Therefore this chapter will first focus on aspects of acid-base physiology that are relevant to most anesthesiologists. It will become clear that acid-base disorders may have a major clinical impact both on the patient scheduled for anesthesia and anesthetic drugs. But even more importantly, many clinical interventions by anesthesiologists may actually profoundly influence $[H^+]$ itself. The importance of $[H^+]$ warrants a thorough understanding of factors influencing it. This is where the Stewart approach may have its greatest value. Obviously, in this chapter this quantitative method will be used where possible and appropriate.

In addition, the short but controversial history of this approach in the anesthesia community is discussed. The last part of this chapter will focus on acid-base physiology in the setting of cardiopulmonary bypass and temperature differences from a quantitative perspective.

29.2 THE EFFECT OF $[H^+]$ ON THE PATIENT UNDERGOING ANESTHESIA

Many physiological alterations occur with acidosis or alkalosis but not all are critical. In anesthesia, ventilation is frequently controlled or assisted. In this setting, spontaneous changes in respiratory rate or volume to compensate for acid-base disturbances are not encountered. Therefore, the effects of $[H^+]$ on the cardiovascular system are far more important. With worsening acidosis ($[H^+] > 60$ nM, $pH < 7.22$), myocardial and smooth muscle depression result in a decreased stroke volume and peripheral resistance [1]. This induces hypotension which may compromise tissue perfusion. Unfortunately the response of both types of muscle to administered inotropes or vasopressors is also impaired in this setting [2]. Conversely pulmonary vascular resistance is increased imposing a greater afterload on the right heart [3]. In addition, the threshold for ventricular fibrillation is decreased [4]. Increased $[H^+]$ is associated with an

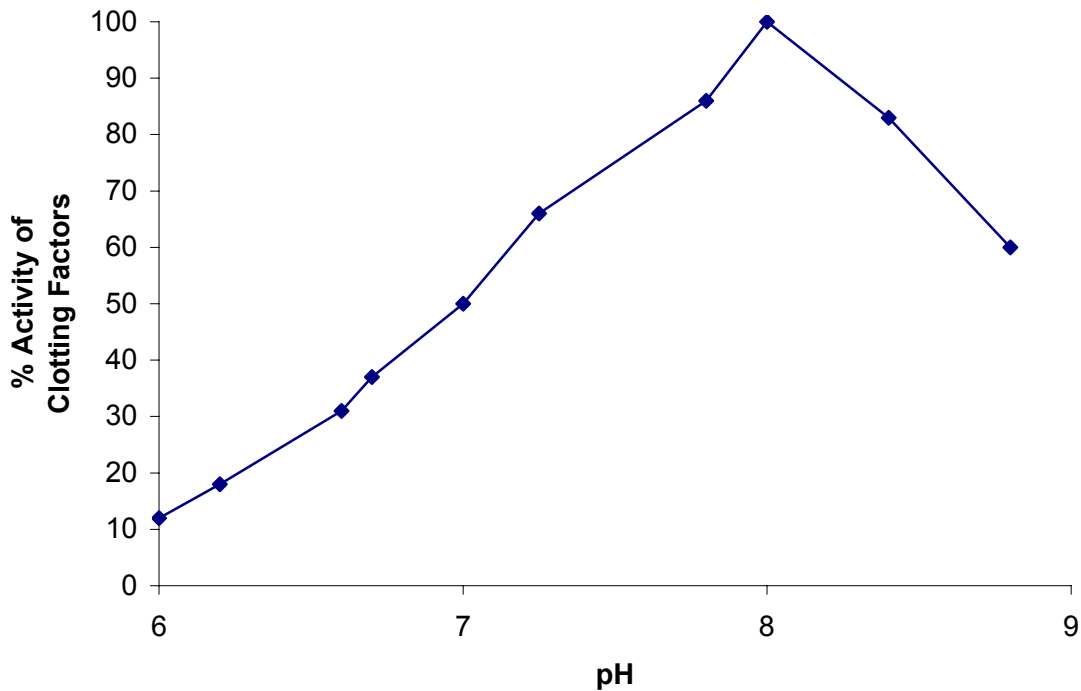


Figure 29.1. Shown is the pH dependency of clotting factor activity. Modified from [7].

increase in plasma $[K^+]$, which may lead to arrhythmias [1]. Whatever the initial cause of the acidemia, cardiovascular derangements may impair oxygen delivery to tissue despite a rightward shift in the Hb- O_2 dissociation curve [1]. This will start a vicious circle of worsening lactic acidosis which will impair cardiovascular performance even more.

With alkalosis, the critical changes are also cardiovascular[3, 4]. The most prominent effect is a leftward shift in the O_2 -Hb dissociation curve, effectively making oxygen offloading more difficult. In addition, $[Ca^{2+}]$ and $[K^+]$ levels are usually lowered. This may give rise to circulatory depression resulting from decreased contractility and hypokalemic arrhythmias respectively. From a respiratory perspective, alkalosis increases bronchial smooth muscle tone [1]. Finally, if plasma alkalosis spreads to the cerebrospinal fluid, cerebral blood flow will be reduced [5]. This will happen quickly with respiratory alkalosis as CO_2 rapidly equilibrates between different compartments [6].

The activity of coagulation factors depends on $[H^+]$ [7]. Perhaps surprisingly, their in vitro activity is maximal at $[H^+]=10$ nM (pH=8.0), which is shown in Figure 29.1. While this extreme of alkalosis is obviously not advisable, it may be useful to regulate $[H^+]$ in the low normal regions in the setting of massive bleeding. Recombinant factor VIIa shows a similar $[H^+]$ dependency with a 70% decrease in activity at $[H^+] = 100$ nM (pH=7.0) and a 100% increase in activity at $[H^+] = 10$ nM compared to that at $[H^+] = 40$ nM (pH=7.40) [8].

29.3 THE EFFECT OF ANESTHETIC DRUGS ON $[H^+]$

Throughout this book it has been argued that $[H^+]$ depends on PCO_2 , $[SID]$ and $[A_{TOT}]$. Thus, in order to determine the effects of anesthetic agents on $[H^+]$ we should look at their effects on those three independent parameters. All anesthetic agents with the possible exception of ketamine induce a dose dependent reduction in respiratory drive [9]. This will lead to an increase in PCO_2 in spontaneously breathing patients. This is most prominent with opioids. This effect is most often seen when using the laryngeal mask airway, which is ideal for spontaneous breathing because of its low resistance to air flow. Of course, in controlled ventilation modes, it is the ventilator settings that determine PCO_2 . However in the emergence phase, many anesthesiologists reduce minute volume to increase onset of spontaneous ventilation. Some even add CO_2 to the breathing circuit or increase dead space in order to speed washout of volatile anesthetics [10]. While this may not cause any adverse effects in relatively healthy patients and respiratory acidosis seems to have a milder effect as compared to other types [11], a word of caution may be warranted. Besides inducing many of the critical effects described above, extremes of CO_2 retention may lead to CO_2 narcosis as a result of severe neuronal intracellular acidosis and intracranial hypertension from increased cerebral blood flow [12].

Effects of anesthetic agents on $[A_{TOT}]$ or $[SID]$ are usually absent because of their relatively low concentrations. In theory, use of fluorinated volatile anesthetics, such as isoflurane, enflurane and sevoflurane, could provide a source for free F^- ions, that would decrease $[SID]$ similar to Cl^- ions. However, even prolonged exposure to these agents do not produce $[F^-]$ concentrations in excess of $60 \mu M$ [13, 14]. Therefore, this will not affect $[SID]$ which is in the mM range. Propofol, however, may have an impact in $[SID]$. When infused for longer periods of time it may give rise to the so-called propofol infusion syndrome. Although causality is subject of debate, propofol is thought to uncouple the respiratory chain and impair beta lipolysis leading to the accumulation of lactate and free fatty acids [15]. This will lead to a decrease in $[SID]$ and an increase in $[A_{TOT}]$ thus leading to acidosis.

29.4 THE EFFECT OF $[H^+]$ ON ANESTHETIC DRUGS

Many anesthetic agents are weak acids or weak bases. While not usually administered in sufficient amounts to influence $[A_{TOT}]$, this does mean that their degree of ionization depends on the three independent variables, and will therefore also vary with $[H^+]$. Unionized fractions of drugs readily diffuse across cell membranes. This contributes to their speed of onset. Similarly, when there are regional acid-base changes that are not directly equilibrated throughout the body, anesthetic agents may become trapped in their effect compartment, for example the extracellular fluid of the brain. Similarly, the ionized fraction of these agents may also be retained in a fetus that has a different acid-base status than the mother, as seen in fetal distress.

Figure 29.2 shows the degree of ionization of commonly used drugs. A number of interesting points can be deduced from this. Looking at opioids, it is obvious that at a normal $[H^+]$, alfentanil and remifentanil will have a much quicker onset than morphine and fentanyl. How-

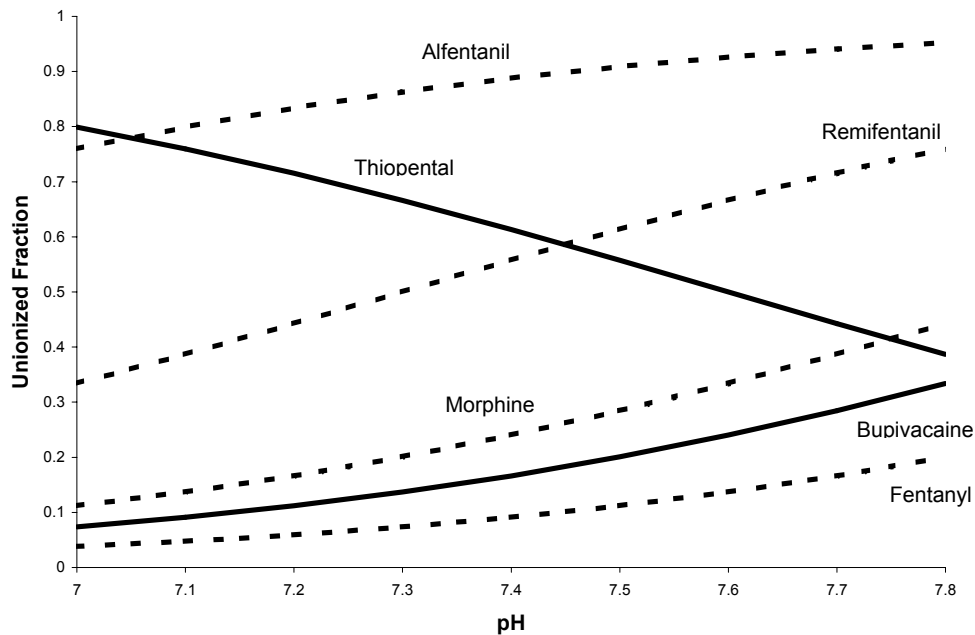


Figure 29.2. The unionized fraction of many commonly used drugs in anesthesia is dependent on $[H^+]$.

ever, the low unionized fraction of the latter means that changing $[H^+]$ from 40 to 60 nM (pH from 7.4 to 7.22), will change that fraction by 35%. Similarly alkalinizing the local anesthetic bupivacaine by adding strong cations using for example $NaHCO_3$, will enhance the speed of onset when for example used for subarachnoid, plexus or epidural blocks. Of note is that the unionized fraction of the hypnotic thiopental will increase with acidosis contrary to the behavior of the other depicted drugs.

As for neuromuscular blocking agents, acidosis potentiates the monoquarternary relaxants (tubocurarine, vecuronium, rocuronium), but antagonizes the effects of the bisquarternary ones (metocurine, pancuronium) [16, 17]. This is thought to be caused by structural changes, but pK_A is unreported. In addition, acid-base imbalance itself interferes with muscle relaxation through various mechanisms, such as alteration in protein binding and acetylcholine release [18]. Interestingly, there are no acid-base effects of the neuromuscular blockade reversal agents neostigmine, a cholinesterase inhibitor [16]. The effects of $[H^+]$ on the new modified gamma-cyclodextrin, sugammadex which reverses neuromuscular blockade by forming a complex with steroidal neuromuscular blocking drugs, has not yet been researched.

As stated above, acidosis reduces cardiac output. This means that onset of anesthesia with volatile anesthetics is shortened while that of intravenous anesthetics is delayed. While cerebral blood flow may actually increase, renal and hepatic blood flow are reduced with increased $[H^+]$

[1]. This means that drugs that are dependent on these organs for their clearance, i.e. the vast majority of anesthetic agents, will be slower to wear off. However, this will not be clinically significant for the initial phases of anesthesia, as these depend on distribution pharmacokinetics.

29.5 ADAPTING TO STEWART

The Stewart approach has yet to gain widespread acceptance within the perioperative medicine community. It started to gain ground in the late 1990's with a renewed interest in acidosis associated with fluid therapy. This gave rise to significant controversy as to whether this acidosis should be viewed as dilution of bicarbonate or a decrease in strong ion difference. Unlike earlier debates, however, the discussion was somewhat less vitriolic [19-31].

As this debate was continued into the new millennium, Bellomo has tried to reconcile camps in stating that it is very difficult to design an experiment that will not simultaneously alter bicarbonate concentration and strong ion difference [28].

This book focuses on the Stewart model. This is not to say that the traditional approach is invalid. In fact, the Henderson equation is one of Stewart's equations. Furthermore, it has been shown mathematically that both theories do not mutually exclude one another [32, 33]. Therefore, it may be perceived that the quantitative approach does not offer new insights or alter management [34]. In addition, it is felt that the approach requires cumbersome calculations [34, 35].

With the advent of information technology and especially personal digital assistants, calculations should not be an object. Further, Stewart's approach may be simplified. The form that may be most useful to anesthesia practice may be the one proposed by Story [36]: This method takes standard base excess (SBE, mEq/L) from a blood gas machine and assesses

1. Sodium/chloride effect ($= [\text{Na}^+] - [\text{Cl}^-] - 38$ (mEq/L)).
2. Albumin effect ($= 0.25 \times (42 - [\text{Albumin} (\text{g/L})])$ (mEq/L)).

It follows that the unmeasured ion effect is

SBE – sodium/chloride effect - albumin effect (mEq/L).

This form was derived from the Fencl-Figge equations [37-39] and their simplification by Balasubramanian [40]. Story extended this simplification by using a rounded and pH-independent calculation factor for albumin contribution, ignoring phosphate. This makes it easy to estimate the individual contribution of factors affecting acid-base balance.

Still, merely lifting obstacles precluding its use does not answer the question why anesthesiologists should use the Stewart approach? There are two very good reasons.

First, using the approach may actually change practice. It may prevent erroneous diagnosis and guide rational therapy. As classic example is the patient with bowel ischemia presenting for laparotomy. The key here is to differentiate between acidosis as a result of massive administra-

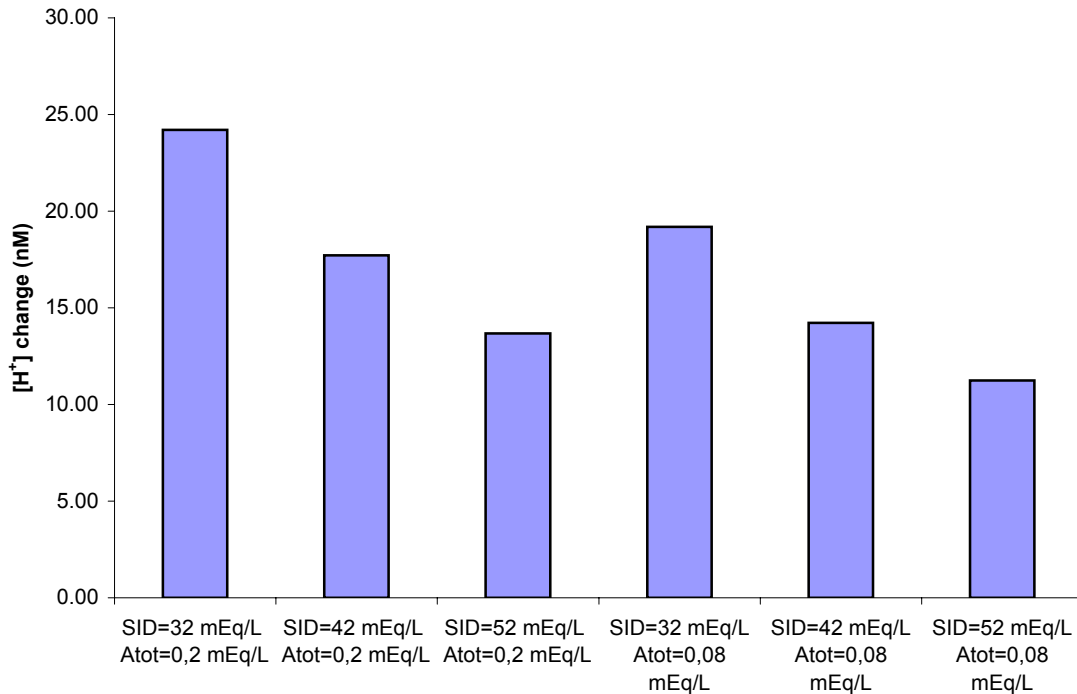


Figure 27.3. Depicted is the response of $[H^+]$ to a change in $P_A CO_2$ from 40 to 60 mmHg. Note that the response alters with differing levels of $[SID]$ and/or $[A_{TOT}]$.

tion of fluids or ischemic lactic acidosis. The latter would lead to more fluid therapy while the former would certainly imply less or different fluids. Stewart's approach would clearly solve this dilemma especially in the face of hypoalbuminemia, which is likely to be present in this ill patient.

Second, the true value of the Stewart approach for anesthesia is that it allows for a fundamental understanding of factors that influence acid-base balance and therefore our patients physiology and pharmacology. It is of great interest that many of these factors can be influenced directly by the anesthesiologist. In fact, many anesthesiologists may already be doing so on a daily basis without realizing so.

This may change however, considering the exponentially increasing number of reviews on the subject in anesthesia journals as well as websites. Even more encouraging is the fact that Stewart's framework is now being taught to anesthesia residents throughout the world and has now hit the textbooks [41, 42].

29.6 MANAGING FLUIDS

As discussed in Chapter 20, administration of fluids exert their acid-base effects by simply mixing and equilibrating with fluids already present in the body. This means that after equili-

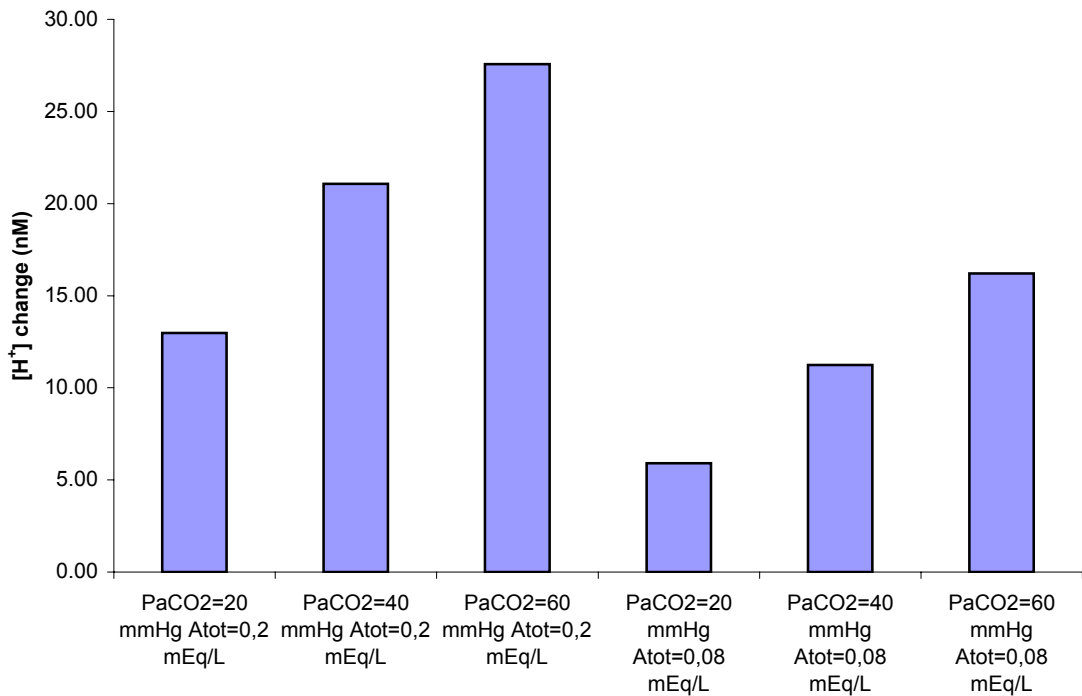


Figure 27.4. Depicted is the response of $[H^+]$ to a change in $[SID]$ from 32 to 42 mEq/L. Note that the response alters with differing levels of $P_A CO_2$ and/or $[A_{TOT}]$.

bration, its independent variables, PCO_2 , $[A_{TOT}]$ and $[SID]$ will therefore be altered towards the values of the administered fluid. This becomes more important as more fluid is administered. Large volumes may be given in anesthetic practice especially for long and invasive surgery to compensate for blood and evaporative losses as well as anesthesia induced vasodilatation.

Scheingraber and colleagues have been instrumental in examining the effects of fluid administration from a Stewartian perspective. They showed that infusion of 30 mL/kg/h of normal saline causes a marked low $[SID]$ metabolic acidosis in the setting of major gynaecological surgery [43]. Later, they showed that the effects of other fluids and different settings can also be accounted for quantitatively, e.g. hemodilution with albumin or HES [44], irrigation in TURP [45] and infusion of 20% albumin [46]. These studies can be regarded as examples of a general principle outlined above. This means that an anesthesiologist should think about fluids in terms of their impact on the independent variables.

Because of respiratory CO_2 equilibration, CO_2 or CO_2 -precursor containing fluids, e.g. $NaHCO_3$ only transiently change PCO_2 . Crystalloids administered in anesthetic practice do not contain weak acids. This means that these fluids decrease plasma $[A_{TOT}]$ which would cause a decrease in $[H^+]$. However, most fluids have a $[SID]$ which is lower than the value of 42 mEq/L for plasma $[SID]$. Usually crystalloid $[SID]$ is actually zero. This means that plasma $[SID]$ will also decrease causing an increase in $[H^+]$. Assuming a healthy patient with normal $[A_{TOT}]$ and

[SID], the reader may verify that at a fluid [SID] of about 24 mEq/L, the alkalinizing effect of a decreasing $[A_{TOT}]$ will approximately offset the acidifying effect of a decreasing [SID]. Similarly, a fluid with a [SID] > 24 mEq will decrease $[H^+]$ while a fluid [SID] < 24 mEq/L will be acidifying [47, 48].

Starch based colloids have an [SID] of zero, just as NaCl 0.9% and D5W. Therefore they will have an acidifying effect. This may even be enhanced by plasma expansion effectively reducing [SID] even more, as may be the case for hypertonic saline. Albumin and Gelatin preparations have [SID] concentrations on the order of 30-50 mEq/L. In addition, they contain $[A_{TOT}]$, which means that the alkalinizing effect of $[A_{TOT}]$ decrease is less pronounced [47].

Blood loss will ultimately lead to lactic acidosis, causing a decrease in [SID]. Interestingly, blood loss also causes a decrease in the [SID], independent of lactate. This has only been shown in an animal model though [49]. Whole blood and packed red blood cells are stored in preservation solutions containing sodium citrate. Citrate is a strong anion that is usually rapidly metabolized by the liver, which renders the effective [SID] positive, causing alkalosis. However, if hepatic metabolism is impaired, the [SID] will be lower. In addition, calcium ions are bound by citrate. In this scenario blood transfusion will be acidifying [50, 51].

The acid-base effects of platelet and fresh frozen plasma transfusion have not been analyzed quantitatively. Platelets are either stored in plasma or in preservation solutions with varying composition. These contain variable amounts of gluconate, acetate and phosphate in addition to about 10 mM of citrate [52]. For platelets in plasma or fresh frozen plasma itself, the story is even more complicated. Analysis shows an [SID] of about 100 mEq/L but there is also a protein content of 50 g/L of which 60% is albumin [53, 54].

29.7 MANAGING PCO_2

PCO_2 is one of the independent variables in Stewart's analysis of acid-base physiology. It is the most directly controllable variable in anesthesia as general anesthesia and a secured airway allows for control of ventilation. However it is important to realize that CO_2 equilibration does not occur instantly. Further, in areas without blood flow, CO_2 equilibration does not occur at all. This means that in situations like adapting ventilation, regional ischemia or cardiovascular collapse, end-tidal CO_2 or even arterial or venous PCO_2 may not correspond to the PCO_2 for the region one is concerned about. The same will then be true for $[H^+]$. In situations where ventilation is less well controlled, such as post emergence extubation and spontaneous ventilation with laryngeal mask, doxapram [55] may be useful to stimulate the respiratory center.

29.8 THE ANESTHESIOLOGIST IS IN CONTROL

Thinking of fluids, ventilation and anesthetics in quantitative terms makes one realize that the anesthetist may profoundly influence [SID], PCO_2 and $[A_{TOT}]$. In turn, these will determine $[H^+]$ and thus influence anesthetic drug pharmacokinetics and patient physiology. If not used

correctly, this influence may lead to a grossly disturbed acid-base balance. On the other hand, it also provides the anesthetist with powerful tools to alter or maintain $[H^+]$ as required.

It is important to realize that different patients may respond differently to acid-base maneuvers. Figures 29.3 and 29.4 show the response of $[H^+]$ to maneuvers that alter PCO_2 or $[SID]$ at different levels of the two other independent variables. For example, in critically ill patients with low $[A_{TOT}]$, $[H^+]$ responds more moderately to a rise in PCO_2 than in those with higher $[A_{TOT}]$. This becomes even more profound if $[SID]$ is higher.

A similar phenomenon occurs with $[SID]$ changes. $[H^+]$ responds much quicker to this when $[A_{TOT}]$ is normal and maximal when PCO_2 is raised as well. The anesthesiologist should be aware of these differences in response. This also implies that balanced infusion fluids may only be balanced for the normal patient.

It should be clear that the armamentarium to control acid-base balance is quite large and may be used to help achieve anesthetic goals. Alternatively, they may serve to correct acid-base disturbances acquired peri- or preoperatively. The fastest of these is PCO_2 manipulation, the second is use of fluids. In spite of the power of these tools, it should not be forgotten that the ultimate cure for an acid-base problem is correcting the underlying disorder.

29.9 CARDIOPULMONARY BYPASS

There are two important causes of acid-base disturbances during cardiopulmonary bypass. One is hypothermia, which is discussed in the next section. The other is pump prime. This fluid mixes with the extracellular body fluids and thus causes $[SID]$ and $[A_{TOT}]$ equilibration towards the values of the pump prime. Currently there is a trend towards the use of miniaturized extracorporeal circuits, using the patients capacitance vessels as the reservoir. This may effectively reduce priming volume to under 500 mL as compared to volumes up to 2 L in conventional systems [56].

It has long been recognized that extracorporeal circulation invokes a metabolic acidosis. The advent of the quantitative approach has settled the dispute on whether this is due to lactate accumulation caused by hypoperfusion or different causes. Using a polygelin pump prime, Hayhoe [57] was the first to quantify acid-base changes caused by cardiopulmonary bypass. He showed that the observed acidosis was largely due to a decrease in $[SID]$ while lactate anion concentration actually fell. The decrease in $[SID]$ was caused by an increase in $[Cl^-]$ and in increase in unmeasured anions. In this study these unmeasured anions were attributed to the ionic charge on the polygelin. Hayhoe [57] also observed a decrease in $[Albumin]$ and thus $[A_{TOT}]$ which partly counteracts the acidifying effects. These findings were confirmed by Alston [58] and Himpe [59]. The latter also showed that the metabolic acidosis could be resolved by using pump prime with a high $[SID]$. By using lactate in his priming fluid, the effective $[SID]$ of the prime rose after lactate was metabolized, thus resolving the initial rise in $[H^+]$. This was confirmed by Liskaser using Plasmalyte 148 as prime [60]. These studies have effectively reduced the acid-base problem of bypass to that of infusion of large volumes of fluids. This means that