Constancy of Blood Carbonic Acid pK' in Patients during Cardiopulmonary Resuscitation*

James A. Kruse, M.D.;† Pankaj Hukku, M.D.;‡
and Richard W. Carlson, M.D., Ph.D.§

Previous studies have suggested that the apparent dissociation constant of blood carbonic acid (pK') may actually vary in acutely ill patients. We prospectively compared the pK' of healthy control subjects to that of patients undergoing cardiopulmonary resuscitation (CPR). Arterial blood obtained from 20 patients undergoing CPR and from 30 healthy volunteers was analyzed for Na+, pH, Pco2, and total CO2 content (tCO2). pK' was calculated from this data, using the Henderson-Hasselbalch equation. Total CO2 was then calculated in the CPR patients, using this equation and the control pK'. Mean pK' was 6.109 ± 0.004 (SEM) for the control group and 6.123 ± 0.007 for the CPR group (p = NS). In the CPR group, calculated tCO2 was not significantly different from measured from tCO2, and the correlation between calculated and measured tCO2 was 0.99. In patients undergoing CPR, pK' does not differ significantly from normal, and tCO2 can be accurately estimated with the Henderson-Hasselbalch equation.

The total carbon dioxide content of serum (tCO2) has become a routine clinical measurement that provides important information regarding acid-base status. The bicarbonate concentration of plasma or serum is closely related to tCO2, and the two terms are often used interchangeably by clinicians. In most hospitals tCO2 is directly measured in the clinical chemistry laboratory, while bicarbonate is typically calculated in the blood gas or emergency department laboratory, using arterial blood pH and Pco2 and solving the Henderson-Hasselbalch equation for bicarbonate (HCO3-):

\[ pH = pK' + \log \left( \frac{[HCO_3^-]}{s \cdot Pco_2} \right) \]

The term s denotes the solubility coefficient for carbon dioxide gas in plasma, which is approximately 0.03 mmol/L/mm Hg at 37°C.1 Since nearly all of the carbon dioxide in plasma is in the form of either bicarbonate or dissolved CO2, tCO2 can be derived from Pco2 and the calculated bicarbonate by the following relationship:1,2

\[ tCO_2 = HCO_3^- + s \cdot Pco_2 \]

These formulas require that the apparent dissociation constant for carbonic acid (pK') be known and be constant. Some investigators have reported that pK' is constant under clinical conditions.3,4 Other studies, however, have concluded that the value of pK' may not be constant, especially under rapidly changing conditions that may characterize the acutely ill.5,7 The literature on this subject does not provide a clear consensus whether pK' can be assumed to be constant under all clinical circumstances.6,16 The issue has substantial clinical relevance. If pK' is not constant, calculated values of bicarbonate or of tCO2 may be inaccurate.

The purpose of this study was to prospectively determine the constancy of pK' in patients undergoing cardiopulmonary resuscitation (CPR). We reasoned that these severely ill and highly unstable patients were suitable to test the hypothesis that pK' may vary in severe clinical states, and that measured and calculated tCO2 may differ significantly.

METHODS

Arterial blood specimens were obtained by one of the investigators from patients in cardiac arrest and undergoing CPR. The samples were obtained either by femoral artery puncture or from an indwelling arterial catheter. Only specimens that were aspirated by one of the investigators during asystole, ventricular fibrillation, or electromechanical dissociation, with CPR (chest compressions) in progress, were included in the study.

In the control group, arterial blood was obtained by radial artery puncture from healthy male and female volunteers aged 20 to 30 years. All blood specimens were drawn into glass syringes that had been rinsed with 1 ml of sodium heparin and the heparin fully expelled. The samples were immediately analyzed in duplicate by the investigators for temperature-corrected pH and Pco2 using an automated blood gas instrument (ABL-2, Radiometer America, Westlake, OH). An aliquot of blood from each sample was centri-
fuged in a vacuum tube and the plasma immediately analyzed in duplicate for tCO2, using the differential pH assay method, and for sodium, using the indirect ion-selective electrode technique (E4A or Astra, Beckman Instruments, Brea, CA). The electrolyte autoanalyzer was calibrated immediately before each assay, and standard quality control measures were used.

**Calculations**

The pK' was calculated from pH, Pco2, measured tCO2 (tCO2m), and the Henderson-Hasselbalch equation as:

\[ pK' = pH - log \frac{tCO2}{0.03 \times Pco2} \]

Using this same equation, calculated total CO2 (tCO2c) was derived for each patient in the CPR group from individual pH and Pco2 values, using the mean pK' of the control group. Since sodium represents the major cation in plasma, ionic strength was estimated from plasma sodium concentration. pK' was then corrected for estimated ionic strength and pH, using previously derived empirical formulas.17

**Statistics**

All values are shown as the mean ± standard error of the mean. Statistics were calculated with both corrected and uncorrected pK'. The pK' of the control group was compared to that of the CPR group, using the two-tailed unpaired t test. The measured and calculated CO2 contents of the CPR group were compared, using the two-tailed paired t test. Product-moment correlation and linear regression analysis were also used to compare measured to calculated CO2 contents. P values less than 0.05 were considered statistically significant.

**RESULTS**

Blood samples were obtained from 20 patients during CPR and from 30 healthy volunteers. The mean pK' of the control group was 6.109 ± 0.004, which compares favorably with previously reported normal values.5,15,18,19,20 Correcting the control pK' for pH and estimated ionic strength did not change the mean or standard error. The mean uncorrected pK' of the CPR group was 6.128 ± 0.008, significantly higher than that of the control group. After correcting this pK' for pH and ionic strength, the mean was 6.123 ± 0.007, which was not significantly different from the control group (Table 1). The measured and calculated CO2 contents of the CPR group were compared using the paired t test. There was no significant difference between tCO2m and tCO2c, regardless of whether or not pK' was corrected for effects of pH or ionic strength. A scatterplot of measured and calculated tCO2 of the CPR group is depicted in Figure 1 and demonstrates a high degree of correlation (r = 0.99, p < 0.00001).

**DISCUSSION**

The study by Trenchard and associates5 was one of the first to question the constancy of pK' in acutely ill patients. They concluded that pK' is not constant under all clinical conditions, particularly in severely ill patients with rapidly changing conditions. However, a subsequent study on acutely ill patients by Austin3 concluded that pK' remains unchanged. Similar findings were reported by De Raedt and colleagues,4 who found close agreement between directly measured PCO2 and calculated PCO2 in patients with acute respiratory insufficiency, assuming a constant pK'. The issue was reexamined by Natelson and Nobel,9 who calculated pK' values in acutely ill patients and found wide variations similar to those previously obtained by Trenchard et al. More recently, Rosanet al10 performed similar studies in children in an intensive care unit and concluded that the value of pK' varies significantly in critically ill patients. Since the Henderson-Hasselbalch equation is applicable only to equilibrium conditions, they argued that this criterion may be satisfied in highly unstable patients. They concurred with Natelson and Nobel that tCO2 should be measured and that calculated values are not reliable for clinical purposes. The recent literature reflects this continuing controversy.5-16

In our study, pK' was determined in patients who were in cardiac arrest and undergoing cardiopulmonary resuscitation with chest compressions and ventilation with a valve-bag system and 100 percent oxygen. Such patients are obviously acutely ill and undoubtedly

| Table 1—Comparison of pK' Data for CPR Patients and Control Subjects |
|-------------------------|-------------------------|
|                        | CPR Patients            | Control Subjects          |
| pH                     | 7.23 (7.02–7.68)        | 7.41 (7.39–7.46)          |
| Pco2                   | 56 (16–119)             | 38 (32–44)               |
| tCO2m                  | 22.2 (10.9–37)          | 24.1 (21–28) mmol/L      |
| Na+                   | 145.2 (123–169)         | 139.5 (134–145) mmol/L   |

Numbers represent means and ranges. pK' is corrected for Na+, temperature, and pH. *p = NS.

![Figure 1](http://journal.publications.chestnet.org/pdFetch.ashx?url=/data/journals/chest/21578/ on 06/24/2017)
undergoing rapid metabolic changes. If pK' is indeed highly variable under unstable clinical conditions, patients undergoing CPR would be expected to represent the epitome of clinical instability and have markedly aberrant pK' values. We found, however, that the pK' in our patients was only slightly different from that of the control group. This degree of variability was not sufficient to significantly alter the tCO₂ calculated from the Henderson-Hasselbalch equation. Our results do reveal, however, that under these conditions pK' can differ significantly from normal if corrections for ionic strength or pH are not made. Even so, since the only known clinical implication of an abnormal pK' is its potential for rendering inaccurate calculations using the Henderson-Hasselbalch equation, no practical significance can be ascribed to this finding.

A variety of factors can explain the alteration in pK' that we and others have observed. Temperature, pH, and ionic strength have been shown to influence pK', and quantitative relationships have been empirically established.21 We have shown that, by correcting for these factors, pK' is not significantly different from control values. A number of surmountable technical problems can lead to discrepancies between the measured tCO₂ and tCO₂ calculated from pH and PCO₂. Arterial blood is most frequently sampled for pH and PCO₂ determination, while tCO₂ is typically assayed from venous specimens. In many institutions the blood gas analysis is performed in a laboratory separate from the main clinical chemistry area where tCO₂ is assayed. Significant differences between arterial and venous values can exist in each of these three measured parameters.21,22 Additionally, if the two specimens are not obtained simultaneously, even relatively short differences in timing could result in alterations in the blood acid-base state, especially in very unstable patients. Inaccuracies in pH and PCO₂ due to suboptimal specimen handling repeatedly have been documented. Such problems include overdilution of the sample with heparin, introduction of air bubbles into the syringe, failure to maintain the sample at 0°C, and undue delays in both transport and analysis.20,23,24 Specimen handling is also important for blood samples submitted for tCO₂ analysis. CO₂ gas can be lost from the specimen, particularly if it is exposed to the atmosphere and the assay is delayed.22,23 Autoanalyzers may have substantial limitations of accuracy at the extremes of tCO₂ concentration (<5 and >40 mmol/L).26 Spurious values of tCO₂ can result from interfering substances such as preservatives in intravenous saline solutions, toxic levels of salicylates and other substances, and abnormal plasma protein concentrations.27,28 Peripheral venous blood samples may not reflect systemic acid-base status, and the use of a tourniquet may further alter pH, PCO₂, and tCO₂.20,22 Other factors may be more difficult to control, even with scrupulous attention to technique. Although bicarbonate and dissolved carbon dioxide account for nearly all of the CO₂ content of plasma, small amounts of carbonic acid, carbonates, and carbamino compounds are not accounted for in the calculation of tCO₂ and may introduce errors.17 Variations in the water content of serum, which are predominantly determined by serum lipid concentration, can spuriously alter the measured tCO₂.14 The solubility coefficient for CO₂ in serum is also influenced by lipid concentration as well as by several other physicochemical phenomena, including solute concentration, protein concentration, and temperature.14,30,38 Finally, even with the most careful calibration and quality control measures, each assay has inherent limitations of accuracy and precision. Calculation of any parameter from two or more measured values will therefore result in multiplication of these inherent inaccuracies.

We have shown that, despite a variety of potential technical and theoretical obstacles, pK' is remarkably constant in normal subjects when precautions are taken to minimize errors due to specimen handling and careful attention is given to the technique of analysis. A statistically significant difference in pK' was demonstrated between the control group and acutely ill patients undergoing CPR. This difference, however, was insufficient to significantly alter total CO₂ content calculated from pH and PCO₂. Further, this difference was not statistically significant after correcting pK' for pH and estimated ionic strength. The fact that the Henderson-Hasselbalch equation can accurately determine total carbon dioxide content in patients during cardiac arrest suggests that bicarbonate and carbon dioxide content can be accurately calculated in critically ill patients in general.

References
8. Austin WH. Further comments on the variation of pK': com-
18 Rispens Pellebarre CW, Eleved D, Helder W, Zijlstra WG. The apparent first dissociation constant of carbonic acid in plasma between 16 and 42.5°C. Clin Chim Acta 1968; 22:627-37
26 Beckman Carbon Dioxide Chemistry Module Operating and Service Instructions. Beckman Instructions 015-556774. Brea, Calif: Beckman Instruments, 1981; 9-1