RELIABILITY OF TRANSCUTANEOUS CARBON DIOXIDE MONITORING IN PREMATURE INFANTS WITH CHRONIC LUNG DISEASE

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SYNOPSIS

We studied 15 premature infants with chronic lung disease (CLD) to evaluate the reliability of using transcutaneous CO_2 (tc PCO_2) measurements in estimating arterial CO_2 ($PaCO_2$) values. The regression equations between tc PCO_2 (Y) and $PaCO_2$ (X) were Y = 0.97 + (1.78) (X) (torr) with r = 0.86 and Sy. x = 13.7 torr, and Y = 2.93 + (1.73) (X) (torr) with r = 0.84 and Sy. x = 15.6 torr for comparisons of 160 arterial samples and 87 capillary samples, respectively. We identified isolated deviant points from serial tc PCO_2 and $PaCO_2$ comparisons. This, together with the observed systematic fluctuations of tc PCO_2 relationship over protracted intervals accounted for the large scatter in the regression data. For the 7 CLD infants studied in time series analysis, there were 5.2 and 6.3% probabilities that this was a random phenomena for two cases. Technical errors or single physiological changes were not associated with these observations. We concluded that tc PCO_2 monitoring is clinically useful in following short-term trends of changing CO_2 status in CLD infants. However, the large scatter in our regression data would preclude using the regression equation to estimate $PaCO_2$ from measured tc PCO_2 in these patients.

INTRODUCTION

Infants with chronic lung disease or bronchopulmonary dysplasia (BPD) are prime candidates for extensive transcutaneous CO_2 monitoring. Hypercarbia, which develops during passive oxygenation of patients with pulmonary edema, during assisted ventilation of those with refractory hypoxia, during weaning from

assisted ventilation, and during apneic episodes, is a frequent problem in such patients but may not be adequately predicted from the combination of transcutaneous O_2 (tc PO_2) monitoring and arterial blood gases (1). Moreover, acceptance of tc PCO_2 monitoring generally is encouraged by the strong correspondence between $PaCO_2$ and tc PCO_2 measurements [reported r values for $PaCO_2$ and tc PCO_2 comparisons in newborn populations range from 0.79 to 0.98 (2)], the associated conservation of patient blood, relative absence of risk, convenience, and continuous nature of tc PCO_2 data. On the negative side, most reports describe tc PCO_2 values as 1.3 to 1.4 times greater than $PaCO_2$ values, so that clinician must a) decide tc PCO_2 information is unique, requiring independent interpretation or b) develop schemes for estimating $PaCO_2$ from tc PCO_2 values. Tremper equate tc PCO_2 and $PaCO_2$ provided temperature and calibration biases are taken into account (2,4). Alternately, Brunstler et al. (5) and others (6,7) have suggested that the tc PCO_2 instrument display be adjusted to $PaCO_2$-like values termed "estimated $PaCO_2$" or "adjusted to PCO_2" based on the equation:

$$\text{adjusted tc } PCO_2 = \frac{\text{measured tc } PCO_2 - \text{intercept}}{\text{slope}}$$

where the slope and intercept are derived from regression analysis of $PaCO_2$ and tc PCO_2 determinations on a population of premature and term infants with mixed diagnoses.

We decided to retrospectively evaluate the reliability of tc PCO_2 as an estimate of $PaCO_2$ and as a trend monitor of chronic lung diseased patients during the course of their therapy. We compared the regression analysis of their tc PCO_2 with blood CO_2 tensions in both arterial and capillary specimens. We questioned how "estimated $PaCO_2$" data based on regression analysis from a mixed newborn population compared with measured blood CO_2 tension during long-term therapy of these infants. Our findings are described in this report.

METHODS AND MATERIALS

Subjects of the study (n = 15) were all premature, sick infants diagnosed as having bronchopulmonary dysplasia. They were treated in the Neonatal Intensive Care Unit of University Hospital during an eight-month interval and had arterial and capillary blood gas determinations performed as part of their routine management. Although all were being treated for BPD, they had a spectrum of concurrent pathologies, including anemia, sepsis, hypoglycemia, patent ductus arteriosus, intracranial hemorrhage (Grade IV), seizures, hyperbilirubinemia, and hypocalcemia. The average gestational age was 29 ± 3 wk (X ± SD). The average birth weight was 1053 ± 361 g. Ventilator regulation and FIO_2 adjustments for the infants studied were based on $PaCO_2$, PaO_2, and tc PO_2 measurements.

One hundred acutely ill premature newborns (including the 15 subjects who later developed BPD) formed the reference group whose tc PCO_2 and $PaCO_2$ comparisons were used to derive the population regression data with which to calculate "estimated $PaCO_2$" values on BPD infants. Diagnosis for the reference group patients was diverse but most had hyaline membrane disease. For regression analysis, we used only one randomly selected transcutaneous and blood CO_2 tension comparison made on each infant. This reference group's least squares regression relationship between tc PCO_2 (Y) and $PaCO_2$ (X) was: $Y = -2.8 + (1.86)(X)$ (torr), $r = 0.86$, and $S_{y.x} = 12.9$ torr as reported elsewhere (8).

Sixteen acutely ill premature neonates without diagnosed BPD who received tc PCO_2 for routine management constituted the control group for the randomness time series analysis (9). $PaCO_2$ and tc PCO_2 comparisons (n = 39) from the control group were limited to one set per day every third day for each infant. Three or fewer comparisons per infant were used. The interval studied was 23 d. These comparisons were "random". They demonstrated that any time dependent instrument, operator, or other method related factors did not account for the time series findings with the BPD patient data.

We determined tc PCO_2 with three different carbon dioxide monitors of the same design (model TCM 20, Radiometer America Inc., Cleveland, OH 44145). Two point calibrations were performed at the beginning of each monitoring session with dry CO_2 standard gases (5% and 10% CO_2 in N_2). In vivo drift was determined at the end of each monitoring session. The maximum allowable drift was 4 torr. Calibrations and patient measurements were made with the electrode temperature at 44°C. Heater power and tc PCO_2 measurements were recorded by an external recorder.

We determined blood gases in duplicate on two blood gas analyzers (Model 813, Instrumentation Laboratory, Inc., Lexington, MA 02173). Standard assay protocols and quality control routines were used (10). Imprecision of $PaCO_2$ measurements as determined by analysis of tonometered blood or commercial control solutions is approximately 3% CV (11).

For BPD patients, a total of 247 blood gas measurements (160 by arterial sample and 87 by capillary sample) were compared with tc PCO_2 concurrently monitored. The arterial blood samples were collected from umbilical, radial or dorsalis pedis arteries. Capillary blood samples were collected from the heel area according to standard protocol. The term $PaCO_2$ will be used for blood CO_2 tensions in either arterial and capillary specimens throughout this report unless noted otherwise. Temperature corrections were not made on either transcutaneous or blood gas data.

There were 221 separate tc PCO_2 monitoring sessions on the BPD patients. The mean duration per session was about 3 h (range: about 1 to 5 h). Transcutaneous PCO_2 electrodes were placed on the shoulder, chest, abdomen or thigh.

Electrode placement site, monitoring duration, quality control and calibration data for blood gas analyzers and monitors, drift, patient information and patient respiratory therapy were recorded, analyzed and reviewed for significance.

RESULTS

To evaluate how reliably tc PCO_2 could be used as an estimate of $PaCO_2$ in chronic lung disease patients, we reviewed 1) the regression relationship of tc PCO_2 and $PaCO_2$ segmented into arterial and capillary groups; 2) the relative agreement of serial tc PCO_2 in the seven infants most frequently monitored during this study; and 3) the distribution of $PaCO_2$: tc PCO_2 ratios for paired measurements.

Table 1 shows the regression analysis of arterial and capillary blood $PaCO_2$ with concurrently measured transcutaneous CO_2 tensions. The measurements were all accepted as valid; i.e., no quality control deviations were apparent to technologists or nurses working with the patients or instruments.

The serial simultaneous tc PCO_2 and $PaCO_2$ determinations on the two most frequently monitored infants are plotted in Figures 1A and 1B. The tc PCO_2-

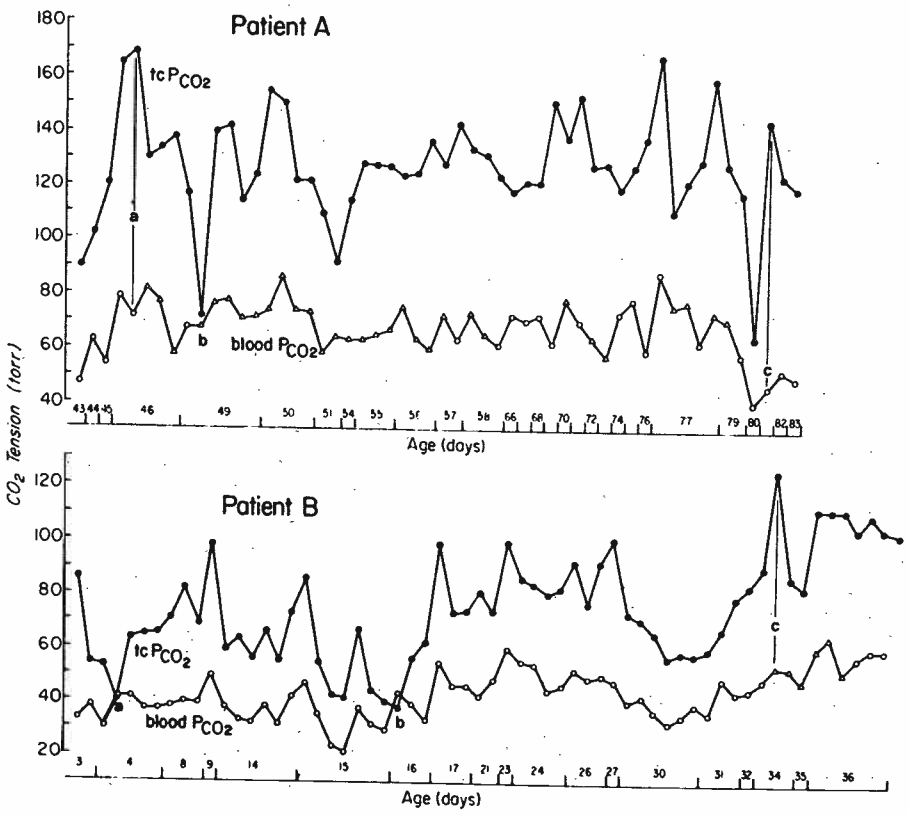

Figure 1
Transcutaneous PCO_2 and blood PCO_2 comparisons made on two chronic lung diseased premature infants (patients A and B) plotted in time sequence by day. Arterial blood specimens are noted with (O); capillary blood specimens with (Δ). The three most unusual comparisons for each patient are labeled a, b and c.

TABLE 1: REGRESSION OF ARTERIAL AND CAPILLARY BLOOD $PaCO_2$ WITH CONCURRENTLY MEASURED TC PCO_2 TENSIONS IN PREMATURE INFANTS WITH CHRONIC LUNG DISEASE[1]

	BLOOD SAMPLE	
	Arterial	**Capillary**
n	160	87
Regression line	tc PCO_2 = 0.97 + 1.78 ($PaCO_2$)	tc PCO_2 = 2.93 + 1.73 ($PaCO_2$)
r	0.86	0.84
Standard deviation of intercept	4.0 torr	7.1 torr
Sy.x	13.7 torr	15.6 torr
Observed tc PCO_2 range	38 — 169 torr	48 — 160 torr
Observed $PaCO_2$ range	20 — 93 torr	31 — 87 torr
Mean tc PCO_2	83 torr	102 torr
Mean $PaCO_2$	46 torr	58 torr
Mean of ratios $PaCO_2$/tc PCO_2	0.57	0.58

[1]Fifteen infants were studied

blood PCO_2 difference (ΔCO_2, or tc: blood bias) showed a gaussian distribution for these patients. For patient A, Figure 1, the CO_2 = 59 ± 18 torr ($\bar{X}$ ± SD). For patient B of that figure, the CO_2 = 32 ± 14 torr. No reason was found to disregard any of the extreme positive or negative values. The extremes of ΔCO_2 (e.g. sets marked a, b and c) were not statistically associated with the fluctuations in patient body temperature, hematocrit, coincident arterial pH, PaO_2, FIO_2, the presence or absence of forced ventilation, patient age, sex or weight. Of the six comparisons labeled (a), (b), or (c) in Figure 1, four were made with abdominal tc electrode placement. Concurrent heater power tracings were not remarkable indicating tissue perfusion was unperturbed and probe attachment satisfactory. The duplication of blood gas analyses, specimen integrity notes, calibration, maintenance, and other control data were consistent with acceptable test performance. The transcutaneous measurement drift in vivo was less than 4 torr in each instance.

To evaluate the long-term reliability of tc PCO_2 for estimating $PaCO_2$ in individual CLD patients, we examined the data from the seven most frequently monitored CLD patients. We calculated the difference between "estimated $PaCO_2$" and observed $PaCO_2$, where "estimated $PaCO_2$" was derived by inserting the observed tc PCO_2 value in the regression equation for the NICU population in general i.e. tc $PCO_2 = -2.8 + (1.86)(PaCO_2)$ (8). Figures 2A and 2B illustrate the differences for the same infants whose data are shown in Figure 1. Of the 54 comparisons for infant A, 31% were different by more than 10 torr. Of the 61 comparisons for infant B, only 8% were different by more than 10 torr. The estimates were more likely to be high for infant A while most were low for infant B.

The influence of time on these matched comparisons was examined. For 2 of 7 the patients, the sequential estimated $PaCO_2$ values deviated from observed $PaCO_2$ with a unidirectional bias for protracted intervals. The probability that these single direction deviations could be random were only 5.2 and 6.3% for the two worst cases. The other 5 on whom there were enough comparisons for valid statistical analysis were as random as the control group. Figures 1A and 2A illustrate a random series of tc PCo_2 and $PaCO_2$ observations and of differences between estimated $PaCO_2$ and corresponding $PaCO_2$. Figures 1B and 2B illustrate a series with 6.3% probability of being random. In it there are more low estimates of $PaCO_2$ from day 15 through day 26 than at other times in the series.

Figure 3 shows the frequency distribution of the $PaCO_2$: tc PCO_2 ratio for all comparisons (n = 247) on the 15 infants with chronic lung disease. The group distribution of ratios was 0.57 ± 0.10 ($\bar{X}$ ± SD). The $PaCO_2$: tc PCO_2 ratios for the infants A and B in Figure 1 were 0.54 ± 0.09 and 0.59 ± 0.11 respectively. They have representative means and precision for the individual data sets. Among all comparisons there are 6 extreme sets with ratios $\geq$ 0.8. These extremes are derived from measurements on 5 infants.

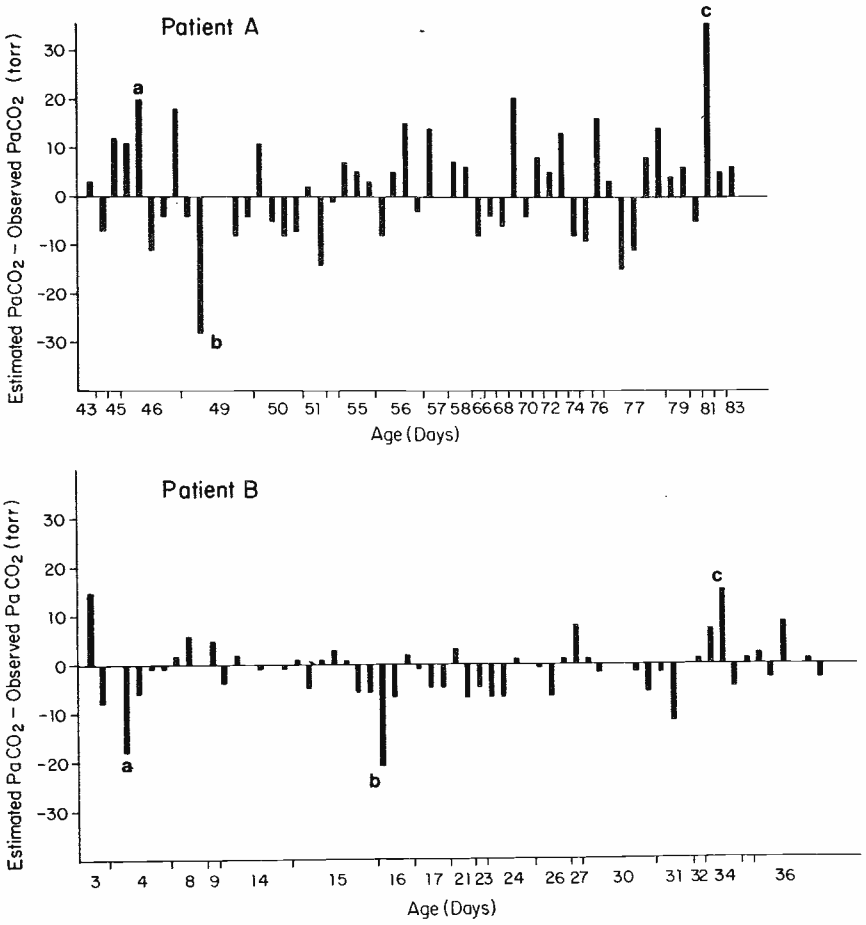

Figure 2
Time series representation of the deviation of estimated $PaCO_2$ from observed $PaCO_2$ on two chronic lung diseased premature infants (patients A and B) over protracted time periods. Points a, b and c denote three extreme deviants of $PaCO_2$ estimation in each patient. See also Figure 1.

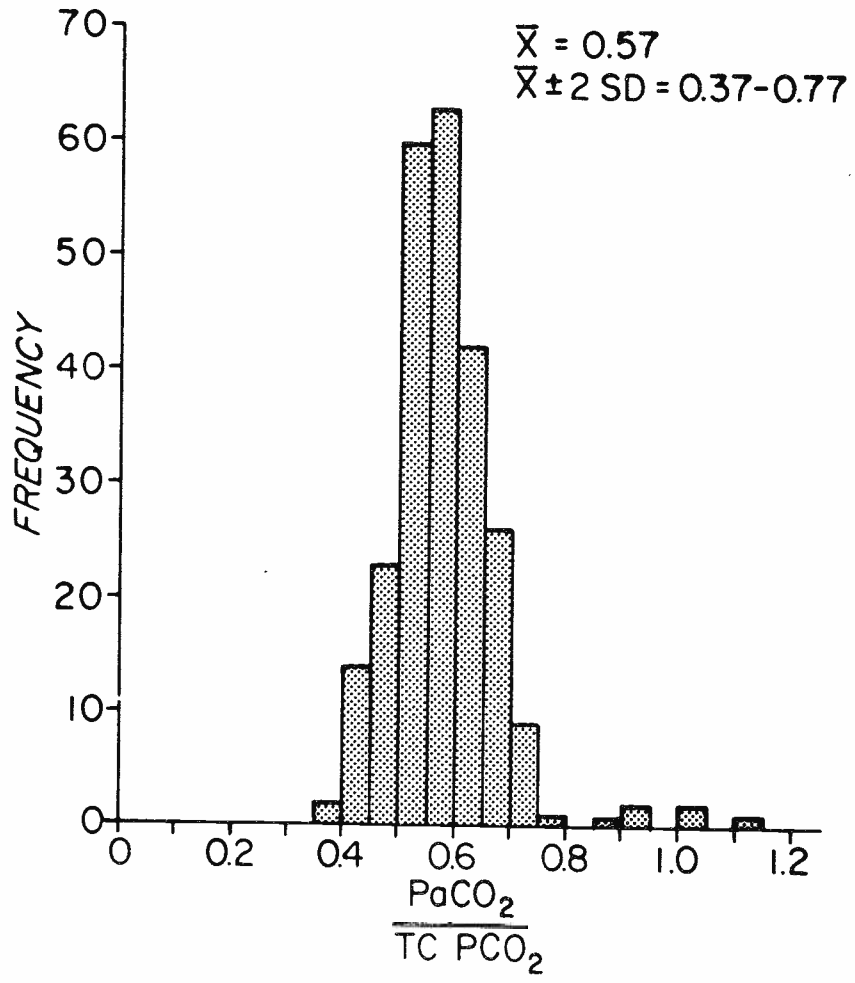

Figure 3
Frequency distribution of $PaCO_2$ to tc PCO_2 ratios in fifteen chronic lung diseased patients from 247 simultaneous measurements.

DISCUSSION

Most correlations of $PaCO_2$ with tc PCO_2 reported in the literature for mixed newborn populations are comparable to our finding with arterial or capillary specimens from chronic lung diseased infants (r = 0.86 and 0.84, respectively). Hazinski and Severinghaus cited 15 clinical trails of transcutaneous PCO_2 sensors with correlations coefficients of 0.80 — 0.98 (2). The y-intercepts and slopes of reported regression equations vary greatly as might be expected among studies using different patient populations and instruments. Again, our data are not remarkable. Transcutaneous CO_2 tensions are generally greater than blood tensions because heat increases local skin metabolism about 7%/°C to produce more CO_2 and raises the anaerobic temperature coefficient of blood PCO_2 by about 4.5%/°C. However, it is interesting that the regression equations reported here are not significantly different from our observations on a mixed population of acutely ill premature newborns made under the same circumstances of NICU operation in this institution (12). This suggests that for transcutaneous PCO_2 measurements infants with chronic lung disease need not be considered separately from the general NICU population.

However, the standard error of the estimates reported here as 13.7 torr and 15.6 torr, for arterial and capillary specimens respectively, are large. Scatter in regression studies has not been generally quantitated in clinical evaluations. Only values reported for newborns are 6.3 torr (13) 6.2 torr (7) and 4.2 torr (5). As there is no difference between the data for the two specimen types here, blood collection probably did not contribute to this scatter. Moreover, our measurements are well controlled in that our blood gas instruments do not have a capillary versus macro sampling bias, blood gas analyses are duplicated to confirm results, our staffs are continuously indoctrinated to note exact times of blood sampling and blood analysis, electrode drift is within the acceptable limits, and the strip chart recorders continuously monitor heater power and tc PCO_2 etc. Thus the technical factors contributing imprecision to this study were limited. We believe that it is representative of the tc PCO_2 and $PaCO_2$ comparisons likely to be made for daily care in a tertiary hopsital's NICU.

Figures 1 and 2 reinforce the suggestion that the wide confidence intervals about our regression lines accurately reflect tissue and blood CO_2 tension status in a sick premature population where weaning is the major use of monitoring. First, there were transient intervals of non-randomness in the tc PCO_2 to $PaCO_2$ relationship measured. This may be expected in a typical neonatal intensive care setting. Bhat et al reported that the Δ CO_2 (tc PCO_2—$PaCO_2$) in infants was effected by hypoxia and acidosis but not blood pressures so long as they were above 30 mmHg (14).

Tremper et al (3) reported that the ΔCO_2 among adults in shock, defined by a cardiac index < 1.5 L/min.M², averaged 61 torr compared with 23 torr for hemodynamically stable patients. Brunstler et al found that only systolic blood pressures below 15 mmHg was consistently associated with deviant transcutaneous and blood comparisons (n = 76) on 24 infants, 23 of whom were mechanically ventilated (5). In their experience, body temperature (33.5—38.1°C), hematocrit (28—65%), and pH (6.89 to 7.61 units) were not implicated. In their regression study the standard error of the estimate was 4.15 torr. (excluding data derived on patients with low blood pressure) Finally, the existence of variable tc PCO_2: $PaCO_2$ relationships specifically in chronic lung disease infants is suggested by Philip who quotes Peabody as reporting that infants with bronchopulmonary dysplasia may require a correction factor (e.g. 2.0) which is different from other children's (e.g. 1.3 or 1.4) (15). While we believe intervals of hypoxia, acidosis, edema, anemia, and/or hypermetabolic states might account for the transient deviant blood and transcutaneous comparisons we described, regression analysis failed to statistically identify a single explanation. Moreover, our patients were in physiological disequalibrium as they were almost all undergoing mechanical ventilation at the time of data collection. There may be transient tissue CO_2 build up associated with incomplete tissue washout (16) or lung inefficiency.

A second explanation of our regression data scatter is also illustrated in the serial plots of figures 1 and 2 as major isolated deviations (e.g. points a, b and c). Hazinski and Severinghaus had noted the occurrence of "single extreme and deviant points" in several published studies but considered them atypical and suggested that they could be eliminated from performance data evaluations (2). We agree that this type of observation does not reflect instrument performance but consider it the outcome of physiological phenomena. In a working NICU, we believe such "poor" tc PCO_2 correlations with $PaCO_2$ should be expected by virtue of the patient clientele.

Several authors (5,6,7) suggested that regression equations for matched tc PCO_2 and $PaCO_2$ comparisons be used to derive "estimated $PaCO_2$" (or "adjusting tc PCo_2") values from measured tc PCO_2. Adjusting instrument output with this kind of in vivo calibration is attractive as it would circumvent inevitable clinician confusion in dealing with the two gas tension values simultaneously. Figure 2 demonstrates that the incidence of "poor" $PaCO_2$estimations varies among patients. The frequency of estimate errors greater than 10 torr for infant A was 31%. This argues against using such system for automatic $PaCO_2$ estimation, because it is impossible to screen out inappropriate infants when we do not fully understand the precipitating phenomena. Secondly, the magnitude of exceptional residuals (to +33 torr) illustrated by points a, b and c in series of Figure 2 also suggests a grave clinical hazard in in vivo calibration. Finally, the time dependent shift in quality of $PaCO_2$ estimates on a given baby cannot be dealt with in a working NICU unless the physiological causes of poor correlation are taken into account. In our population, the observed scatter in the regression studies precludes using tc PCO_2 to estimate $PaCO_2$. For example, a measured tc PCO_2 of 83 torr would correspond to estimated $PaCO_2$ values between 33 and 59 torr using the prediction bands with 95% confidence for the regression equation tc PCO_2 = 0.97 + (1.78) ($PaCO_2$).

The time series analysis was done to demonstrate the pitfall of relying on tc PCO_2 measurements for too precise an estimate of $PaCO_2$ in CLD patients and/or the inaccuracy of assuming a simple CO_2 can be used to estimate $PaCO_2$ for very long. The lack of randomness in the time series also suggests that unidentified physiological events which may last for several days are influencing the predictability of blood PCO_2 from transcutaneous PCO_2 measurements. These phenomena may be different from those associated with the extreme points. However, in the series for patient B, Figure 2, the extremes a, b and c occur during intervals of apparent "non-randomness".

Figure 3 illustrates the distribution of $PaCO_2$: tc PCO_2 ratios to be experienced with this populations. We suggest that while the trends in changing tc PCO_2 demonstrate shifting $PaCO_2$ status, a change in the ratio of paired tc PCO_2 and $PaCO_2$ values is the simplest bedside indicator that the aberrant physiological phenomena we have alluded to above is occurring. It is a useful in vivo "quality control" indicator, not in the sense of identifying error per se but in the sense of masking shifts in the relationship of measureable tissue PCO_2 to $PaCO_2$. A prospective study might help to identify combinations of clinical factors which change the expected tissue: blood PCO_2 status.

Contrary to our expectations, the regression studies of transcutaneous and blood PCO_2 for infants with chronic lung disease were not significantly different in r, y intercept, slope, or scatter from earlier data derived for acutely ill premature infants. The data from CLD infants did demonstrate time, dependent, nonrandom shifts in the tc PCO_2: $PaCO_2$ relationship and interinfant differences in the frequency of such phenomena. The findings are consistent with the proposition that transcutaneous PCO_2 measurements are a useful short-term trend monitor. They suggest that in vivo calibrations may sometimes be of limited value or misleading. The expected scatter in our comparisons of tc PCO_2 and $PaCO_2$ is unexplained. In view of it, we suggest that a population regression line be developed for each clinical care setting into which tc PCO_2 is introduced in order to assess the relative reliability of estimating $PaCO_2$ from tc PCO_2 data.

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