

Temperature correction of blood gas and pH measurement - an unresolved controversy

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The process of blood gas and pH measurement involves preheating the arterial blood sample to normal body temperature (37 °C) prior to measurement of pH, partial pressure of oxygen (pO_2) and partial pressure of carbon dioxide (pCO_2).

This ensures that results reflect in vivo temperature condition. A minority of patients who require blood gas analysis do not have a normal body temperature and are, because of their illness or treatment, either hypothermic or hyperthermic.

Under such circumstances it seems intuitively appropriate to take advantage of the algorithms commonly provided within blood gas analyzers that allow measurements made at 37 °C to be mathematically corrected to the actual body temperature of the patient.

In fact, there has always been controversy surrounding the validity of this intuitive approach, with resulting lack of consistency in application of the “temperature correction” facility available on blood gas analyzers. In this literature review article the detail of temperature correction will be described, along with relevant physiological issues surrounding the effect of temperature on blood gas parameters that inform the controversy.

Recent clinical study examining the variability in the use of temperature correction and its overall efficacy, in terms of patient outcome, will also be discussed. But first, by way of introduction to the topic, there follows a brief discussion of incidence and causes of abnormal body temperature among the critically ill – the patient group most likely to require blood gas analysis.

Abnormal body temperature among the acutely/critically ill

The unquestionable dilemma for clinical staff as to whether or not they should apply temperature correction to blood gas results obviously only occurs in the context of hyperthermia or hypothermia during an acute or critical illness that demands blood gas monitoring. So what is the extent of the problem?

A recent study of 10,962 critically ill adults [1] found the incidence of mild hyperthermia (core temperature 38.3-39.5 °C) and moderate to severe hyperthermia (>39.5 °C) to be 21 % and 5 % respectively.

The same study found that 10 % of patients were mildly hypothermic (in the range of 35.0-36.0 °C), 5 % were moderately hypothermic (in the range of 32.0-35.9 °C) and 1 % were severely hypothermic (core temperature <32 °C).

The causes and effects of hyper- and hypothermia among the critically ill are recently reviewed [2].

The causes of hyperthermia include: fever due to infection, sepsis (the two most common causes), heat stroke, malignant hyperthermia, endocrine emergencies (severe thyrotoxicosis, pheochromocytoma, adrenal crisis) and brain injuries (trauma, tumors, subarachnoid hemorrhage, etc.) that affect the thermoregulatory center of the hypothalamus.

The causes of hypothermia include severe sepsis, cold exposure, endocrine emergencies (e.g. severe hypothyroidism) and overdose of some drugs.

Quite separately from the pathological and environmental causes of hypothermia, an ever-growing number of critically ill patients are deliberately cooled – a care strategy known as therapeutic hypothermia (TH) (or targeted temperature management) that slows metabolism and thereby potentially prevents or minimizes extension of hypoxic brain injury in critical illness.

Currently, TH is sufficiently established for it to be considered a standard of care for only two groups of patient: adults who have been resuscitated from cardiac arrest and neonates with hypoxic ischemic encephalopathy [3], a sequela of birth asphyxia.

There is, however, considerable evidence to suggest that TH has clinical application beyond these two patient groups and those suffering any one of the following life-threatening conditions might be temporarily hypothermic because of the TH treatment they are receiving: myocardial infarction, ischemic stroke, traumatic brain injury, hepatic encephalopathy and septic shock [3].

Induced hypothermia may also be used during cardiac and brain surgery [4, 5].

It seems that it is the increasing use of TH in recent years that has rekindled research interest in addressing the controversy surrounding temperature correction of blood gas and pH values.

Background physiology – effect of abnormal body temperature on blood gas parameters

Henry's fundamental law of gases determines that the solubility of oxygen and carbon dioxide in water varies with temperature; decreased temperature causes increased solubility of both oxygen and carbon dioxide.

This general relationship between temperature and gas solubility is reflected in human physiology [6]. Hypothermia is associated with decreased $p\text{CO}_2$ and $p\text{O}_2$, consequent on increased solubility, and hyperthermia is associated with increased $p\text{CO}_2$ and $p\text{O}_2$, consequent on decreased solubility [7].

The temperature-dependent change in $p\text{CO}_2$ secondarily affects blood pH; hypothermia is associated with increased pH and hyperthermia with decreased pH [7].

Two other effects of change in body temperature are relevant to blood gas analysis: shifts in the oxyhemoglobin dissociation curve; and altered oxygen consumption and carbon dioxide production.

Decreased body temperature (hypothermia) causes a leftward shift in the oxyhemoglobin dissociation curve, i.e. increases hemoglobin affinity for oxygen, whereas increased body temperature (hyperthermia) causes a rightward shift, i.e. decreases hemoglobin affinity for oxygen [8].

The change in hemoglobin affinity for oxygen induced by change in body temperature has the theoretical potential of impeding oxygen delivery to tissues in hypothermia and impeding binding of oxygen to hemoglobin at the lungs in hyperthermia.

The sigmoidal shape of the oxyhemoglobin curve determines that the potential for these body temperature effects is greatest in those who are hypoxemic ($pO_2 < 10$ kPa) [8].

Hypothermia is associated with reduced oxygen consumption and carbon dioxide production, whereas hyperthermia is associated with increased oxygen consumption and carbon dioxide production.

What is the magnitude of change in pH, pCO_2 and pO_2 induced by hypothermia/hyperthermia?

One way of answering this question is to compare blood gas values measured at 37 °C with values obtained after mathematical correction of these measured values to the actual temperature of the patient.

Bisson and Younker [8] provide the following data generated by a blood gas analyzer, which reveals

measured values and the temperature-corrected values of the same sample, assuming the patient was hypothermic (actual body temperature 30 °C) and hyperthermic (actual body temperature 40 °C).

Design of blood gas analyzers only allows for samples to be pre-warmed to a single temperature, 37 °C prior to measurement. The temperature-corrected values, which can be obtained by simply inputting the patient's temperature to the analyzer, are the true *in vivo* values of the hypothermic/hyperthermic patient.

The formulae used in blood gas analyzers to correct blood gas values to patient's actual body temperature were devised over 40 years ago by a combination of theoretical modeling and experimental verification that is discussed in some detail in a much referenced review article [9].

The following are the correction formulae for pH and pCO_2 used in Radiometer analyzers:

$$pH(T) = pH(37) - [0.0146 + 0.065 \times (pH(37) - 7.40)] [T - 37] \quad [10]$$

$$pCO_2(T) = pCO_2(37) \cdot 10^{[0.021 \cdot (T-37)]} \quad [11]$$

where, pH(T) = patient's temperature-corrected pH
 pH(37) = patient's pH measured at 37 °C
 $pCO_2(T)$ = patient's temperature-corrected pCO_2
 $pCO_2(37)$ = patient's pCO_2 measured at 37 °C
 T = patient's core temperature (°C)

The temperature correction formula for pO_2 is considerably more complex and takes into account

Measured values at 37 °C (NORMOTHERMIA)	Temperature-corrected values assuming a body temperature of 30 °C (HYPOTHERMIA)	Temperature-corrected values assuming a body temperature of 40 °C (HYPERTHERMIA)
pH 7.405	pH 7.508	pH 7.362
pCO_2 43.0 mmHg (5.72 kPa)	pCO_2 30.6 mmHg (4.07 kPa)	pCO_2 49.7 mmHg (6.6 kPa)
pO_2 94.2 mmHg (12.5 kPa)	pO_2 61.6 mmHg (8.2 kPa)	pO_2 112.8 mmHg (15 kPa)

The temperature-corrected values are those that would have been obtained by measurement if the sample had been warmed not to 37 °C but to the temperature of the patient (in this case 30 °C and 40 °C).

the effect of body temperature on the patient's oxygen dissociation curve and concentration of hemoglobin and dyshemoglobin (methemoglobin and carboxyhemoglobin).

The formula and its theoretical derivation is described by Siggaard-Andersen [12, 13].

The controversy – “pH-stat” versus “alpha-stat” hypothesis

It is not disputed that “temperature-corrected” values are the true values for arterial blood flowing through the body of a hypothermic or hyperthermic patient; the correction formulae are well validated.

However, the clinical significance of the corrected values and therefore the validity of temperature correction remain controversial. The controversy, so far as pH and $p\text{CO}_2$ are concerned, hinges on two opposing hypotheses: the “pH-stat” and “alpha-stat” hypothesis [7].

Those who adopt a policy of temperature correction are effectively subscribing to the “pH-stat” hypothesis and those who adopt a policy of not applying temperature correction are effectively subscribing to the “alpha-stat” hypothesis.

The controversy was first expressed as a clinical problem by anesthesiologists responsible for the acid-base management of patients who are deliberately cooled during cardiopulmonary bypass surgery [14].

The issue for them was (and still is): should ventilation be adjusted to achieve a temperature-uncorrected $p\text{CO}_2$ of 40 mmHg (5.3 kPa) (the alpha-stat strategy) or adjusted to achieve a temperature-corrected $p\text{CO}_2$ of 40 mmHg (the pH-stat strategy)?

The second of these two options (the pH-stat strategy) assumes that the ideal pH and $p\text{CO}_2$ of blood is around 7.40 and 40 mmHg, respectively, irrespective of body temperature.

The alpha-stat strategy, by contrast, assumes that the

acid-base change induced by hypothermia (apparent respiratory alkalosis) and hyperthermia (apparent respiratory acidosis) is appropriate, and by extension, pH 7.40 and $p\text{CO}_2$ 40 mmHg is only ideal when body temperature is 37 °C.

The reference ranges that are used to interpret blood gas values are derived from healthy individuals with a normal body temperature (37 °C). There is no equivalent data relating to hypothermic/hyperthermic patients; we simply do not know with certainty what “normal” acid-base and oxygenation status is at body temperatures other than 37 °C. Hypothermia and hyperthermia are by definition abnormal (pathological) states.

Scientists grappling with the problem have sought evidence from the animal world by examining the acid-base changes during natural body temperature changes (e.g. hypothermia associated with hibernation) and normal acid-base status of cold-blooded animals.

This provides conflicting evidence, as although most animals effectively adopt an alpha-stat strategy, others adopt a pH-stat strategy.

Overall, the literature [6-9] suggests greater approval for the alpha-stat hypothesis (i.e. no temperature correction) than for the pH-stat hypothesis. (i.e. temperature correction). The argument for a policy of not correcting pH and $p\text{CO}_2$ depends on the groundbreaking work of Reeves and Rahn, who first proposed the alpha-stat hypothesis in the 1970s [15, 16].

This work challenged the conventional wisdom at the time, which was that the ideal pH of 7.40 and $p\text{CO}_2$ 40 mmHg applied irrespective of body temperature (this is in essence of course what we now call the pH-stat hypothesis).

The alpha-stat hypothesis holds that the imperative of acid-base homeostasis is to maintain intracellular pH at the pH of neutrality (pN), that is when hydrogen ion concentration equals hydroxyl ion concentration $[\text{H}^+] = [\text{OH}^-]$. This state of electrochemical neutrality is, according to the hypothesis, optimal for cellular function.

Since pN is a temperature-dependent parameter it follows that, if the hypothesis is correct, intracellular pH changes and therefore extracellular pH changes with temperature change.

Central to the hypothesis is the notion that the mechanism of the maintenance of intracellular pH at the pH of neutrality is constancy of the degree of dissociation (α) of the functional imidazole group of the amino acid histidine present in all proteins. The necessity for α to stay constant gave the hypothesis its name, alpha-stat.

Temperature correction of pO_2 - also controversial

The pH-stat versus alpha-stat controversy highlights the difficulty of interpreting pH and pCO_2 (i.e. acid-base balance) in patients with abnormal body temperature. It is the paucity of knowledge surrounding the physiological effect of abnormal body temperature on acid-base balance that underpins this controversy.

The same paucity of knowledge applies to the physiological effect of abnormal body temperature on blood and tissue oxygenation, with resulting difficulty in correctly interpreting temperature-corrected pO_2 .

For example, for a patient with normal body temperature, it is well established that, so long as normal hemoglobin and cardiac output is assured, a pO_2 equal to or greater than 60 mmHg (8 kPa) ensures adequate tissue oxygenation. According to Shapiro there is no equivalent data that allows definition of minimal pO_2 for tissue oxygenation in hypothermia [17].

He argues that although temperature correction provides us with the “true” *in vivo* pO_2 value, since it is unclear what it should be at that temperature, there is little value in knowing what it is. He states that “temperature corrected pO_2 values do not improve our ability to make clinically relevant decisions”.

A conflicting view is held by Bacher [6] who seems to imply that temperature-corrected pO_2 results can

be validly interpreted using the pO_2 reference range generated in individuals with normal body temperature.

He states: “to maintain true pO_2 in the normal range the measured pO_2 should always be corrected for current body temperature in hypothermic patients”. So here are two conflicting views: one suggesting temperature correction of pO_2 is unhelpful and the other that it is useful and necessary.

Current practice relating to temperature correction of blood gas results is variable

Despite a considerable body of evidence from animal experimental study in support of the alpha-stat hypothesis, which has tended to shift opinion away from recommendation of temperature correction and towards recommendation of no temperature correction, there remains no detailed, explicitly expressed, expert consensus on the issue, and consequently actual practice remains inconsistent.

Bisson and Younker surveyed intensive care clinical staff in the UK and Australia and found differing opinions on best practice. Some thought temperature correction not necessary if the patient was near-normothermic (in the range of 36.3-37.3 °C), some always recorded temperature-corrected results, irrespective of the patient’s temperature; and others only ever recorded temperature-uncorrected results.

Even within a single institution, policy relating to temperature correction varies, as evidenced by a very recent study conducted at a US hospital [18]. This was a study of 122 patients who all received therapeutic hypothermia (target body temperature 33 °C) following resuscitation from cardiac arrest, and therefore required frequent blood gas monitoring.

In total 1223 blood gas analyses were performed on these 122 hypothermic patients. Temperature correction of blood gas results was never determined in 72 (59 %) patients; made available in 1-74 % of blood gas results from 17 (13.9 %) patients; and made available in >75 % of blood gas results from 33 (27 %) patients.

In a sentence that reflects the currently unresolved controversy, the authors of this study explicitly state that it is “unknown if arterial blood gas measurements should be temperature corrected”.

Recent study addressing the controversy

It seems that the only way of resolving the controversy surrounding temperature correction might be empirical, clinical outcome study. If application of the pH-stat (temperature correction) hypothesis results in a demonstrably more favorable outcome than application of the alpha-stat (no temperature correction) hypothesis, then blood gas values should presumably be corrected for temperature.

Therapeutic hypothermia for specific clinical conditions has allowed such an empirical approach that has been exploited in two recent studies [18, 19].

Terman *S et al* [18] utilized the variability in temperature correction of blood gas policy at their hospital (outlined above) to determine if availability of temperature-corrected blood gas values had any impact in terms of neurological outcome among their 122 study patients who had been resuscitated from cardiac arrest.

They compared outcome of the 72 patients for whom temperature-corrected values were not available with the outcome of the 33 patients for whom temperature-corrected values were available.

In essence they found that after adjusting for covariates knowledge of corrected blood gas values had no effect on outcome. The study thus provides evidence that for the management of hypothermic patients resuscitated from cardiac arrest, temperature correction of blood gases is not necessary.

Aziz and Meduoye [19] identified 16 clinical studies conducted between 1992 and 2009 that had all been designed to answer the question: Is pH-stat or alpha-stat the best technique to follow for patients deliberately rendered severely hypothermic in order to arrest heart activity during cardiac surgery.

Their analysis of these 16 studies revealed conflicting results, but allowed the conclusion that best evidence suggests alpha-stat is most appropriate for adults and pH-stat is the most appropriate for pediatric patients.

In other words, for adult patients rendered severely hypothermic during cardiac surgery it would seem most appropriate to monitor acid-base status using blood gas results uncorrected for body temperature, whereas for pediatric patients, undergoing similar treatment during cardiac surgery, it is most appropriate to use temperature-corrected blood gas results.

Summary

The controversy over whether it is necessary to temperature-correct blood gas results derived from patients with abnormal body temperature remains unresolved, and as a result, practice varies. Current expert opinion is that in most circumstances it is not necessary, but detailed explicit guidance remains lacking.

It is undisputed that in patients with abnormal body temperature corrected blood gas results differ in a predictable way from temperature-uncorrected results. It is essential that if a policy of temperature correction is adopted, both temperature-corrected and temperature-uncorrected results are reported for clinical staff to interpret.

Potentially unsafe clinical decisions will be made if temperature-corrected results are wrongly assumed to be temperature-uncorrected results. Further research is required to better define the effect of abnormal body temperature on acid-base homeostasis and oxygen uptake and delivery in critical illness.

The results of such research will allow more accurate interpretation of blood gas results in patients with abnormal body temperature and better define the circumstances in which temperature correction of blood gas results is necessary.

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