Physiological effects of hyperchloraemia and acidosis

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The advent of balanced solutions for i.v. fluid resuscitation and replacement is imminent and will affect any specialty involved in fluid management. Part of the background to their introduction has focused on the non-physiological nature of ‘normal’ saline solution and the developing science about the potential problems of hyperchloraemic acidosis. This review assesses the physiological significance of hyperchloraemic acidosis and of acidosis in general. It aims to differentiate the effects of the causes of acidosis from the physiological consequences of acidosis. It is intended to provide an assessment of the importance of hyperchloraemic acidosis and thereby the likely benefits of balanced solutions.

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Hyperchloraemic acidosis is increasingly recognized as a clinical entity, a new ‘enemy within’, that had gone otherwise unnoticed for decades. Although any associated morbidity may be subtle at present, there is a trend in current evidence to suggest that hyperchloraemic acidosis may have adverse consequences which may be circumvented by the use of balanced solutions. These consequences, both theoretical and clinical, may result from hyperchloraemia, acidosis, or both. There is some evidence of hyperchloraemia causing problems, but at present the clinical relevance is uncertain. The literature does appear to be unified in stating that acidosis results in adverse physiological effects but usually fails to differentiate between those effects attributable to the cause of the acidosis and the acidosis itself. Neither is there differentiation between types of acidosis. A popular current focus is on the benefits of the Stewart hypothesis in assessing acid–base balance, but there is relatively little published discussion on whether acidosis per se is of physiological harm and if so whether the nature or the magnitude of the acidosis is relevant.

Several baseline statements can be made.

(i) Extracellular acidosis derived from hypoperfusion or from hypoxia is a sign of organ distress and is known to be associated with increased morbidity and mortality. The mechanism causing the acidosis, such as hypoperfusion or hypoxia, if unchecked or untreated will result in damage.

(ii) Profound intracellular acidosis is deleterious to cell metabolism in its own right, but the magnitude of the required acidosis is ill defined.

(iii) In many clinical circumstances, acidosis is the direct consequence of a physiological disturbance and it is the physiological disturbance rather than the acidosis to which damage should be attributed.

We aim to review the current knowledge of the effects of the exogenous acidosis caused by hyperchloraemia. To do this, the known cellular effects of acidosis will be reviewed, as will the literature on the effects of two types of endogenous acidosis that are associated with severe exercise and with ketoacidosis.

Hyperchloraemia and acidosis

Three factors have increased recent interest in hyperchloraemic acidosis: the observation that normal saline causes hyperchloraemic acidosis; the renewed interest in the Stewart hypothesis; and the advent of new balanced solutions. For more than 50 yr, normal saline solution has been used as intraoperative, resuscitation, and maintenance fluid therapy and for a multitude of clinical conditions including trauma and diabetic ketoacidosis (DKA). Yet, it is neither normal nor physiological, a fact that has been acknowledged by physiologists for more than 100 yr. Isolated tissues and cell cultures succumb rapidly in saline. Unprotected cells and even organs cannot function...
in that milieu. Yet infused liberally into a human, saline appears relatively problem free. At least two factors influence this difference.

(i) An isolated heart immersed in saline has no buffering mechanisms and so the extracellular and intracellular milieu will be directly influenced by the perfusing solution.

(ii) In vivo, the effects are reduced by the immediate effective dilution in a large extracellular volume and the formidable buffering capability of the extra- and intracellular compartments.

It is clear that relatively small volumes of saline (30 ml kg\(^{-1}\) h\(^{-1}\)) produce a hyperchloraemic acidosis with this acidosis derived from the hyperchloraemia and not from other causes.\(^{32, 88, 89, 91, 106}\) The nature and longevity of the acidosis has been described by Bruegger and colleagues\(^{17}\) who showed an acidosis developing intraoperatively which then cleared spontaneously within 24 h. The mechanism for this can be explained using the Stewart hypothesis through the strong anion effects of chloride.\(^{10}\)

Clinically, studies show similar outcomes when comparing saline with other fluids.\(^{105}\) In the SAFE study, the administration of saline did not differ from albumin.\(^{98}\) It is important to note the latter is formulated in saline and that albumin may confer some acidosis in its own right. There was less improvement in acidosis in an albumin resuscitated group than a saline group, but more hyperchloraemia and more acidosis in the albumin group; however, no clear clinical detriment.\(^{8}\) The authors commented that the acidosis was more reflective of the volume rather than the type of fluid used.

Adverse effects from saline use, including gastrointestinal symptoms have been described. Volunteers given saline had more gastrointestinal symptoms ranging from nausea and vomiting to abdominal pain when compared with non-saline-based fluids. It has been suggested that these effects may be centrally mediated and this is supported by another study suggesting that volunteers had altered ability to perform tasks, in addition to nausea and drowsiness, following 50 ml kg\(^{-1}\) of saline given over more than 1 h.\(^{110}\)

In animals, a range of effects are seen. Pigs developed pyloric dysfunction, rats ‘intestinal injury’, and there is a suggestion of effects on splanchic perfusion.\(^{69, 99, 109, 110}\) Chloride is implicated in impaired renal function with hyperchloraemia resulting in less naresis than might be expected after a saline infusion.\(^{109}\) There is less of a diuresis when compared with Hartmann’s and 5% dextrose solutions. This may reflect the toxicity of the respective solutions and the amount of free water, particularly in normovolaemic healthy volunteers where the responses to alterations in osmolarity are impressive.\(^{22, 23}\)

Chloride may influence the renal vasculature. Renal vasoconstriction during dehydration is associated with altered tubular chloride reabsorption, though this has not been confirmed. There is also some evidence that renin secretion is mediated by chloride, based on the observation that sodium chloride causes increases in arterial pressure whereas sodium bicarbonate did not.\(^{55}\) Other renal effects include hyperkalaemia, noted in renal transplant patients, and postulated to be due to transmembrane shifts secondary to hyperchloraemia, but with no effect on renal function.\(^{72}\)

Hyperchloraemia may also influence coagulation. In aortic aneurysm surgery, it was shown that although there were no major differences between using saline and Ringer’s lactate, there was an increased blood product requirement in the saline group.\(^{105}\) This has been observed in several studies.\(^{39, 65, 105}\) Thromboelastography indicates more effects on coagulation and platelet function with saline when compared with a balanced salt solution.\(^{13}\)

Saline may also result in the release of more inflammatory markers.\(^{52–54}\)

In summary:

(i) hyperchloraemic acidosis is seen with the use of large volumes of saline and is almost certainly due to the chloride load;

(ii) there appear to be some side-effects associated with saline use, but to date these have not translated into clinically important outcomes, though this may be through lack of data.

To completely review the implications of the exogenous acidosis caused by hyperchloraemia, it is necessary to review the physiological effects of acidosis.

**Acidosis**

In discussing acidosis, differentiation must be made between the extracellular and the intracellular pH. Intracellular pH is fundamentally important to cell function. Extracellular pH does not indicate the intracellular pH, but is in equilibrium with the intracellular milieu and is important as it can be manipulated to alter the latter. Importantly, the extracellular compartment has various mechanisms by which excess acid can be controlled which assist the cell in maintaining its pH.

Most endogenous acidosis is generated by a specific causative mechanism that may be the source of morbidity in its own right. A major problem establishing the physiological effects of acidosis \textit{per se} is the almost impossible task of segregating the physiological effects of acidosis from those of underlying pathological processes, such as sympatho-adrenal stimulation, altered electrolyte flux, hyperlactataemia, and other commonly associated metabolic disturbances. It should be noted that correction of the underlying pathological cause results in correction of the acidosis and improved outcome. However, it is unusual for correction of the acidosis to reverse the cause or to influence outcome. Failure to reverse the underlying pathological cause for acidosis, whether hypoxic, ischaemic, or due to mitochondrial dysfunction, is universally associated with poor outcome. The crucial question is therefore ‘how damaging is acidosis in its own right?’.
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The clinical effects of acidosis

There is little doubt that in cellular and isolated preparations, acidosis causes changes in muscle contractility and, specifically, in cardiac muscle contractility. In vivo, however, the origin of the acidosis is pivotal. Cells may be exposed to metabolic acidosis developed from within, or from elsewhere in the body. Respiratory acidosis will influence extra- and intracellular pH as carbon dioxide moves freely into cells. Conversely, exogenous metabolic acidosis is distinct from the normal metabolic activities of the cells. However, clinical application of in vitro data is flawed. In nature, acidosis inevitably results in an integrated host response that encompasses far more than the metabolic functions of the cell. These include buffering and compensatory mechanisms, ion flux and channel activity, lactate shuttles, and far greater responses such as those of the sympathetic nervous system. All of these contribute to cell homeostasis.

There are several considerations that make the literature hard to interpret.

(i) There is tremendous species variation and some of the published studies are non-mammalian, such as trout and turtles.44 61–64 74 94
(ii) The nature of much of the isolated tissue work was such that it was carried out at relatively low temperature, some around 28°C. A surprising amount of the cardiac contractility work falls into this category.42 73 82
(iii) The pH produced, whether metabolic or respiratory, has often been in the order of 6.8 or even lower. 25 85
(iv) Some of the studies induced ischaemia or hypoxia in order to produce acidosis.56 79 81
(v) Some studies induced intracellular and others extracellular acidosis.2 46 47 77

Acidosis and contractility

Acidosis and hyperkalaemia have both been shown to influence cardiac contractility and tend to reduce it. In humans, these effects may be counterbalanced by increased catecholamine and calcium production. In the early work based in turtles and trout, significant cross-species variation in response to acidosis cannot be excluded. Significantly, turtles can naturally cope with prolonged hypoxia and cold both of which will affect their response to acidosis.44 61–64 74 94 There are, however, some similar reports from mammals.

A range of preparations have been used in these studies with a complex array of results. In isolated heart preparations, acidosis reduces tension development and the effects of pH on isolated human cardiac muscle contractility are linear for either metabolic or respiratory mechanisms.28 A number of studies showed a 50% reduction in contractility albeit at a pH of 6.82 and at low (room) temperature.42 73 82 In rat hearts, there was minimal change in contractility with pH but very major alterations when there was hypercapnoea.96 In rabbits, a pH change from 7.4 to 6.3 resulted in a 50% reduction in contractility.25 In skinned cells, lactate depresses muscle activity at a pH of 7.0, albeit at 24°C.3 21 Later studies show diminished effects of induced acidosis in skinned or intact muscle fibres.20 Curiously, lactic acid appears to provide partial protective effect from potassium-depressed muscle contraction in skeletal muscle.30 71

Acidosis and inotropes

The impaired response to catecholamines during acidosis is a commonly observed phenomenon. In isolated tissue, there is reduced beta responsiveness at pH 6.6.80 85 Studies in dogs have highlighted a number of phenomena. The cardiac index responds to dopamine at normal pH but not when acidic95 and exogenous acidosis using hydrochloric acid altered responsiveness to inotropes.49 A diminished ventricular performance at a pH of 7.26 was attributed to reduced response to catecholamines.7 Conversely, it can be shown that the contractility changes caused either by potassium or by acidosis are offset by increased catecholamine production.35 58 This concept was supported by the observation in rabbits that although hypercapnoeic acidosis caused a 16% decrease in contractility, a thoracolumbar epidural increased this depression considerably by blocking sympathetic activity.68 The depression of myocardial contractility produced by respiratory acidosis is also significantly increased after beta-blockade implying a systemic catecholamine effect.102 In the pulmonary vasculature, however, acidosis increases the response to norepinephrine.16

In the gut, acidosis appears to block the effects of norepinephrine on vasoconstriction through a selective α2 effect26 and reduce muscle responsiveness in mesenteric vessels.34 86 Interestingly, bicarbonate correction of sepsis-induced acidosis in humans did not correct the haemodynamic abnormalities.29 From the plethora of in vitro work, it can be seen that the observation of acidosis causing impaired contractility is simplistic and that there may be significant differences between mild and severe acidosis and between species.

Intra- and extracellular acidosis

In isolated rat hearts combined intra- and extracellular acidosis resulted in more profound effects on tension development than intracellular acidosis alone, even when there were minimal effects on the final developed pressure.47 This conflicts with the evidence from an isolated Langendorff preparation where a perfusate pH change from 7.5 to 7.0 had profound effects on both contractility and function through intracellular acidosis.45 This mechanism has been investigated in isolated myocytes. A decrease in pH affects sarcoplasmic reticulum calcium by reducing Ca2+ spark frequency so that, as intracellular pH decreases, there is calcium channel opening in the
sarcoplasmic reticulum that may result in a negative inotropic effect.\(^5\)

An interesting finding is that infusion of lactic acid may cause an extracellular acidosis but does not necessarily cause intracellular acidosis in living rats.\(^{112}\)

In anaesthetized dogs, lactic acidemia decreased contractility with reduction in both stroke volume and arterial pressure but partly as a consequence of raised pulmonary artery pressures.\(^{97,98}\) Conversely, a study, also in dogs, showed little effect of lactic acid on cardiac output.\(^4\) In lambs, a change in pH from 7.4 to 6.97 was associated with a 45% decrease in cardiac output, due to a decrease in stroke volume secondary to increased systemic vascular resistance.\(^{36}\) However, in a study of dogs with Escherichia coli endotoxaemia and progressive lactic acidosis, there was no change in left ventricular contractility.\(^{78}\) To add further complexity to the situation, the role of lactate per se may be important. In haemorrhagic shock in dogs in which dichloroacetate was used to block lactate, the subsequent reduction of lactate availability impaired cardiac function. This suggests an important protective role for lactate.\(^6\) Indeed, some workers have shown that the myocardium prefers lactate to other substrates.\(^{32,60}\) In a classic paper by Poole-Wilson,\(^{79,81}\) it was demonstrated that although severe acidosis impaired myocardial function, a mild acidosis seemed to be beneficial in recovery on return of oxygenation.

Respiratory acidosis

The effects of respiratory acidosis have also been examined. Carbon dioxide can move relatively freely into the cell, and there has been some suggestion that this may result in both more rapid and more profound effects than occur with an equivalent metabolic acidosis. Both respiratory and metabolic acidosis depress the action potential plateau and prolong repolarization of the cell membrane. Intracellular acidosis tends to reduce calcium flux which may be adequate to explain contractility changes.\(^{37}\) This is similar in isolated human muscle.\(^{27}\) Most of these studies are in isolated cells or in isolated organs and the situation in the whole animal may be different.

In piglets, respiratory acidosis increases contractility significantly at a pH of 7.0 due to increased systemic epinephrine and norepinephrine release.\(^{15,57}\) In anaesthetized humans, hypercapnoea affects predominantly the systemic vascular resistance rather than contractility.\(^{51}\) The predominant effects of hypercapnoea appear to be through the renin–angiotensin system.\(^{33,84}\) There has also been the suggestion that respiratory acidosis causes reduced skeletal muscle contraction in humans.\(^{101}\)

What is clear is that the genuine role of acidosis on contractility has not been as convincingly established, as is often stated, especially when the fully integrated effects in intact mammals are evaluated.

Teleology

Acidosis is a common occurrence in mammals. Indeed, any burst of exercise results in an acidosis and the ability of mammals to recover from extreme exercise and from pathophysiological acidosis of respiratory and metabolic origin is impressive.

The pH and lactate in blood returning to the heart in a severely exercised athlete are very low and very high, respectively. If a low pH and hyperlactataemia was damaging to the heart and muscles, they should demonstrate increasing dysfunction as exercise continued. Such a position would be disastrous for the hunting or hunted mammal and would result in cardiac failure being a regular occurrence during exercise! If acidosis had a major impact on contractility either in heart or muscle, humans would never have evolved the ability to perform high-intensity exercise as this would be lethal. In exercise, muscles do eventually fail but only at very low pH values. Although the disease state may be different, there is little doubt that normal mammalian physiology is designed to deal with acidosis, at least initially. It is worth considering this approach further through the rigorously studied model of exercise physiology.

Exercise: a physiological model of acidosis

Although there is no doubt of the association between acidosis in critical illness and poor outcome, there is little convincing evidence of causation. Exercise physiology provides the perfect model to study the effects of acidosis in isolation from underlying pathological processes and allows its evolutionary role to be considered.

Under the anaerobic conditions of exercise, hydrolysis of ATP is in excess of its production through the phosphorylation of ADP and so net hydrogen production occurs with a resultant acidosis.\(^{83}\) The breakdown products associated with this acidosis are the progenitors of cell energy recovery and the magnitude of the acidosis has been measured in several studies.\(^{24,92}\)

In one study of the transition between rest and exercise, volunteers had a pulmonary artery catheter inserted and mixed venous measurements made while exercising on a cycle ergometer. During the first 4 min of exercise, the mixed venous measurements demonstrated a decrease in the partial pressure of oxygen (\(Pv_o2\)) by 3.3 kPa; oxygen saturation (\(Sv_o2\)) decreased by 40%; partial pressure of carbon dioxide (\(Pv_co2\)) increased; and the pH decreased to around 7.3.\(^{24}\)

In a study of \textit{severe} exercise using a cycle ergometer, femoral vein sampling demonstrated that: the pH decreased to 7.1; \(Pv_co2\) increased to 10.5 kPa; oxygen saturation (\(Sv_o2\)) was 15%, and lactate increased to >12 mmol litre\(^{-1}\). This clearly illustrates association between a ‘bolus’ of acid and other metabolites returning from the lower body and \textit{enhanced} myocardial performance—contrary to the more common perception of acidosis associated with
impaired cardiac function. Indeed, exercise-induced acidosis almost certainly has an anti-arrhythmic effect. 76

Severe i.m. acidosis with pH<6.7 is associated with a reduction in contractility. However, a decrease in pH of 0.3 from normal has minimal effect. This fits with a cycling study where there were only small effects on muscle contractility at an i.m. pH of 6.8. 11 19 90

Furthermore, force can be recovered while the muscle is still acidotic. 31 67

In vitro preparations at physiological temperatures seem to show that pH has far less effect on contractility than previously thought, 75 111 and the effects of carbon dioxide are also attenuated at these temperatures. 18 67 107 108 111

When considering the metabolic function of the cell, there is some evidence that the redox potential influences metabolic activity with increasing metabolites increasing the aerobic metabolic activity. 50 87

Recent information suggests that both acidosis and catecholamines protect against potassium-induced contractility depression in skeletal muscle in exercise. The combined effect is greater than either individual effect. 30

Again, during mild acidosis, there are clear parallels between these effects and those seen in cardiac muscle. 79 81

Acidosis may be helpful in exercising muscle by decreasing the permeability of the chloride channel that facilitates conduction of the action potential 77 and by effecting calcium release after depolarization.

In summary:

(i) acidosis does reduce contractility, but the association is less clear than is often supposed;
(ii) it is unclear what pH changes are required to produce these effects on contractility, but almost certainly they would need to be severe and probably at the extreme end of the spectrum seen clinically.
(iii) the correlation and association between observed extracellular pH and intracellular pH is complex and not measurable. Intracellular pH may be the more relevant.
(iv) acidosis may be protective against the effects of other changes such as those of potassium.
(v) the combined effects of acidosis concurrent with associated metabolic alterations in the whole organism may be markedly different from those seen in isolated preparations.

Diabetic ketoacidosis: a pathological model of acidosis

There are a number of studies that have examined the effects of acidosis during DKA. This disease state provides a unique perspective of pathological acidosis as the precipitating trigger is often of trivial physiological importance compared with the metabolic derangement that ensues. It is often held that patients with DKA present much earlier than those with hyperosmolar hyperglycaemic state (HHS) due to the earlier development of symptoms and signs.

The main difference between DKA and HHS is the presence or absence of ketoacidosis. The presence of ketoacidosis in DKA is associated with more abdominal discomfort and vomiting, earlier clinical presentation, less dehydration, and better prognosis than HHS.

The clinical literature regarding cardiac function during ketoacidosis is revealing. Maury and colleagues 66 reported echocardiographic information from 10 patients who presented with ketoacidosis over a 6 month period. Seven had DKA, three had alcoholic ketoacidosis. For all patients, the left ventricular fractional shortening was normal at the time of presentation and once the acidosis had resolved, after 24–36 h of treatment. Three of the patients had pH values of 6.9, 6.76, and 6.75. A comparison of patients presenting with hyperglycaemia, with and without ketoacidosis, 40 found that in the ketotic group, myocardial performance was enhanced during the acute phase and later returned to normal. In the non-ketotic group, it remained normal throughout. Both groups had normal lactate, creatinine phosphokinase, and cardiac enzyme levels throughout the study period.

Retrospective and prospective studies of bicarbonate therapy during DKA have consistently shown no benefit in correcting acidosis even at pH values of <7.1. 38 41 59 70 100

Several of these studies showed greater morbidity among patients in whom the acidosis had been corrected by the administration of bicarbonate.

Positive effects of acidosis

No discussion of the effects of acidosis in mammals could be complete without mention of the Bohr effect, described in 1904. 12 48 The oxyhaemoglobin dissociation curve of red blood cells is heavily influenced by acidosis. Both pH change and local carbon dioxide levels will alter haemoglobin’s (Hb) affinity for oxygen. The shape of the curve dictates that in regions of high oxygen tension, such as the lungs, uptake of oxygen is similar through a large pH range, whereas the bound carbon dioxide is readily off-loaded. When blood reaches areas of low oxygen tension, the shift in the curve shape has a very profound effect on oxygen off-loading.

In athletes, venous blood returning from exercising muscles may have a pH as low as 7.0 with impressively high levels of lactate of up to 10 mmol litre⁻¹. In vitro studies show an increase in tissue oxygen tension of 6% for each 1 mmol litre⁻¹ increase in lactic acid concentration. 14

The additional oxygen extraction resulting from the pH change in exercising muscle may account for up to 60% of the oxygen availability. This acid-induced extraction maintains and ‘promotes’ aerobic metabolism in exercise. 13

Such an elegant mechanism allows increased oxygen delivery to match local demands. Increased energy utilization results in increased production of hydrogen ions and
carbon dioxide and, when the anaerobic threshold is breached, lactate. The combination of lactic acid and high carbon dioxide reduces pH. This is seen in any situation where energy utilization and tissue oxygen requirements exceed delivery and are an evolutionary mechanism for increasing oxygen release from Hb. The magnitude of this effect is increasingly impressive when saturations and tissue oxygen tension ($P_O_2$) levels are low; paradoxically, a pH change when the $P_O_2$ is high has little effect on saturation as it occurs on the flat part of the dissociation curve.

In normal tissues, oxygen tensions ($P_O_2$) of 5.3 kPa are common while during exercise 2.6 kPa and lower are frequently seen. This equates to saturations of 70% in the first instance and substantially lower, as $P_O_2$ decreases due to the steep nature of the dissociation curve at these tensions.

There is plenty of information indicating the magnitude of the effect of a change in pH. At pH 7.4, with tissue $P_O_2$ of 5.3 kPa and saturation of 70%, a decrease in pH by 0.2 will result in a decreased saturation to 60% (Fig. 1), with a predictable increase in oxygen release. The effects are even greater at lower tissue $P_O_2$ values (Fig. 2). It is this mechanism that is probably protective in cardiac failure as it allows greater oxygen availability to hypoxic tissues. The magnitude of these effects can be demonstrated in a static model of ‘optimization’ based on Figure 1. For the purpose of illustration in this worked example, the values have been rounded down to figures that are easier to work with. However, not only are the principles the same but the magnitude of effect may be larger than that illustrated here.

(i) In a patient with Hb level of 10 g dl$^{-1}$, oxygen saturation of 100% and cardiac output of 5 litre min$^{-1}$, oxygen delivery ($DO_2$) = 670 ml min$^{-1}$.
(ii) If cardiac output is increased by 20% to 6 litre min$^{-1}$, the $DO_2$ increases to 804 ml min$^{-1}$ (an increment of 134 ml min$^{-1}$).
(iii) If the oxygen saturation at tissue level is 70%, then 30% of the delivered oxygen has been liberated. Thus, from an increase in cardiac output of 20% with change in $DO_2$ of 134 ml min$^{-1}$, the additional oxygen made available at tissue level each minute is 40.2 ml (30% of 134 ml). Some of this will be used in extracardiac work.

If we consider a similar patient with cardiac output of 5 litre min$^{-1}$, Hb 10 g dl$^{-1}$, oxygen saturation of 100%, and $DO_2$ of 670 ml min$^{-1}$:

(i) at a tissue pH of 7.4 and $P_O_2$ of 5.3 kPa, the Hb saturation will be 70%. Thus of the 670 ml of oxygen delivered every minute, 30% is released equivalent to 201 ml;
(ii) the pH-based Bohr effect is large at the $P_{50}$ and thus if the pH drops to 7.2, the Hb saturation will decrease to below 60%;
(iii) if we are conservative and use the figure of 60%, this results in 40% of the delivered oxygen being liberated (268 ml) at pH 7.2 vs 30% (201 ml) at pH 7.4, a difference of 67 ml min$^{-1}$.

In short, as a result of the Bohr effect, a decrease in pH of 0.2 results in a greater increase in oxygen delivery than a 20% increase in cardiac output. To produce a comparable increase in $DO_2$, cardiac output would need to increase by 30%.

From an evolutionary perspective, this is ideally suited to oxygen uptake in oxygen-rich areas and oxygen unloading in oxygen-deprived tissues. Such a situation is conducted by the presence or absence of energetic metabolites, lactate, acid, and carbon dioxide. In a study of patients with congestive heart failure, the administration of bicarbonate reduced systemic and myocardial oxygen consumption, increased mixed venous carbon dioxide, but most impressively increased myocardial lactate production. The inference is that the bicarbonate administration caused reduced oxygen availability and increased anaerobic activity.
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Conclusion
From the discussions above, it is clear that the laboratory and clinical evidence are complex, inconsistent, and often at odds. This is hardly surprising given that, as a complex organism, we have evolved a multitude of interacting physiological systems designed to maintain homeostasis during a variety of challenges. Isolation of these systems under laboratory conditions provides a ‘clean’ environment for study, but renders the experiments deficient of the complex interactions that would come into play in the organism as a whole. The application of evidence across species should be done with caution given the differing adaptations that will have evolved to protect against inconsistent environmental challenges.

There is a trend in emerging evidence that hyperchloraemia and hyperchloraemic acidosis have subtle, but potentially significant, physiological, and clinical sequelae. Although the acidosis, or pH change, is often quoted as the cause, this assumption may be erroneous; it may genuinely be the aberrant electrolyte state that is the culprit.

With regard to acidosis, the clinical literature is remarkable in its lack of conclusive evidence to support the perception that the acidosis itself is a detrimental state in need of direct correction. There is plenty of evidence that the mechanism causing acidosis such as hypoxia, ischaemia, and mitochondrial poisoning are damaging and eventually lethal if not reversed. Correcting the cause is not in contention but correcting the effect, acidosis, may be. The ‘basic’ sciences provide a multitude of theories as to why physiological acidosis may be of benefit; and an evolutionarily approach raises the question of why we would be continuously releasing and consuming such a substance if it were toxic. Exercise physiology shows acidosis at its best; critical illness at its worst. Yet, we perpetuate the latter, sometimes with little thought of the implications of our interventions.

The biochemistry of exercise-induced acidosis clearly shows that the substrates produced set the scene for later adaptations that will have evolved to protect against inconsistent environmental challenges.

Where does that leave hyperchloraemic acidosis? There is little evidence that in the 50 yr of normal saline usage, there has been significant morbidity from the use of this fluid. A mild exogenous acidosis may even be protective before or during an insult, setting the scene for immediate enhanced oxygen delivery.

Teleologically, it is clear that the clinical effects of acidosis need revisiting. In the era of ‘balanced solutions’, where non-physiological saline use and hyperchloraemic acidosis may become a trend of the past, an open mind will be required to determine whether we have moved forward or sideways.

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