Letter

Letter to the editor

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In the recent Bench-to-bedside review from Gehlback and Schmidt [1] there are several discrepancies with the literature. For the readers of *Critical Care*, it would be useful if the authors could provide explanations for the following.

On page 260 the authors wrote that, '… lowering the arterial pH has rather convincingly been shown to cause a decrease in cardiac contractility.' According to Maury and coworkers [2], in contrast to experimental animals and isolated organs or cells, in humans very low blood pH has no adverse effects on the cardiovascular system. Are there any published reports that refute the findings of Maury and coworkers? On the other hand, the authors did not mention that low blood pH has detrimental effects on the central nervous system (e.g. see the report by Alberti and coworkers [3]). The glycolytic enzyme phosphofructokinase is pH dependent and its activity decreases with decreasing pH; thus, utilization of glucose is impaired with reduced pH levels. Because glucose is the main energy yielding substrate for brain cells, the clinical consequences of decreasing blood pH are drowsiness, stupor, coma and, ultimately, death.

On page 261 the authors wrote, 'No benefit from sodium bicarbonate has been found in the management of diabetic ketoacidosis.', citing reports from Lever and Jaspan [4] and from Morris and coworkers [5]. This is a misinterpretation. In the study conducted by Lever and Jaspan [4], those investigators described 27 patients with diabetic ketoacidosis in a 'deep coma' and blood pH below 7.10. After administration of sodium bicarbonate, the blood pH normalized and all 27 patients recovered to full alertness. Are there any published reports indicating zero death rates in a similar number of comatose patients with diabetic ketoacidosis and very low blood pH, without increasing blood pH and without administering sodium bicarbonate? Morris and coworkers [5] did not report on comatose patients, and therefore it is impossible to conclude whether the applied therapies were life saving or not.

On page 259 the authors wrote, '… we understand poorly both the effects of an elevated arterial H^+ concentration ($[H^+]$) as well as the effects of attempting to correct it …', and on page 263 they state that, '… it is unclear whether it is ever advantageous to administer a buffering agent to a patient with lactic acidosis …'. Ahmad and Beckett [6] described a comatose patient with extreme lactic acidosis (blood pH 6.389, lactate 24.0 mmol/l) caused by metformin treatment for diabetes mellitus. After infusions of sodium bicarbonate, blood pH increased to normal values, the patient recovered to full alertness and was later discharged from hospital. According to the authors, what would be the correct therapy in a similar patient?

Competing interests

The author(s) declare that they have no competing interests.

Authors' response

Brian K Gehlbach and Gregory A Schmidt

We appreciate the opportunity to amplify the points we made in our recent review [1]. It has been known for more than a century that acidosis impairs cardiac contractility [7], and this has also been shown for human atrial and ventricular muscle [8]. Dr Rosival cites a study of echocardiographic fractional shortening to support his assertion that low blood pH has no adverse effects on the cardiovascular system [2]. The 10 patients reported in that brief letter were found to have 'normal' fractional shortening, but there was no formal comparison of fractional shortening before and after treatment. Furthermore, fractional shortening is a crude measurement that groups not only ventricular contractility but also loading conditions and compensatory responses. We find the results of that study to be in general agreement with our review, which stated that, 'The net influence of acidosis on the cardiovascular

system is complicated, however, by concomitant stimulation of the sympathetic-adrenal axis.'

Low blood pH may have detrimental effects on the nervous system, as suggested by Dr Rosival, but there are few data to support this assertion. The glycolytic enzyme phosphofructokinase is affected by pH, but also by insulin levels and host of other mediators. Whether any alteration in glycolytic activity relates to the encephalopathy of ketoacidosis is unknown. Very little research into the mechanisms of brain dysfunction in this condition has been conducted, but it has been speculated that disturbances in pH, electrolytes, and osmolality, as well as ketone body effects, endothelial injury, lipid peroxidation, vascular dysregulation and nitric oxide-induced disruption of the blood–brain barrier, may be to blame. Cerebral edema, which plays a role in some patients [9], has been linked to treatment with bicarbonate [10].

In rebutting the conclusion of Lever and Jaspan's retrospective analysis of 95 patients with diabetic ketoacidosis [4], Dr Rosival cites the 100% survival of 27 patients in 'deep coma' and with a blood pH below 7.10 who received sodium bicarbonate as proof of the efficacy of this therapy. To suggest that the benefit of a therapy is established through such a *post hoc* subgroup analysis of a negative retrospective study perpetuates the idea that sodium bicarbonate should not be subjected to the same burden of proof as any other therapy. Moreover, all of the patients who were not subjected to bicarbonate infusion also survived, and the mean time to achieve complete return of consciousness was identical (4 hours) in those treated with and those treated without bicarbonate.

Dr Rosival asks us what therapy we would prescribe for a patient with severe lactic acidosis due to metformin. This is easy; because metformin is readily dialyzable, we would perform dialysis.

Competing interests

The author(s) declare that they have no competing interests.

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