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Alkali Therapy in Lactic Acidosis

Zeid J. Khitan, MD; Deepak Malhotra, MD; Dominic S. Raj, MD; Antonios H. Tzamaloukas, MD; and Joseph I. Shapiro, MD

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References with DOI

1. Jung B, Rimmele T, Le Goff C, Chanques G, Corne P, Jonquet O, Muller L, Lefrant JY, Guervilly C, Papazian L, Allaouchiche B and Jaber S. Severe metabolic or mixed acidemia on intensive care unit admission: incidence, prognosis and administration of buffer therapy. A prospective, multiple-center study. *Crit Care*. 2011;15:R238. <https://doi.org/10.1186/cc10487>
2. Kraut JA and Madias NE. Metabolic acidosis: pathophysiology, diagnosis and management. *Nat Rev Nephrol*. 2010;6:274-85. <https://doi.org/10.1038/nrneph.2010.33>
3. Lee SW, Hong YS, Park DW, Choi SH, Moon SW, Park JS, Kim JY and Baek KJ. Lactic acidosis not hyperlactatemia as a predictor of in hospital mortality in septic emergency patients. *Emerg Med J*. 2008;25:659-65. <https://doi.org/10.1136/emj.2007.055558>
4. Gabow PA, Kaehny WD, Fennessey PV, Goodman SI, Gross PA and Schrier RW. Diagnostic importance of an increased serum anion gap. *N Engl J Med*. 1980;303:854-8. <https://doi.org/10.1056/nejm198010093031505>
5. Kraut JA and Madias NE. Lactic acidosis. *N Engl J Med*. 2014;371:2309-19. <https://doi.org/10.1056/nejmra1309483>
6. Luft FC. Lactic acidosis update for critical care clinicians. *J Am Soc Nephrol*. 2001;12 Suppl 17:S15-9.
7. Adeva-Andany M, Lopez-Ojen M, Funcasta-Calderon R, Ameneiros-Rodriguez E, Donapetry-Garcia C, Vila-Altesor M and Rodriguez-Seijas J. Comprehensive review on lactate metabolism in human health. *Mitochondrion*. 2014;17:76-100. <https://doi.org/10.1016/j.mito.2014.05.007>
8. Madias NE. Lactic acidosis. *Kidney Int*. 1986;29:752-74. <https://doi.org/10.1038/ki.1986.62>
9. Cingolani HE, Mattiazzi AR, Blesa ES and Gonzalez NC. Contractility in isolated mammalian heart muscle after acid-base changes. *Circ Res*. 1970;26:269-78. <https://doi.org/10.1161/01.res.26.3.269>
10. Fabiato A and Fabiato F. Effects of pH on the myofilaments and the sarcoplasmic reticulum of skinned cells from cardiac and skeletal muscles. *J Physiol*. 1978;276:233-55. <https://doi.org/10.1113/jphysiol.1978.sp012231>
11. Solaro RJ, Lee JA, Kentish JC and Allen DG. Effects of acidosis on ventricular muscle from adult and neonatal rats. *Circ Res*. 1988;63:779-87. <https://doi.org/10.1161/01.res.63.4.779>
12. Shapiro JI. Functional and metabolic responses of isolated hearts to acidosis: effects of sodium bicarbonate and Carbicarb. *The American journal of physiology*. 1990;258:H1835-9.
13. Schotola H, Toischer K, Popov AF, Renner A, Schmitto JD, Gummert J, Quintel M, Bauer M, Maier LS and Sossalla S. Mild metabolic acidosis impairs the beta-adrenergic response in isolated human failing myocardium. *Crit Care*. 2012;16:R153. <https://doi.org/10.1186/cc11468>
14. Kimmoun A, Ducrocq N and Levy B. New conclusive data on human myocardial dysfunction induced by acidosis. *Crit Care*. 2012;16:160. <https://doi.org/10.1186/cc11520>
15. Shapiro JI. Pathogenesis of cardiac dysfunction during metabolic acidosis: therapeutic implications. *Kidney international Supplement*. 1997;61:S47-51.
16. Shapiro JI, Whalen M and Chan L. Hemodynamic and hepatic pH responses to sodium bicarbonate and Carbicarb during systemic acidosis. *Magn Reson Med*. 1990;16:403-10. <https://doi.org/10.1002/>

mrm.1910160306

17. Suleymanlar G, Zhou HZ, McCormack M, Elkins N, Kucera R, Reiss OK and Shapiro JI. Mechanism of impaired energy metabolism during acidosis: role of oxidative metabolism. *The American journal of physiology*. 1992;262:H1818-22.
18. Harrison SM, Frampton JE, McCall E, Boyett MR and Orchard CH. Contraction and intracellular Ca²⁺, Na⁺, and H⁺ during acidosis in rat ventricular myocytes. *The American journal of physiology*. 1992;262:C348-57.
19. Choi HS, Trafford AW, Orchard CH and Eisner DA. The effect of acidosis on systolic Ca²⁺ and sarcoplasmic reticulum calcium content in isolated rat ventricular myocytes. *The Journal of physiology*. 2000;529 Pt 3:661-8.
20. Sikes PJ, Zhao P, Maass DL, White J and Horton JW. Sodium/hydrogen exchange activity in sepsis and in sepsis complicated by previous injury: 31P and 23Na NMR study. *Crit Care Med*. 2005;33:605-15. <https://doi.org/10.1097/01.ccm.0000155910.89252.fe>
21. DeSantiago J, Maier LS and Bers DM. Phospholamban is required for CaMKII-dependent recovery of Ca transients and SR Ca reuptake during acidosis in cardiac myocytes. *J Mol Cell Cardiol*. 2004;36:67-74. <https://doi.org/10.1016/j.yjmcc.2003.10.012>
22. Wu LL, Tang C, Dong LW and Liu MS. Altered phospholamban-calcium ATPase interaction in cardiac sarcoplasmic reticulum during the progression of sepsis. *Shock*. 2002;17:389-93. <https://doi.org/10.1097/00024382-200205000-00008>
23. Dong LW, Wu LL, Ji Y and Liu MS. Impairment of the ryanodine-sensitive calcium release channels in the cardiac sarcoplasmic reticulum and its underlying mechanism during the hypodynamic phase of sepsis. *Shock*. 2001;16:33-9. <https://doi.org/10.1097/00024382-200116010-00007>
24. Katz AM and Hecht HH. Editorial: the early "pump" failure of the ischemic heart. *Am J Med*. 1969;47:497- 502. [https://doi.org/10.1016/0002-9343\(69\)90180-6](https://doi.org/10.1016/0002-9343(69)90180-6)
25. Miller RG, Boska MD, Moussavi RS, Carson PJ and Weiner MW. 31P nuclear magnetic resonance studies of high energy phosphates and pH in human muscle fatigue. Comparison of aerobic and anaerobic exercise. *J Clin Invest*. 1988;81:1190-6. <https://doi.org/10.1172/jci113434>
26. Kimmoun A, Novy E, Auchet T, Ducrocq N and Levy B. Hemodynamic consequences of severe lactic acidosis in shock states: from bench to bedside. *Crit Care*. 2015;19:175. <https://doi.org/10.1186/s13054-015-0896-7>
27. Mitchell JH, Wildenthal K and Johnson RL, Jr. The effects of acid-base disturbances on cardiovascular and pulmonary function. *Kidney international*. 1972;1:375-89. <https://doi.org/10.1038/ki.1972.48>
28. Darby TD and Watts DT. ACIDOSIS AND BLOOD EPINEPHRINE LEVELS IN HEMORRHAGIC HYPOTENSION. *The American journal of physiology*. 1964;206:1281-4.
29. Nahas GG, Zagury D, Milhaud A, Manger WM and Pappas GD. Acidemia and catecholamine output of the isolated canine adrenal gland. *The American journal of physiology*. 1967;213:1186-92.
30. Nahas GG, Ligou JC and Mehlman B. Effects of pH changes on oxygen uptake and plasma catecholamine levels in the dog. *The American journal of physiology*. 1960;198:60-6.
31. Campbell GS. Cardiac arrest: further studies on the effect of pH changes on vagal inhibition of the

heart. *Surgery*. 1955;38:615-34.

32. Cooper DJ, Walley KR, Wiggs BR and Russell JA. Bicarbonate does not improve hemodynamics in critically ill patients who have lactic acidosis. A prospective, controlled clinical study. *Annals of internal medicine*. 1990;112:492-8. <https://doi.org/10.1097/00132586-199012000-00067>

33. Teplinsky K, O'Toole M, Olman M, Walley KR and Wood LD. Effect of lactic acidosis on canine hemodynamics and left ventricular function. *The American journal of physiology*. 1990;258:H1193-9.

34. Davies AO. Rapid desensitization and uncoupling of human beta-adrenergic receptors in an in vitro model of lactic acidosis. *J Clin Endocrinol Metab*. 1984;59:398-405. <https://doi.org/10.1210/jcem-59-3-398>

35. Kellum JA, Song M and Venkataraman R. Effects of hyperchloremic acidosis on arterial pressure and circulating inflammatory molecules in experimental sepsis. *Chest*. 2004;125:243-8. <https://doi.org/10.1378/chest.125.1.243>

26. Orchard CH and Cingolani HE. Acidosis and arrhythmias in cardiac muscle. *Cardiovasc Res*. 1994;28:1312-9. <https://doi.org/10.1093/cvr/28.9.1312>

37. Arieff AI, Leach W, Park R and Lazarowitz VC. Systemic effects of NaHCO₃ in experimental lactic acidosis in dogs. *The American journal of physiology*. 1982;242:F586-91.

38. Graf H, Leach W and Arieff AI. Evidence for a detrimental effect of bicarbonate therapy in hypoxic lactic acidosis. *Science*. 1985;227:754-6. <https://doi.org/10.1126/science.3969564>

39. Adler S, Roy A and Relman AS. Intracellular Acid-Base Regulation. I. The Response of Muscle Cells to Changes in Co₂ Tension or Extracellular Bicarbonate Concentration. *J Clin Invest*. 1965;44:8-20.

40. Kraut JA and Madias NE. Treatment of acute metabolic acidosis: a pathophysiologic approach. *Nat Rev Nephrol*. 2012;8:589-601. <https://doi.org/10.1038/nrneph.2012.186>

41. Shapiro JI, Whalen M, Kucera R, Kindig N, Filley G and Chan L. Brain pH responses to sodium bicarbonate and Carbicarb during systemic acidosis. *The American journal of physiology*. 1989;256:H1316-21.

42. Kindig NB, Sherrill DS, Shapiro JI and Filley GF. Extracorporeal bicarbonate space after bicarbonate or a bicarbonate-carbonate mixture in acidotic dogs. *J Appl Physiol* (1985). 1989;67:2331-4.

43. Shapiro JI, Mathew A, Whalen M, Honigman B, Kaehny WD, Petty TL and Chan L. Different effects of sodium bicarbonate and an alternate buffer (Carbicarb) in normal volunteers. *Journal of Critical Care*. 1990;5:157-160. [https://doi.org/10.1016/0883-9441\(90\)90036-9](https://doi.org/10.1016/0883-9441(90)90036-9)

44. Olson DE, Dart GA and Filley GF. Pressure drop and fluid flow regime of air inspired into the human lung. *J Appl Physiol*. 1970;28:482-94.

45. Shapiro JI, Elkins N, Logan J, Ferstenberg LB and Repine JE. Effects of sodium bicarbonate, disodium carbonate, and a sodium bicarbonate/carbonate mixture on the PCO₂ of blood in a closed system. *J Lab Clin Med*. 1995;126:65-9.

46. Kimmoun A, Ducrocq N, Sennoun N, Issa K, Strub C, Escanye JM, Leclerc S and Levy B. Efficient extra- and intracellular alkalinization improves cardiovascular functions in severe lactic acidosis induced by hemorrhagic shock. *Anesthesiology*. 2014;120:926-34. <https://doi.org/10.1097/01.sa.0000459223.08417.bf>

-
47. Allegretti AS, Flythe JE, Benda V, Robinson ES and Charytan DM. The effect of bicarbonate administration via continuous venovenous hemofiltration on acid-base parameters in ventilated patients. *BioMed research international*. 2015;2015:901590. <https://doi.org/10.1155/2015/901590>
48. Rocktaschel J, Morimatsu H, Uchino S, Ronco C and Bellomo R. Impact of continuous veno-venous hemofiltration on acid-base balance. *Int J Artif Organs*. 2003;26:19-25.
49. Nahas GG, Sutin KM, Fermon C, Streat S, Wiklund L, Wahlander S, Yellin P, Brasch H, Kanchuger M, Capan L, Manne J, Helwig H, Gaab M, Pfenninger E, Wetterberg T, Holmdahl M and Turndorf H. Guidelines for the treatment of acidaemia with THAM. *Drugs*. 1998;55:191-224. <https://doi.org/10.1007/bf03259987>
50. Moon PF, Gabor L, Gleed RD and Erb HN. Acid-base, metabolic, and hemodynamic effects of sodium bicarbonate or tromethamine administration in anesthetized dogs with experimentally induced metabolic acidosis. *American journal of veterinary research*. 1997;58:771-6.
51. Wildenthal K, Mierzwiak DS, Myers RW and Mitchell JH. Effects of acute lactic acidosis on left ventricular performance. *The American journal of physiology*. 1968;214:1352-9.
52. Sirieix D, Delayance S, Paris M, Massonnet-Castel S, Carpentier A and Baron JF. Tris-hydroxymethyl aminomethane and sodium bicarbonate to buffer metabolic acidosis in an isolated heart model. *American journal of respiratory and critical care medicine*. 1997;155:957-63. <https://doi.org/10.1164/ajrccm.155.3.9117032>
53. Hoste EA, Colpaert K, Vanholder RC, Lameire NH, De Waele JJ, Blot SI and Colardyn FA. Sodium bicarbonate versus THAM in ICU patients with mild metabolic acidosis. *Journal of nephrology*. 2005;18:303-7. <https://doi.org/10.1203/00006450-197605000-00018>
54. Stacpoole PW. The pharmacology of dichloroacetate. *Metabolism: clinical and experimental*. 1989;38:1124-44.
55. Wilkerson DP, Campbell IT, Blackwell JR, Berger NJ and Jones AM. Influence of dichloroacetate on pulmonary gas exchange and ventilation during incremental exercise in healthy humans. *Respiratory physiology & neurobiology*. 2009;168:224-9. <https://doi.org/10.1016/j.resp.2009.07.004>
56. Stacpoole PW, Wright EC, Baumgartner TG, Bersin RM, Buchalter S, Curry SH, Duncan CA, Harman EM, Henderson GN, Jenkinson S and et al. A controlled clinical trial of dichloroacetate for treatment of lactic acidosis in adults. The Dichloroacetate-Lactic Acidosis Study Group. *N Engl J Med*. 1992;327:1564-9. <https://doi.org/10.1056/nejm199211263272204>
57. Filley GF and Kindig NB. Carbicarb, an alkalinizing ion-generating agent of possible clinical usefulness. *Trans Am Clin Climatol Assoc*. 1985;96:141-53.
58. Li YC, Wiklund L and Bjerneroth G. Influence of alkaline buffers on cytoplasmic pH in myocardial cells exposed to hypoxia. *Resuscitation*. 1997;34:71-7. [https://doi.org/10.1016/s0300-9572\(96\)01047-7](https://doi.org/10.1016/s0300-9572(96)01047-7)
59. Li YC, Wiklund L, Tarkkila P and Bjerneroth G. Influence of alkaline buffers on cytoplasmic pH in myocardial cells exposed to metabolic acidosis. *Resuscitation*. 1996;32:33-44. [https://doi.org/10.1016/0300-9572\(95\)00939-6](https://doi.org/10.1016/0300-9572(95)00939-6)
60. Bersin RM and Arieff AI. Improved hemodynamic function during hypoxia with Carbicarb, a new agent for the management of acidosis. *Circulation*. 1988;77:227-33. <https://doi.org/10.1161/01.cir.77.1.227>
61. Leung JM, Landow L, Franks M, Soja-Strzepa D, Heard SO, Arieff AI and Mangano DT. Safety and efficacy of intravenous Carbicarb in patients undergoing surgery: comparison with sodium bicarbonate in

the treatment of mild metabolic acidosis. SPI Research Group. Study of Perioperative Ischemia. Critical care medicine. 1994;22:1540-9. <https://doi.org/10.1097/00003246-199422100-00007>

62. Kolloffel WJ, de Vroom TE, Weekers LE and Woittiez AJ. Severe cutaneous side effects of peripheral infusions with bicarb half strength. Intensive Care Med. 1994;20:531. <https://doi.org/10.1007/bf01711912>

Alkali Therapy in Lactic Acidosis

Zeid Khitan MD¹, Deepak Malhotra MD PhD², Dominic S Raj MD³,

Antonios H. Tzamaloukas MD⁴, and Joseph I Shapiro MD¹

Author affiliations:

1: Department of Medicine, Marshall University Joan C. Edwards School of Medicine

2: Department of Medicine, University of Toledo School of Medicine

3: Department of Medicine, George Washington University School of Medicine

4: Department of Medicine, University of New Mexico School of Medicine.

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Corresponding author:

Joseph I. Shapiro, MD

Dean, Marshall University Joan C Edwards School of Medicine

Professor of Medicine

Email: shapiroj@marshall.edu

Abstract

This report attempts to frame the debate about clinical administration of sodium bicarbonate in the setting of lactic acidosis in terms of simple questions. Specifically, we address why we develop lactic acidosis in some circumstances, how acute lactic acidosis impairs cardiovascular function and why sodium bicarbonate may have deleterious effects which limit its utility. We also attempt to explore treatment alternatives to sodium bicarbonate

Keywords

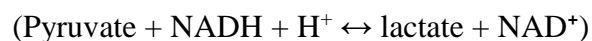
lactic acidosis, sodium bicarbonate, carbicarb

Introduction

The treatment of lactic acidosis remains controversial. Although many in vitro and animal studies were performed over the past 40 years, there is still a dearth of clinical data addressing simple questions such as whether sodium bicarbonate therapy is deleterious or beneficial or whether alternative buffers such as tris (hydroxymethyl)aminomethane (THAM) or a combination of sodium bicarbonate with disodium carbonate (Carbicarb) offer advantages to patients. In this report we will attempt to highlight the key issues that may be useful in the design of subsequent clinical treatments and studies. To this end, we plan to frame and answer some very simple questions.

Why do we generate lactic acidosis?

The end product of anaerobic glycolysis is pyruvate, which can be metabolized to carbon dioxide by the energy efficient Krebs cycle in the mitochondria. Alternatively, pyruvate can be metabolized by an energy inefficient pathway by the enzyme lactate dehydrogenase to lactate:



Lactic acidosis, one consequence of the shock state is associated with cellular dysfunction and is a predictor of mortality and morbidity.¹⁻³ Together with diabetic ketoacidosis, it accounts for approximately 85% of the cases of acute severe metabolic acidosis.⁴ The major causes of lactic acidosis are typically divided into disorders associated with tissue hypoxia (type A) and disorders in which tissue hypoxia is absent (type B). Cardiogenic or hypovolemic shock, severe heart failure, severe trauma and sepsis are the most common causes of type A lactic acidosis.⁵ Normally, approximately 1400 mmol of lactic acid are produced daily, primarily by skeletal muscle and gut. The production of lactic acid is balanced by the metabolism of an equivalent amount of the compound in the liver, which constitutes the Cori cycle. Other tissues including the kidneys are capable of metabolizing lactate as well. In humans, the kidneys contribute approximately 10-20% of lactate removal.⁶ On the other hand, tissue hypoxia results in excessive lactate production which can increase under pathological conditions nearly 100 fold.⁶

Lactate removal takes place via its oxidation to pyruvate by lactate dehydrogenase. Pyruvate may be either oxidized to carbon dioxide producing energy or transformed into glucose through

gluconeogenesis. Pyruvate oxidation requires oxygen supply and the cooperation of pyruvate dehydrogenase, the tricarboxylic acid cycle, and the mitochondrial respiratory chain. Congenital or acquired deficiencies in gluconeogenesis including tissue hypoxia may induce lactate accumulation.⁷ Impaired mitochondrial oxidative function, as occurs in hypoxic states, leads to accumulation of pyruvate in the cytosol and thus to increased lactate production. The accumulation of pyruvate in the hypoxic state reflects both overproduction of pyruvate and reduced utilization of pyruvate through its two pathways, the oxidative decarboxylation to acetyl-coenzyme A (acetyl-CoA) and gluconeogenesis.⁸

Is the development of acidosis a “bad” thing?

Clearly there are some “good” things about acidosis. On a tissue level, a moderate degree of acidosis allows for greater delivery of oxygen, the shortage of which often underlies the basic pathophysiology of lactic acidosis (see above). Acidosis also appears to decrease the ongoing rate of lactic-acid generation (or ketoacid generation). This negative feedback attenuates the net degree of acidemia.⁹

However, if we examine the effect of acidosis on the heart and the vascular system, one must conclude that it is generally deleterious. In cardiac cells, the drop in intracellular pH is known to have deleterious effects on myocardial contractile function.⁹⁻¹¹ This has been clearly shown in the isolated perfused rat heart.¹² Schotola, et al studied the effect of incremental dose of the beta agonist isoproterenol on human ventricular trabeculae at pH 7.20 and 7.40. They observed a reduction in cardiac contractility and rightward shift of the isoproterenol dose response curve at pH 7.20.^{13,14} In intact animals, compensatory mechanisms related to the neuroendocrine response initially maintain cardiac output, but ultimately cardiac output falls with severe acidosis^{15,16} as we discuss below.

Several cellular and functional processes have been implicated in the pathogenesis of cardiac contractile dysfunction in severe acidemia. These include impairment of energy production,^{15,17} disturbances in intracellular calcium transport and cycling,¹⁸⁻²⁴ and impairment of actin-myosin cross-bridge cycling by inorganic phosphate (Pi) and H⁺ accumulation.²⁵ In myocardial cells metabolic acidosis results in increased energy demand that exceeds energy production.¹⁵ This discrepancy between demand and production of energy is evidenced by decreases in creatinine phosphate (PCr) and reciprocal increases in inorganic phosphate (Pi) beyond what would be expected from the calculated increases in [H⁺].¹⁶ The decrease in energy production in the isolated perfused heart appears to be the result of inhibition of the mitochondrial oxidative phosphorylation more than direct effects on glycolysis through allosteric effects on phosphofructokinase.¹⁷

Intracellular pH also has a considerable impact on the amplitude of the systolic calcium transient and subsequent excitation-contraction coupling pathway. The net impact of intracellular acidosis is an increase in the calcium transient amplitude due to increased sarcoplasmic reticulum calcium content which subsequently affects the excitation-contraction coupling pathway. It was also demonstrated that global acidosis or ischemia modifies Ca_i²⁺ cycling in myocytes causing a rise

in the diastolic Ca_i^{2+} and prolongation of the cellular calcium transient characterizing a potential pro-arrhythmic state.²⁶

As mentioned earlier, it is apparent that the sympathoadrenal system constitutes an important aspect of the heart's response to acidosis.²⁷ Increased release of catecholamines in response to the acidic environment from cardiac nerve endings and adrenal medulla was observed but myocardial responsiveness to catecholamines was found to be altered along with markedly enhanced vagal stimulation.²⁸⁻³² Mitchell et al demonstrated that in moderate acidosis (pH > 7.2), there is actually an increase in the maximal rate of left ventricular pressure (max dp/dt) and stroke volume related to the increased catecholamine levels, but with severe acidosis, the contractile state of the left ventricle is significantly depressed.²⁷ Teplinsky and colleagues showed that experimental lactic acidosis caused a 40% reduction in stroke volume without reducing venous return in animals suggesting impaired myocardial contractility.³³ Davies demonstrated that human beta 2-adrenergic receptors were altered in an in vitro model of lactic acidosis accompanied by resistance to the inotropic and vasoconstrictive effects of infused catecholamines.³⁴ In another study by Kellum and colleagues, moderate and severe acidosis caused hypotension in animals without affecting plasma levels of inflammatory markers.³⁵ Conduction abnormalities which predispose to ventricular arrhythmias are often found in animal models of metabolic acidosis. This finding can explain the ventricular irritability observed during myocardial ischemia.³⁶

If acidosis is “bad,” why isn’t the administration of sodium bicarbonate “good?”

It is very clear that therapy directed to the specific cause of the acidosis is rational. Clinical outcomes are in fact quite good when such intervention effectively normalizes the production of acid as is the case with diabetic ketoacidosis and some cases of toxic alcohol ingestion where the process of organic acid production can be stopped. On the other hand, conditions presenting with type A lactic acidosis and associated circulatory disturbances and tissue hypoxia as in sepsis or cardiac arrest seem to require addressing the acidosis directly. In fact, given the potential deleterious effects of severe acidosis, some experts recommend intravenous sodium bicarbonate therapy although its value in reducing mortality or improving hemodynamics remains unproven.⁵

Questioning the utility of bicarbonate therapy began in the late 1970s with the observation in experimental lactic acidosis that bicarbonate therapy worsened outcomes. In animal models of lactic acidosis, administration of $NaHCO_3$ increased lactate production by the splanchnic bed.³⁷ Graf et al³⁸ compared the effect $NaHCO_3$ therapy in dogs with hypoxic lactic acidosis with the effects of sodium chloride or no therapy. Treatment with $NaHCO_3$ was associated with decreases in cardiac output and blood pressure compared with the other two groups. Moreover and despite the infusion of $NaHCO_3$, both arterial pH and bicarbonate concentration decreased by a similar amount in all three groups of dogs. This was postulated to result primarily from a paradoxical intracellular acidosis resulting from the rapid equilibrium of CO_2 across the cell membrane and the delayed equilibration of bicarbonate.³⁹ Other possible adverse effects of sodium bicarbonate therapy include hypertonicity and delayed metabolic alkalosis,^{32,40} but the paradoxical intracellular acidosis is probably the most important. Graf and colleagues measured intracellular liver pH with DMO distribution and found bicarbonate actually lowered this value in their

animal model.³⁸ This has been confirmed using other methods of intracellular pH determination.^{12,15,16,41} To fully understand this, we can look at what happens when the bicarbonate buffer system is open vs. closed.

In an open system (i.e., when tissue perfusion and pulmonary ventilation is adequate), CO₂ tension is controlled by the brain stem through respiratory drive and the CO₂ which is generated from oxidative metabolism of carbon containing organic compounds and the dehydration of H₂CO₃ by carbonic anhydrase (figure 1) is eliminated by the lungs. This has been shown in both experimental animals⁴² and humans⁴³. Such a system can be modelled experimentally using an instrument called a tonometer where the CO₂ tension can be held constant.⁴⁴ However, when tissue perfusion and/or pulmonary ventilation are compromised as occurs during circulatory shock, the clinical scenario more closely approximates a closed system. A simple model for a closed system is a glass syringe with a gas tight rubber stopper.⁴⁵

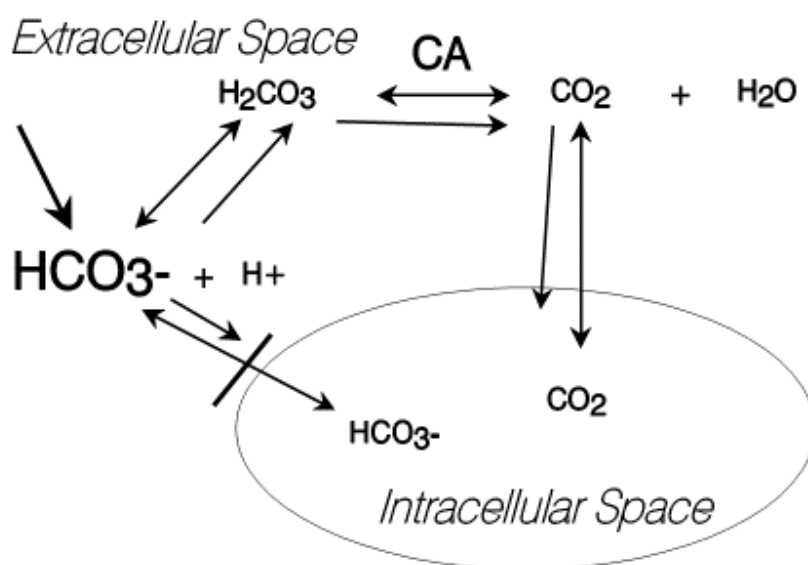


Figure 1

Figure 1: Schematic illustrating effects of sodium bicarbonate (HCO_3^-) administration into an acidotic milieu. Other abbreviations: H^+ - protons, H_2CO_3 carbonic acid, CO_2 - carbon dioxide, CA - carbonic anhydrase.

Kimmoun et al⁴⁶ investigated the cardiovascular and metabolic effects of an adaptive sodium bicarbonate therapy, including ventilation of CO₂ increase with hyperventilation and ionized calcium decrease with calcium administration. Their strategy normalized extra- and intracellular pH, improved cardiac elastance and improved aortic and mesenteric vasoactivity compared with controls. Small studies have shown promising results when high dose bicarbonate was administered via continuous venovenous hemofiltration to treat acidosis and renal failure.^{47,48} The harmful effect of bicarbonate-induced widespread intracellular acidosis on cellular and metabolic function, particularly the heart, suggests that alternative buffers compatible to bicarbonate but without the CO₂ generating potential might offer clinical advantages.

Alternative Buffers

In an effort to overcome the side effects of sodium bicarbonate, other alkali therapies have been developed. THAM, (tris-hydroxymethyl-aminomethan), dichloroacetate and Carbicarb constitute the most prominent molecules in this context. THAM was first introduced into clinical practice in 1959.⁴⁹ 30% of this compound exists in the nonionized form where it can penetrate cells and thereby raise the intracellular pH by buffering protons by virtue of the ammonia moiety.⁴⁰ In experimental studies, THAM was found to have a comparable buffering capacity to bicarbonate but without intracellular acidosis.⁵⁰ Moreover, THAM was found to have a favorable effect on myocardial contractility when used in dogs with lactic acidosis⁵¹ as well as in perfused isolated heart model during metabolic acidosis⁵² (pH=7.0).

Clinical trials assessing THAM in patients with lactic acidosis are limited. Hoste and colleagues showed that administration of THAM to patients in ICU with mild metabolic acidosis was as effective as sodium bicarbonate.⁵³ Further studies looking at outcome and cardiovascular function are needed to examine the use of THAM in the treatment of acute metabolic acidosis. THAM has considerable side effect profile including hepatic failure and hyperkalemia. Moreover, THAM is excreted by the kidney in its protonated form. Therefore, its usefulness would appear to be limited to acidosis in the presence of significant renal failure.⁴⁰

Dichloroacetate (DCA) is another investigational drug that has been studied in lactic acidosis. DCA exerts multiple effects on pathways of intermediate metabolism resulting in stimulation of peripheral glucose utilization and inhibition of gluconeogenesis.⁵⁴ In lactic acidosis, DCA is believed to facilitate the oxidation of lactate by stimulating the activity of pyruvate dehydrogenase. In healthy volunteers during incremental exercise, DCA resulted in the reduction of blood lactate accumulation accompanied by reduction in pulmonary CO₂ output without enhancing exercise tolerance.⁵⁵ However, in a randomized controlled trial in patients with lactic acidosis, DCA resulted in statistically significant but clinically unimportant changes in arterial-blood lactate concentrations and pH and fails to alter either hemodynamics or survival.⁵⁶ DCA is not currently available in the United States for clinical use.

Carbicarb, a mixture of equimolar quantities of sodium bicarbonate and sodium carbonate was first formulated in 1983 by Filley and Kindig.⁵⁷ Sodium carbonate in the mixture reacts with carbonic acid (H₂CO₃) to generate bicarbonate via the following reaction.^{45,57}



Thus, the carbonate component of Carbicarb consumes CO₂ while the HCO₃⁻ component and the newly generated HCO₃⁻ will form CO₂ when protons are buffered. At the cellular level, systemic [administration of] Carbicarb to treat severe acidosis resulted in systemic alkalization without major changes in PaCO₂ and intracellular pH in hepatocytes¹⁶, isolated heart^{12,58,59} and brain cells⁴¹ compared with NaHCO₃ therapy which resulted in paradoxical intracellular acidosis. In animals [with lactic acidosis], Carbicarb was found to be superior to NaHCO₃ with improved tissue pH, lactate production and cardiac hemodynamics.⁶⁰ In healthy volunteers, Carbicarb was associated with transient decrease in PaCO₂ compared with sodium bicarbonate.⁴³

In a study of 36 patients undergoing surgery who developed mild acidosis, Carbicarb was found to be safe and comparable to NaHCO_3 .⁶¹ Controlled studies of the impact of Carbicarb in patients with severe acidosis have not been reported and the drug is not currently available in the United States.

Carbicarb is an efficient buffer that does not cause intracellular acidosis. It has the potential for treating acute acidosis without impairing cellular and cardiac function. Each molecule of CO_3^{2-} will effectively eliminate one hydrogen ion in the blood, thereby directly lowering the proton concentration and raising pH. In addition, HCO_3^- , the product of CO_3^{2-} buffering is the main component of the sodium bicarbonate solution that is safe in humans and has excellent cellular permeability. On the other hand, Carbicarb can be damaging to the adjacent tissues after injection due to its hypertonic nature and the high level of alkalinity.⁶² Moreover, stability problems with the mixture and the proposed delivery syringe have slowed its entry into the clinic. Specifically, the extremely high pH of Carbicarb appears to degrade the rubber stoppers which can safely be used to seal bicarbonate ampules (unpublished observations).

Simulations of different combinations of bicarbonate and carbonate:

As mentioned above, Carbicarb, like THAM, was developed with the aim of avoiding “paradoxical” intracellular acidosis. To examine what changes in PaCO_2 and pH might be anticipated, we performed the following simulations guided by the observed responses seen with closed and open systems.⁴⁵ Specifically, we found in the past that when bicarbonate was added to a closed system, we observed very little change in pH but rather marked increases in PaCO_2 . In contrast, the addition of carbonate to a closed system resulted in the rapid consumption of CO_2 as new HCO_3^- was generated. Using these principles and the known values for CO_2 solubility and the equilibrium constant for the $\text{H}_2\text{CO}_3 - \text{HCO}_3^-$ system, simulations were performed using the programming language Matlab™ (R2014a, the Mathworks, Inc.) using code detailed in Appendix 1.

We first examined the effects of NaHCO_3 addition in an “open” system where PaCO_2 was maintained at 40 torr. Bicarbonate caused no changes in PaCO_2 (by definition, figure 2a) and increase in final pH in proportion to the change in HCO_3^- (figure 2b). In such a system, addition of carbonate was twice as potent as bicarbonate as the reaction $\text{CO}_3^{2-} + \text{CO}_2 \rightarrow 2 \text{HCO}_3^-$ predicted, but no qualitative differences were noted (data not shown). In contrast, when bicarbonate was added to a closed system, increases in PaCO_2 were seen in proportion to the initial $[\text{H}^+]$ with essentially no change in pH as we observed in the aforementioned experimental publication⁴⁵, (figures 2c and 2d, respectively). Disodium carbonate however was a very effective alkalinizing agent over a wide range of pH values (figure 3 panel a and b). When we looked at varying the proportion of carbonate to bicarbonate in a mixture, it appeared that CO_2 neutrality was achieved at relatively low proportions of carbonate, especially when the initial PaCO_2 was high (figure 4, panels a and b).

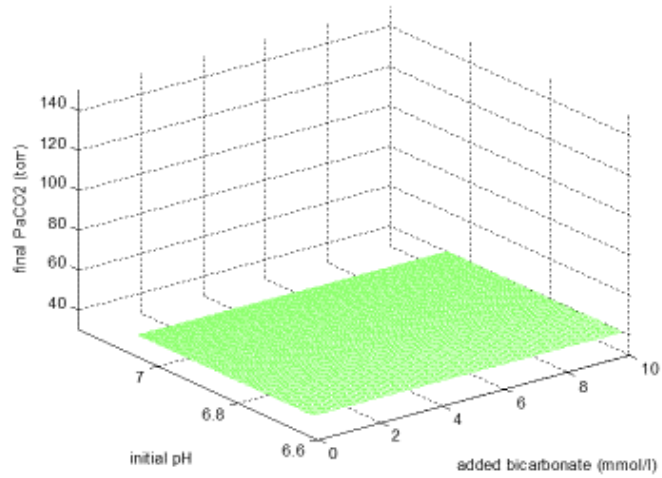


Figure 2a

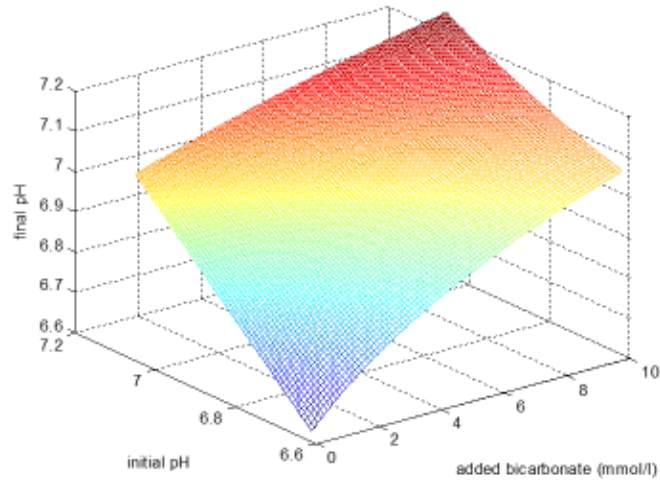


Figure 2b

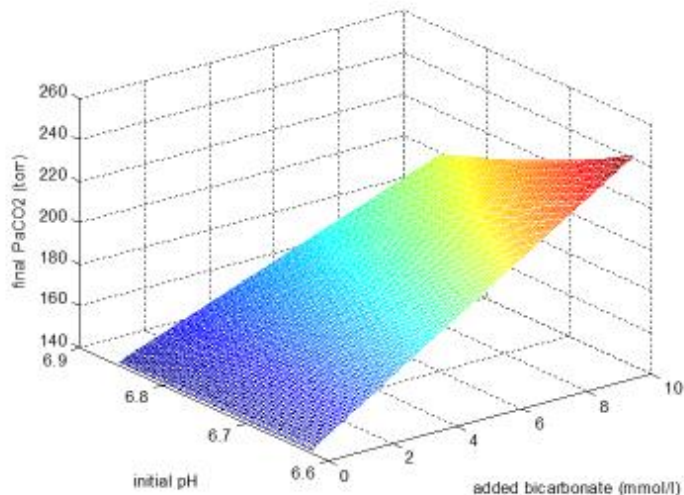


Figure 2c

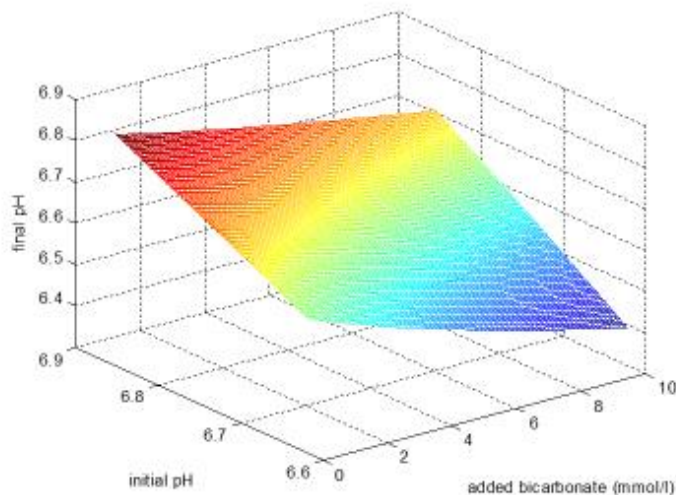


Figure 2d

Figure 2: Simulated changes in PaCO₂ and pH in open and closed system following addition of HCO₃⁻ (0 – 10 meq/l) with starting PaCO₂ of 40 torr and initial pH (6.4 to 7.0). Panels 2a and 2b show PaCO₂ and pH (respectively) in open system and Panels 2c and 2d show PaCO₂ and pH (respectively) in closed system.

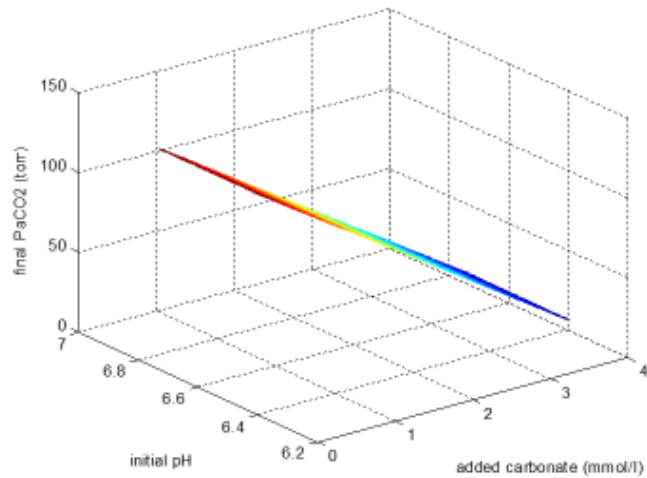


Figure 3a

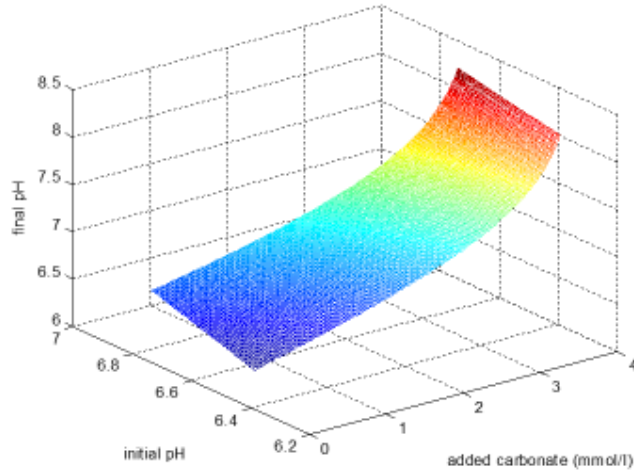


Figure 3b

Figure 3: Simulated changes in PaCO₂ (Panel 3a) and pH (Panel 3b) in a closed system following addition of disodium carbonate (0-4 mmol/l) with initial pH varied between 6.4 and 7 with initial PaCO₂ of 100 torr.

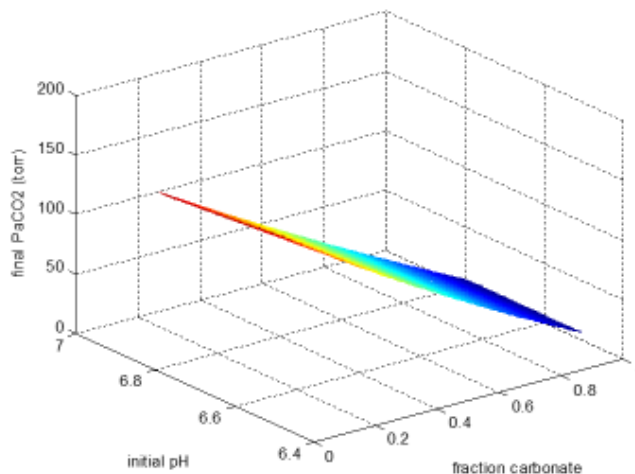


Figure 4a

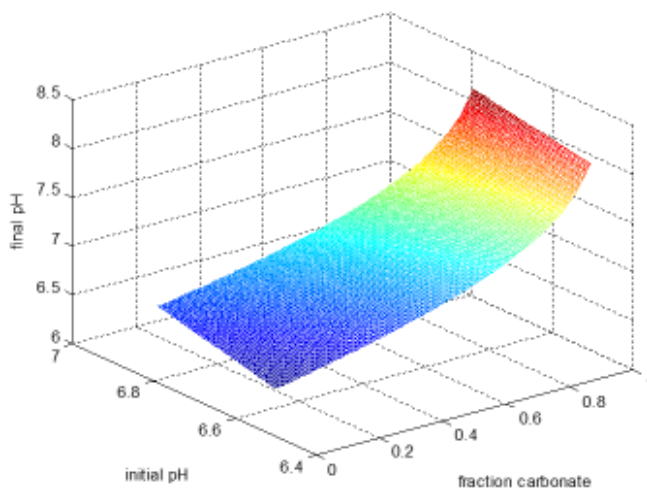


Figure 4b

Figure 4: Simulated changes in PaCO₂ (Panel 4a) and pH (Panel 4b) in a closed system following addition of a mixture of disodium carbonate and sodium bicarbonate (total 2 mmol/l of carbonate + bicarbonate) with initial pH varied between 6.4 and 7 with initial PaCO₂ of 100 torr.

Conclusions:

It is very clear that, while cardiovascular function is embarrassed by acute lactic acidosis, treatment with sodium bicarbonate may have deleterious effects that appear largely related to its propensity to generate CO₂ in a closed system. As there is no accepted methodology for assessing whether the patient's milieu is more closely approximated by a closed or an open system, it is very difficult to advise physicians whether or how to administer sodium bicarbonate in the clinical setting of lactic acidosis. Although some experimental buffers have been developed which appear promising, further clinical proof is necessary before their use can be advocated. Our simulations showed that solutions containing carbonate to bicarb ratios less than 1:1 might be useful in treating lactic acidosis. It needs to be examined if these solutions with different ratios will differ from carbicarb in terms of stability and administration issues.”

Appendix 1: Matlab™ code

```

%bicarbonate addition simulation open
for i=1:100
    HCO3m(i)=4+i/10;
    aHCO3(i)=i/10;
    pCO2=40;
end
for i=1:100
    for j=1:100
        pH(i,j)=6.1+log10(HCO3m(i)+ aHCO3(j))/1.2;
        pCO2(i,j)=40;
    end
end
mesh(aHCO3,pH(:,1),pH)
axis([0 10 6.6 7.2 6.6 7.2])
xlabel('added bicarbonate (mmol/l)')
ylabel('initial pH')
zlabel('final pH')
figure
mesh(aHCO3,pH(:,1),pCO2)
axis([0 10 6.6 7.2 30 150])
xlabel('added bicarbonate (mmol/l)')
ylabel('initial pH')
zlabel('final PaCO2 (torr)')

%bicarbonate addition simulation open
for i=1:100
    HCO3m(i)=14+i/10;
    aHCO3(i)=i/10;
    pCO2=140;
    pH(i,1)=6.1+log10(HCO3m(i)/(pCO2*0.03));
end
for i=1:100
    for j=1:100
        pCO2(i,j)=((HCO3m(i)+aHCO3(j))*10^-pH(i,1))/(0.03*10^(-6.1));
        pH(i,j)=6.1+log10(HCO3m(i)/(0.03*pCO2(i,j)));
    end
end
mesh(aHCO3,pH(:,1),pH)
%axis([0 10 6.6 7.2 6.6 7.2])
xlabel('added bicarbonate (mmol/l)')
ylabel('initial pH')
zlabel('final pH')
figure
mesh(aHCO3,pH(:,1),pCO2)
%axis([0 10 6.6 7.2 30 150])
xlabel('added bicarbonate (mmol/l)')
ylabel('initial pH')
zlabel('final PaCO2 (torr)')

%carbonate addition simulation closed

```

```

pCO20=140;
keq=1.2/((40e-6)*24);

for i=1:100
    HCO3m(i)=8+i/10;
    CN(i)= i/25;
end
for i=1:100

    for j=1:100
        x=pCO20*0.03;
        a=HCO3m(i)+ 2*CN(j);
        z=6.1+log10(a/x);
        x=x-CN(j);
        z=6.1+log10(a/x);
        x=1000*a*keq*10^-z;
        z=6.1+log10(a/x);
        x=1000*a*keq*10^-z;

        pH(i,j)=z;
        PCO2(i,j)= x/0.03;
    end
end
mesh(CN,pH(:,1),pH)
%axis([0 1.0 6.6 7.2 6.6 8.0])
xlabel('added carbonate (mmol/l)')
ylabel('initial pH')
zlabel('final pH')
figure
mesh(CN,pH(:,1),PCO2)
%axis([0 1.0 6.6 7.2 0 40])
xlabel('added carbonate (mmol/l)')
ylabel('initial pH')
zlabel('final PaCO2 (torr)')

%mixture of carbonate/bicarbonate closed
pCO20=140;
keq=1.2/((40e-6)*24);
d=input('enter dose of bicarbonate/carbonate mixture');

%set up intial bicarb concentrations and fraction of carbonate
for i=1:100
    HCO3m(i)=12+i/10;
    FCN(i)= (i-1)/100;
end

% develop simulations
for i=1:100

    for j=1:100
        % initial H2CO3
        x=pCO20*0.03;

```

```

%reaction of carbonate with CO2 generating new bicarbonate
a=HCO3m(i)+ 2*d*FCN(j);
% new pH
z=6.1+log10(a/x);
% reduction in CO2 tension from carbonate
x=x-2*d*FCN(j);
%new pH
z=6.1+log10(a/x);
%new H2CO3 based on bicarbonate addition
x=1000*a*keq*10^-z;
%new pH
z=6.1+log10(a/x);
%recalculate H2CO3
xx=1000*(a+d*(1-FCN(j)))*keq*10^-z;
%recalculate pH
z=6.1+log10(a/xx);
%enter data into matrices
pH(i,j)=z;
PCO2(i,j)= xx/0.03;
end
end
%plots
mesh(FCN,pH(:,1),pH)
%axis([0 1.0 6.6 7.2 6.6 8.0])
xlabel('fraction carbonate')
ylabel('initial pH')
zlabel('final pH')
figure
mesh(FCN,pH(:,1),PCO2)
%axis([0 1.0 6.6 7.2 0 40])
xlabel('fraction carbonate')
ylabel('initial pH')
zlabel('final PaCO2 (torr)')

```

References:

1. Jung B, Rimmele T, Le Goff C, Chanques G, Corne P, Jonquet O, Muller L, Lefrant JY, Guervilly C, Papazian L, Allaouchiche B and Jaber S. Severe metabolic or mixed acidemia on intensive care unit admission: incidence, prognosis and administration of buffer therapy. A prospective, multiple-center study. *Crit Care*. 2011;15:R238.
2. Kraut JA and Madias NE. Metabolic acidosis: pathophysiology, diagnosis and management. *Nat Rev Nephrol*. 2010;6:274-85.
3. Lee SW, Hong YS, Park DW, Choi SH, Moon SW, Park JS, Kim JY and Baek KJ. Lactic acidosis not hyperlactatemia as a predictor of in hospital mortality in septic emergency patients. *Emerg Med J*. 2008;25:659-65.
4. Gabow PA, Kaehny WD, Fennessey PV, Goodman SI, Gross PA and Schrier RW. Diagnostic importance of an increased serum anion gap. *N Engl J Med*. 1980;303:854-8.
5. Kraut JA and Madias NE. Lactic acidosis. *N Engl J Med*. 2014;371:2309-19.
6. Luft FC. Lactic acidosis update for critical care clinicians. *J Am Soc Nephrol*. 2001;12 Suppl 17:S15-9.
7. Adeva-Andany M, Lopez-Ojen M, Funcasta-Calderon R, Ameneiros-Rodriguez E, Donapetry-Garcia C, Vila-Altesor M and Rodriguez-Seijas J. Comprehensive review on lactate metabolism in human health. *Mitochondrion*. 2014;17:76-100.
8. Madias NE. Lactic acidosis. *Kidney Int*. 1986;29:752-74.
9. Cingolani HE, Mattiazzi AR, Blesa ES and Gonzalez NC. Contractility in isolated mammalian heart muscle after acid-base changes. *Circ Res*. 1970;26:269-78.
10. Fabiato A and Fabiato F. Effects of pH on the myofilaments and the sarcoplasmic reticulum of skinned cells from cardiac and skeletal muscles. *J Physiol*. 1978;276:233-55.
11. Solaro RJ, Lee JA, Kentish JC and Allen DG. Effects of acidosis on ventricular muscle from adult and neonatal rats. *Circ Res*. 1988;63:779-87.
12. Shapiro JI. Functional and metabolic responses of isolated hearts to acidosis: effects of sodium bicarbonate and Carbicarb. *The American journal of physiology*. 1990;258:H1835-9.
13. Schotola H, Toischer K, Popov AF, Renner A, Schmitto JD, Gummert J, Quintel M, Bauer M, Maier LS and Sossalla S. Mild metabolic acidosis impairs the beta-adrenergic response in isolated human failing myocardium. *Crit Care*. 2012;16:R153.
14. Kimmoun A, Ducrocq N and Levy B. New conclusive data on human myocardial dysfunction induced by acidosis. *Crit Care*. 2012;16:160.
15. Shapiro JI. Pathogenesis of cardiac dysfunction during metabolic acidosis: therapeutic implications. *Kidney international Supplement*. 1997;61:S47-51.
16. Shapiro JI, Whalen M and Chan L. Hemodynamic and hepatic pH responses to sodium bicarbonate and Carbicarb during systemic acidosis. *Magn Reson Med*. 1990;16:403-10.
17. Suleymanlar G, Zhou HZ, McCormack M, Elkins N, Kucera R, Reiss OK and Shapiro JI. Mechanism of impaired energy metabolism during acidosis: role of oxidative metabolism. *The American journal of physiology*. 1992;262:H1818-22.
18. Harrison SM, Frampton JE, McCall E, Boyett MR and Orchard CH. Contraction and intracellular Ca²⁺, Na⁺, and H⁺ during acidosis in rat ventricular myocytes. *The American journal of physiology*. 1992;262:C348-57.
19. Choi HS, Trafford AW, Orchard CH and Eisner DA. The effect of acidosis on systolic Ca²⁺ and sarcoplasmic reticulum calcium content in isolated rat ventricular myocytes. *The Journal of physiology*. 2000;529 Pt 3:661-8.
20. Sikes PJ, Zhao P, Maass DL, White J and Horton JW. Sodium/hydrogen exchange activity in sepsis and in sepsis complicated by previous injury: 31P and 23Na NMR study. *Crit Care Med*. 2005;33:605-15.
21. DeSantiago J, Maier LS and Bers DM. Phospholamban is required for CaMKII-dependent recovery of Ca transients and SR Ca reuptake during acidosis in cardiac myocytes. *J Mol Cell Cardiol*. 2004;36:67-74.
22. Wu LL, Tang C, Dong LW and Liu MS. Altered phospholamban-calcium ATPase interaction in cardiac sarcoplasmic reticulum during the progression of sepsis. *Shock*. 2002;17:389-93.

23. Dong LW, Wu LL, Ji Y and Liu MS. Impairment of the ryanodine-sensitive calcium release channels in the cardiac sarcoplasmic reticulum and its underlying mechanism during the hypodynamic phase of sepsis. *Shock*. 2001;16:33-9.
24. Katz AM and Hecht HH. Editorial: the early "pump" failure of the ischemic heart. *Am J Med*. 1969;47:497-502.
25. Miller RG, Boska MD, Moussavi RS, Carson PJ and Weiner MW. ³¹P nuclear magnetic resonance studies of high energy phosphates and pH in human muscle fatigue. Comparison of aerobic and anaerobic exercise. *J Clin Invest*. 1988;81:1190-6.
26. Kimmoun A, Novy E, Auchet T, Ducrocq N and Levy B. Hemodynamic consequences of severe lactic acidosis in shock states: from bench to bedside. *Crit Care*. 2015;19:175.
27. Mitchell JH, Wildenthal K and Johnson RL, Jr. The effects of acid-base disturbances on cardiovascular and pulmonary function. *Kidney international*. 1972;1:375-89.
28. Darby TD and Watts DT. ACIDOSIS AND BLOOD EPINEPHRINE LEVELS IN HEMORRHAGIC HYPOTENSION. *The American journal of physiology*. 1964;206:1281-4.
29. Nahas GG, Zagury D, Milhaud A, Manger WM and Pappas GD. Acidemia and catecholamine output of the isolated canine adrenal gland. *The American journal of physiology*. 1967;213:1186-92.
30. Nahas GG, Ligou JC and Mehlman B. Effects of pH changes on oxygen uptake and plasma catecholamine levels in the dog. *The American journal of physiology*. 1960;198:60-6.
31. Campbell GS. Cardiac arrest: further studies on the effect of pH changes on vagal inhibition of the heart. *Surgery*. 1955;38:615-34.
32. Cooper DJ, Walley KR, Wiggs BR and Russell JA. Bicarbonate does not improve hemodynamics in critically ill patients who have lactic acidosis. A prospective, controlled clinical study. *Annals of internal medicine*. 1990;112:492-8.
33. Teplinsky K, O'Toole M, Olman M, Walley KR and Wood LD. Effect of lactic acidosis on canine hemodynamics and left ventricular function. *The American journal of physiology*. 1990;258:H1193-9.
34. Davies AO. Rapid desensitization and uncoupling of human beta-adrenergic receptors in an in vitro model of lactic acidosis. *J Clin Endocrinol Metab*. 1984;59:398-405.
35. Kellum JA, Song M and Venkataraman R. Effects of hyperchloremic acidosis on arterial pressure and circulating inflammatory molecules in experimental sepsis. *Chest*. 2004;125:243-8.
36. Orchard CH and Cingolani HE. Acidosis and arrhythmias in cardiac muscle. *Cardiovasc Res*. 1994;28:1312-9.
37. Arieff AI, Leach W, Park R and Lazarowitz VC. Systemic effects of NaHCO₃ in experimental lactic acidosis in dogs. *The American journal of physiology*. 1982;242:F586-91.
38. Graf H, Leach W and Arieff AI. Evidence for a detrimental effect of bicarbonate therapy in hypoxic lactic acidosis. *Science*. 1985;227:754-6.
39. Adler S, Roy A and Relman AS. Intracellular Acid-Base Regulation. I. The Response of Muscle Cells to Changes in Co₂ Tension or Extracellular Bicarbonate Concentration. *J Clin Invest*. 1965;44:8-20.
40. Kraut JA and Madias NE. Treatment of acute metabolic acidosis: a pathophysiologic approach. *Nat Rev Nephrol*. 2012;8:589-601.
41. Shapiro JI, Whalen M, Kucera R, Kindig N, Filley G and Chan L. Brain pH responses to sodium bicarbonate and Carbicarb during systemic acidosis. *The American journal of physiology*. 1989;256:H1316-21.
42. Kindig NB, Sherrill DS, Shapiro JI and Filley GF. Extracorporeal bicarbonate space after bicarbonate or a bicarbonate-carbonate mixture in acidotic dogs. *J Appl Physiol* (1985). 1989;67:2331-4.
43. Shapiro JI, Mathew A, Whalen M, Honigman B, Kaehny WD, Petty TL and Chan L. Different effects of sodium bicarbonate and an alternate buffer (Carbicarb) in normal volunteers. *Journal of Critical Care*. 1990;5:157-160.
44. Olson DE, Dart GA and Filley GF. Pressure drop and fluid flow regime of air inspired into the human lung. *J Appl Physiol*. 1970;28:482-94.
45. Shapiro JI, Elkins N, Logan J, Ferstenberg LB and Repine JE. Effects of sodium bicarbonate, disodium carbonate, and a sodium bicarbonate/carbonate mixture on the PCO₂ of blood in a closed system. *J Lab Clin Med*. 1995;126:65-9.
46. Kimmoun A, Ducrocq N, Sennoun N, Issa K, Strub C, Escanye JM, Leclerc S and Levy B. Efficient extra- and intracellular alkalinization improves cardiovascular functions in severe lactic acidosis induced by hemorrhagic shock. *Anesthesiology*. 2014;120:926-34.

47. Allegretti AS, Flythe JE, Benda V, Robinson ES and Charytan DM. The effect of bicarbonate administration via continuous venovenous hemofiltration on acid-base parameters in ventilated patients. *BioMed research international*. 2015;2015:901590.
48. Rocktaschel J, Morimatsu H, Uchino S, Ronco C and Bellomo R. Impact of continuous veno-venous hemofiltration on acid-base balance. *Int J Artif Organs*. 2003;26:19-25.
49. Nahas GG, Sutin KM, Fermon C, Streat S, Wiklund L, Wahlander S, Yellin P, Brasch H, Kanchuger M, Capan L, Manne J, Helwig H, Gaab M, Pfenninger E, Wetterberg T, Holmdahl M and Turndorf H. Guidelines for the treatment of acidaemia with THAM. *Drugs*. 1998;55:191-224.
50. Moon PF, Gabor L, Gleed RD and Erb HN. Acid-base, metabolic, and hemodynamic effects of sodium bicarbonate or tromethamine administration in anesthetized dogs with experimentally induced metabolic acidosis. *American journal of veterinary research*. 1997;58:771-6.
51. Wildenthal K, Mierzwiak DS, Myers RW and Mitchell JH. Effects of acute lactic acidosis on left ventricular performance. *The American journal of physiology*. 1968;214:1352-9.
52. Sirieix D, Delayance S, Paris M, Massonnet-Castel S, Carpentier A and Baron JF. Tris-hydroxymethyl aminomethane and sodium bicarbonate to buffer metabolic acidosis in an isolated heart model. *American journal of respiratory and critical care medicine*. 1997;155:957-63.
53. Hoste EA, Colpaert K, Vanholder RC, Lameire NH, De Waele JJ, Blot SI and Colardyn FA. Sodium bicarbonate versus THAM in ICU patients with mild metabolic acidosis. *Journal of nephrology*. 2005;18:303-7.
54. Stacpoole PW. The pharmacology of dichloroacetate. *Metabolism: clinical and experimental*. 1989;38:1124-44.
55. Wilkerson DP, Campbell IT, Blackwell JR, Berger NJ and Jones AM. Influence of dichloroacetate on pulmonary gas exchange and ventilation during incremental exercise in healthy humans. *Respiratory physiology & neurobiology*. 2009;168:224-9.
56. Stacpoole PW, Wright EC, Baumgartner TG, Bersin RM, Buchalter S, Curry SH, Duncan CA, Harman EM, Henderson GN, Jenkinson S and et al. A controlled clinical trial of dichloroacetate for treatment of lactic acidosis in adults. The Dichloroacetate-Lactic Acidosis Study Group. *N Engl J Med*. 1992;327:1564-9.
57. Filley GF and Kindig NB. Carbicarb, an alkalinizing ion-generating agent of possible clinical usefulness. *Trans Am Clin Climatol Assoc*. 1985;96:141-53.
58. Li YC, Wiklund L and Bjerneroth G. Influence of alkaline buffers on cytoplasmic pH in myocardial cells exposed to hypoxia. *Resuscitation*. 1997;34:71-7.
59. Li YC, Wiklund L, Tarkkila P and Bjerneroth G. Influence of alkaline buffers on cytoplasmic pH in myocardial cells exposed to metabolic acidosis. *Resuscitation*. 1996;32:33-44.
60. Bersin RM and Arieff AI. Improved hemodynamic function during hypoxia with Carbicarb, a new agent for the management of acidosis. *Circulation*. 1988;77:227-33.
61. Leung JM, Landow L, Franks M, Soja-Strzepa D, Heard SO, Arieff AI and Mangano DT. Safety and efficacy of intravenous Carbicarb in patients undergoing surgery: comparison with sodium bicarbonate in the treatment of mild metabolic acidosis. SPI Research Group. Study of Perioperative Ischemia. *Critical care medicine*. 1994;22:1540-9.
62. Kolloffel WJ, de Vroom TE, Weekers LE and Woittiez AJ. Severe cutaneous side effects of peripheral infusions with carbicarb half strength. *Intensive Care Med*. 1994;20:531.