JACOBS PUBLISHERS

OPEN ACCESS

Jacobs Journal of Pulmonology

Mini Review

The Impact of Acid-Base Imbalance on the Diaphragm (a Mini Review)

Robert S. Fitzgerald*

Departments of Environmental Health Sciences, of Physiology, and of Medicine, The Johns Hopkins Medical Institutions of the Johns Hopkins University

**Corresponding author: Dr. Robert S. Fitzgerald, Program in Physiology, Toxicology, and Molecular Mechanisms, Department of Environmental Health Sciences, Bloomberg School of Public Health, 615 N. Wolfe St., Baltimore, MD 21205, Tel: 410-614-5450; Email: rfitzger@jhsph.edu.*

Received: 09-22-2015

Accepted: 10-16-2015

Published: 11-19-2015

Introduction

In these days of beautiful cell, sub-cell, gene explorations few studies focus on the performance of an organ and the mechansims responsible for that performance. For the pulmonary clinician it might be helpful to review how different forms of acid-base imbalance affect one of the pumps responsible for providing the organism with oxygen, the diaphragm (D).

Respiratory and metabolic acidoses can be compensated suggesting that if the uncompensated acidoses produced a deleterious effect, the compensation of that form would attenuate or even abolish the deleterious effect. The four forms of imbalance can appear in several pathologies such as COPD, asthma, diabetes, kidney malfunction.

The impact of AB imbalance on muscle tissue focused initially on limb skeletal muscles (smitendinosus, EDL, soleus) and cardiac muscle. Studies on the D were exceedingly few, very probably due to the fact that the D is not a readily accessbile skeletal muscle. What must be kept in mind is that the D, though a skeletal muscle, is much like the heart in that both are continuously contracting in a way that limb muscles are not. And whereas both the heart and D need external calcium for contraction, it is not clear that all limb muscles are so obligated. Hence, it would seem advisable to avoid a too facile extrapolation of results from limb muscle studies to the D.

Most clinicians treating COPD understandably focus on the major problems of gas exchange. Very little, if any, attention is paid to the impact on the functioning of the D. Yet attendant on poor gas exchange in addition to hypoxemia could be an increase in $PaCO_2$. As we shall see, hypercapnia can compromise the force of contraction (FC) of the D, thus initiating a chemoreceptor-mediated injurious positive feedback circle. The increased $PaCO_2$ would stimulate an increase in ventilation. But the very muscle charged with increasing the ventilation is being rendered less able to contract. Other clinical conditions involving increased airways resistance, hypoventilation, or kidney malfunction can also generate an acid-base imbalance.

Effect of Respiratory Acidosis on Skeletal Muscles

The deleterious effect of respiratory acidosis on the force of contraction (FC) of skeletal muscle is well documented [1-6]. Patients with moderate to severe COPD commonly experience mild to moderate hypercapnia. Skeletal muscle dysfunction in COPD patients has also been reported [7]. Hence, it is not surprising that several studies on the D have shown that increased CO_2 reduces the D's FC, including in vitro studies of the rat D [8], in vivo studies of the dog D [9], and some human studies [7,10].

Though some studies have reported that the D does not increase its FC when challenged with a lowered PCO_2 (hypocapnia, alkalosis), fewer studies have focused on the results of a compensated respiratory acidosis. In the in vitro rat D study [8] when bath PCO_2 was set at 119.5 ± 4.4 mmHg and $[H^+]$ was 97.7±5.9 nM, the FC decreased to 89% of the control at 1 min and remained there for the entire 15 min

exposure. But with the addition of HCO_3^- to the bath, when PCO_2 was set at 114.0±4.5 mmHg and $[H^+]$ was recorded at 34.9± 1.3 nM, the FC decreased to ~95% of the control at 1 min but then rose to control levels out to the 15 min of exposure. We are unaware of any study of HCO_3^- compensated respiratory acidosis in other animal models, human subjects, or patients. Consistent with these results are the studies of the interaction of fatigue and acidosis [11,12].

Effect of Metabolic Acidosis on the D

In response to metabolic acidosis the same ten in vitro rat Ds as above [8] showed that the FC was reduced. When HCO_3^- was reduced from 28.0 to 11.3 mM, the $[H^+]$ increased from 30.5±1.6 to 57.8±3.5 nM. The lowered HCO_3^- dropped the PCO_2 of the bath from 40.9±3.2 to 34.8±1.7. The FC decreased to 92% of the control in the first min. And though recovering somewhat over the next 14 min, FC remained significantly lower at 95% of the control. When these same ten rat Ds were challenged with a compensated metabolic acidosis by lowering the bath PCO_2 from 40.6±3.2 to 18.7±1.8 mmHg with $[H^+]$ going from 33.8±1.7 to 32.5±2.4, the FC significantly decreased to 89% of the control by the first min; by min 5 FC was at 86% of the control and remained there through min 15.

A similar regimen was followed in a canine model in which 13 open-chested dogs had their abdomens tightly casted. This makes any contraction of the D virtually isometric. Their phrenic nerves were stimulated at frequencies 5 -70 Hz. FC was assessed by the pressure changes (Pdi) in a balloon placed immediately under the D [13]. Table 1 presents the in vivo blood gas values. Metabolic acidosis was induced by infusion 0.6 N HCl into the left femoral artery.

Table 1

	Control	Metabolic Acidosis	Compensated Acidosis
pHa	7.38±.01	7.00±.03	7.34±.02
$PaCO_2$ (torr)	36.2±2	36.2±2	12.8±1
PaO_2 (torr)	260±19	268±19	171±1

And again the FC, measured as transdiaphragmatic pressure, during metabolic acidosis was significantly less than control at all frequencies of stimulation greater then 5Hz. The FC during the compensated acidosis was significantly less than metabolic acidosis at all stimulation frequencies. So with both the in vitro rat model and the in vivo dog model the D reduced its FC more during the compensated metabolic acidosis (lowered PCO_2) than during metabolic acidosis.

A significant corpus of literature supports this brief overview of the response of skeletal muscle, particularly the D, to changes in acid-base balance. The attempts to compensate either respiratory or metabolic acidosis are usually successful with respect to bringing the intracellular $[H^+]$ back towards the normal value. For example, an earlier study of the resting rat D, using ^{31}PNMR spectroscopy, reported [14] that during metabolic acidosis when the superfusate pH fell from 7.42 to 7.00 the intracellular pH dropped from ~7.05 to ~6.85 in the course of a two hour exposure. However, during the two hour exposure to compensated metabolic acidosis when superfusate pH fell from 7.40 to 7.35, the intracellular pH changed from ~7.05 to ~ 7.08; the trend was alkalotic probably due to the superfusate's very low PCO_2 (31.6 to 10.2 mmHg). But restoring FC is not always so uniform, and sometimes seems paradoxical. However, Bettice [15], examining the rat thigh muscle, did not see an intracellular acidosis when the animal was made systemically acidotic with an intraperitoneal injection of 6mEq/kg HCl. Somewhat puzzling is the report of Burnell [16] who also states that acidification by reducing extracellular HCO_3^- did not produce intracellular acidosis. Yet his table 1 and the connected text presents just the opposite. The pHi dropped from 6.84 to 6.78 ($P<0.02$). The seminal work of Heisler [17] in the in vitro rat D showed that when pHe was varied between 7.15 and 7.40, pHi remained relatively constant during both respiratory and metabolic acidosis. This suggested that during metabolic changes there was a bicarbonate efflux from the intracellular compartment. During respiratory changes there was a bicarbonate influx into the intracellular compartment.

Effect of Respiratory Acidosis on Muscle Mechanics

A brief inspection of what happens to the twitch characteristics of skeletal muscle gives some insight into the mechanics of why the FC is compromised by acidosis. Peak twitch tension (PTT), Time to peak tension (TPT), and 1/2 relaxation time (1/2RT) are the characterisics usually studied.

In the in vivo canine model during normocapnia a single supramaximal impulse to the phrenic nerves generated a PTT of ~20 cmH_2O in the sub-diaphragmatic balloon (Pdi).

Hypercapnia ($PaCO_2$ ~ 87 mmHg) uniformly reduced PTT to 83% of the control. TPT was not altered significantly in these 18 exposures in the six animals [18]. Other studies of both diaphragm [12,9] and other skeletal muscles [5] have shown results consistent with these findings. The major impact of the increased CO_2 is on the PTT. Frequently the TPT and the 1/2RT are unaffected. As remarked above we are unable to find any report of the the D's performance or its twitch characteristics when challenged with compensated respiratory acidosis.

Effect of Metabolic Acidosis on Muscle Mechanics

With the canine diaphragm challenged with metabolic acidosis one study [13] reports the PTT was reduced but not significantly. However, with compensated metabolic acidosis the decrease became significant. There was no impact on the TPT. But the 1/2RT was significantly reduced in both forms, suggesting a more rapid disappearance of calcium from the sarcoplasm into the sarcoplasmic reticulum. Frequently the changes in the twitch characteristics explain why the FC was changed, but this is not always the case. The decrease in 1/2RT suggests the possibility that different mechanisms operate behind the decreased FC in metabolic acidosis.

Potential Souces of Decreased FC and Mechanics

Seeking an explanation of why the FC and these twitch characteristics behaved in the manner in which they did, one finds that sources of the weakness include changes in fiber types. In COPD more Type IIb fibers are present than Type I. Type IIb are fast twitch, develop tension, and are prone to fatiguibility. Type I are slow twitch and fatigue resistant. Also reported have been reduced capillarity, decreased oxidative enzyme capacity, altered cellular bioenergetics [19].

Further, of course, one might look to energy stores, calcium handling, and influence on the myofibril itself. In the ^{31}PNMR spectroscopic study of the resting rat in vitro D exposed to two hours of hypercapnia [20] (superfusate PCO_2 of 109 mmHg; pH of 6.99; pHi of ~6.88) PCr, ATP, Pi values did not differ significantly from those during the normocapnic exposure (supefusate PCO_2 of 37.3 mmHg; pH of 7.43; pHi of ~7.03). The companion study [15] using the same preparation and same technique with exposures to metabolic acidosis and compensated metabolic acidosis (cf. above for pH values) again PCr, ATP, and Pi values between the two forms of acidosis were virtually identical. These results suggest that acidoses per se might have no effect on the energy stores in the rat and dog D. However, Dawson et al. [21], using the ^{31}PNMR technique with the frog gastrocnemius, report the stimulus-driven contractions increased [H^+] and decreased [ATP] and the FC. And Fiaccadori et al. [22] report that in muscle biopsies from quadriceps of patients with severe COPD ATP and PCr contents were reduced, accompanying the intracellular acidosis related to hypercapnia.

Of major, indeed critical, importance is the effect of acidosis on free Ca^{++} in the muscle. The report of Fabiato and Fabiato [23] thoroughly explores the response of Ca^{++} in the sarcolemma-free semitendinosus of the frog. Decreasing the pH of the fluid bathing the sarcolemma-free muscle from 7.4 to 6.2 required a 3-fold increase in the fluid's concentration of free Ca^{++} for the myofilaments to develop 50% of the maximum tension. Further, acidosis depressed the maximum tension developed in the presence of a saturating concentration of free Ca^{++}. Moderate fluid acidosis caused an effect on the semitendinosus sarcoplasmic reticulum that could compensate for the depressant action of acidosis on the myofilament. Finally, their data from the skinned muscle cells did not suggest a simple competition between H^+ and Ca^{++} for a single class of binding sites on troponin. Indeed, the troponin-tropomyosin system may not be the only Ca^{++}-regulatory system in skeletal muscles.

The movement of potassium ions (K^+) greatly impacts the condition of the resting membrane potential of a muscle. This would condition the D's susceptibility to stimulation.

Table 2

Species	Treatment	Species	Treatment
dog, cat, rabbit, man	1	dog, cat, rat, rabbit, man	4
dog, cat man	2	dog, cat, rat, guinea pig	5
dog, cat, rabbit, man	3	dog, cat, rabbit, man	6

where treatment 1 = acute mineral acid acidosis; 2 = acute organic acid acidosis; 3 = acute metabolic alkalosis; 4 = acute mild respiratory acidosis; 5 = acute extremely severe respiratory acidosis; 6 = acute respiratory alkalosis

The comprehensive review of Androgue and Madias [24] explores the role of acute changes in acidity on the movement of K^+ ion in various body compartments. Acute respiratory acidosis promotes a rise in plasma [K^+], but one that is significantly less than that observed during mineral acid acidosis. Interestingly, whereas this type of metabolic acidosis alters the plasma [K^+], organic acid acidosis, such as lactic, acetic, -OH-butyric acids, do not produce a significant change in plasma [K^+]. And in the diabetic the ketoacidosis is usually associated with a normal or even an elevated plasma [K^+]. Acute respiratory alkalosis leads to a decrement in plasma [K^+]. Sodium bicarbonate-induced metabolic alkalosis generally leads to a decrement in plasma [K^+]. They have studied the acid-base distribution effect on plasma [K^+] in several species (cf. Table2). And Fraley and Adler [25] show in the rat that acute variations in plasma [HCO_3^-] under isohydric conditions (by manipulating the PCO_2) are accompanied by reciprocal

changes in plasma.

Further, acute hypercapnia is known to trigger increased sympathetic activity and a catecholamine-induced release of glucose and potassium from the liver [26,27]. An overall summary shows that acute acidemia usually results in hyperkalemia and acute alkalemia usually reduces plasma potassium, though these changes can be modified by an interplay of other factors. Hence, it appears that the D's FC and PTT could be reduced during acidosis at least in part by the impact of increased plasma [K^+] on the D's resting membrane potential.

Pharmacological Agents Correcting the Effect of Acidoses on the D

Many such agents are capable of correcting the reduced contractility of the D during acidoses. However, the elements within the muscle which they are capable of affecting are several. The sarcoplasmic reticulum, the myofibril itself, the sarcolemma, the neuromuscular junction as well as enzyme systems such as ATPase make any analysis of where agents such as aminophylline, isoproterenol, neostigmine have their effect(s) highly complex and complicated. Presenting a helpful schema of their multiple effects would extend this mini review beyond a reasonable length and in large part be speculative. Hence, we shall note that such agents have been reported to have correcting effects [18], and leave it to the clinician reader to pursue such explanations if helpful.

Conclusion

A clear, precise understanding of how H^+ ion affects the D's FC remains to be found. That H^+ ion affects critical processes in skeletal muscle performance is well documented. All of these effects would seem to compromise FC. But then how does one explain the largest decrease in FC observed, during compensated metabolic acidosis where the pHi of the muscle is somewhat alkalotic? This apparent paradox suggests multiple mechanisms must operate in conditions involving some sort of acidosis. Possibly the interplay of H^+ ion in nanomolar concentrations with HCO_3^- ion in millimolar concentrations, or their effect on plasma [K^+] affects a mechanism involving the excitation-contraction processes of FC. Firmly established mechanisms accounting for both the expected and the apparently paradoxical phenomena in striated muscles await further investigation. But for the clinician to be sensitive to the potential of an acid-base imbalance to impact the performance of the D seems advisable. Helpful information, even though not focused specifically on acid-base imbalance per se, are the studies found in Roussos [28] and Laghi's study of respiratory muscles [29] which focus more on COPD and other pulmonary problems capable of creating systemic acid-base problems.

References

1. Crul-Sluljter E, Crul J. Acidosis and neuromuscular blockade. In Acta Anaethesiol Scand. 1974, 18(3): 224-236.

2. Fitzgerald R, Garfinkel F, Silbergeld E, Loscutoff S. Factors in the interpretation of mouth occlusion pressure during measurements of chemosensitivity. In Chest. 1976, 70 (Suppl 1): 145-149.

3. Hill D. Tension due to interaction between the sliding filaments in resting striated muscle. The effect of stimulation. In J Physiol Lond. 1968, 199(3): 637-684.

4. Pannier J, Weyne J, Leusen I. Effects of PCO_2, becarbonate and lactate on the isometric contractions of isolated soleus muscle of the rat. In Pfluegers Arch. 1970, 320(2): 120-132.

5. Sahlin K, Edstrom L, Sjoholm H. Fatigue and phosphocreatine depletion during carbon dioxide-induced acidosis in rat muscle. In Am J Physiol 1983, 245 (Cell Physiol 14): C15-C20.

6. Vianna L, Koulouris N, Lanigan C, Moxham J. Effect of acute hypercapnia on limb muscle contractility in humans. In J Appl Physiol 1990, 69(4): 1486-1493.

7. Juan G, Calverley P, Talamo C, Schnader J, Roussos C. Effect of carbon dioxide on diaphragmatic function in human beings. In N Eng J Med. 1984, 310(14): 874-879.

8. Fitzgerald R, Hauer M, Bierkamper G, Raff H. Responses of in vitro rat diaphragm to changes in acid-base environment. In J Appl Physiol. 1984, 57(4): 1202-1210.

9. Schnader J, Juan G, Howell S, Fitzgerald R, Roussos C. Arterial CO_2 partial pressure affects diaphragmatic function. In J Appl Physiol 1985, 58(3): 82_3-829.

10. Rochester D, Braun N, Arora N. Respiratory muscle strength in chronic obstructive pulmonary disease. In Am Rev Respir Dis. 1979, 119: 151-154.

11.Jones N, Sutton J, Taylor R, Toews C. Effect of pH on cardiorespiratory and metabolic responses to exercise. In J Appl Physiol : Respirat Environ Exercise Physiol. 1977, 43(6): 959-964.

12. Schnader J, Howell S, Fitzgerald R, Roussos C. Interaction of fatigue and hypercapnia in the canine diaphragm. In J Appl Physiol. 1988, 64(4): 1636-1643.

13. Howell S, Fitzgerald R, Roussos C. Effects of uncompensated and compensated metabolic acidosis on canine diaphragm. In J Appl Physiol. 1985, 59(5): 1376-1382.

14. Fitzgerald R, Howell S, Pike M, Jacobus W. NMR study of rat

diaphragm exposed to metabolic and compensated metabolic acidosis. In J Appl Physiol. 1988, 65(5): 2278-2284.

15. Bettice J. Effect of hypocapnia on intracellular pH during metabolic acidosis. In Respir Physiol. 1979, 38(3): 257-266.

16. Burnell J. In vivo response of muscle to changes in CO_2 tension or extracellular bicarbonate. In Am J Physiol. 1968, 215(6): 1376-1383.

17. Heisler, N. Intracellular pH of isolated rat diaphragm muscle with meabolic and respiratory changes of extracellular pH. In Respir. Physiol. 1975, 23(2): 24_{3-}255.

18. Howell S, Fitzgerald R, Roussos C. Effects of aminophylline, isoproterenol, and neostigmine on hypercapnic depression of diaphragmatic contractility. In Am Rev Resp Dis. 1985, 132(2): 241-247.

19. Mador MJ, Bozkanat E. Skeletal muscle dysfunction in chronic obstructive pulmonary disease. In Respir Res. 2001, 2(4): 216-224.

20. Fitzgerald R, Howell S, Jacobus W. ^{31}PNMR study of resting in vitro rat diaphragm exposed to hypercapnia. In J Appl Physiol. 1988, 65(5): 2270-2277.

21. Dawson M, Gadian D, Wilkie D. Muscular fatigue investigated by phosphorus nuclear magnetic resonance. In Nature. 1978, 274: 861-866.

22. Fiaccadori E, Del Canale S, Vitali P, Coffrini E, Ronda N et al. Skeletal muscle energetics, acid-base equilibrium and lactate metabolism in patients with severe hypercapnia and hypoxemia. In Chest. 1987, 92(5): 88_{3-}887.

23. Fabiato A, Fabiato F. Effects of pH on the myofilaments and the sarcoplasmic reticulum of skinned cells from cardiac and skeletal muscles. In J Physiol. 1978, 276: 23_{3-}255.

24. Adrogue H, Madias N. Changes in plasma potassium concentration during acute acid-base disturbances. In Am J Med. 1981, 71(3): 456-467.

25. Fraley D, Adler S. Isohydric regulation of plasma potassium by bicarbonate in the rat. In Kidney Int. 1976, 9(4): 33_{3-}343.

26. Fenn W, Asano T. Effects of carbon dioxide inhalation on potassium liberation from the liver. In Am J Physiol. 1956, 185(3): 567-576.

27. Mackay J. Effects of a narcotic level of carbon dioxide on the plasma potassium and respiration of cats. In Am J Phsiol. 1947, 151(2): 469-478.

28. Roussos C. The Thorax Part A Physiology. New York, Marcel Dekker, 1995.

29. Laghi F, Tobin J. Disorders of the respiratory muscles. In Amer J Respir Crit Care Med. 2003, 168(1): 10-48.