

# Assessment of Hyperlactatemia and Acidosis in patients with Cardiac Dysfunctions

<sup>1,2</sup>Junaid Mahmood Alam, <sup>2</sup>Jawaid Altaf Baig, Rabia Shaheen, Aijaz Ahmad, Sarah Sughra Asghar, <sup>3</sup>Suad Naheed, Ishrat Sultana and <sup>4</sup>Siddiqua Jamall.

## ABSTRACT:

**Background:** It has been postulated that hyperlactatemia is not the only cause of acidosis in cardiac dysfunction and there are other factors such as un-measured anions also that significantly participate in its development.

**Aim:** The present study is designed to determine different components of metabolic acidosis in cardiac dysfunctions and cardiac arrest patients in order to assess the degree to which lactate is responsible for the acidosis.

**Methods and Materials:** Forty two patients with out-of-hospital cardiac dysfunctions and cardiac arrest, admitted to the hospital were included in present study. All arterial blood gases and plasma biochemical parameters were estimated by standard methods on automated analyzers. Modified [by Figge and colleagues] form of Stewart's quantitative biophysical methods including formula for apparent strong ion difference "SIDa" and strong ionic gap "SIG" were used to evaluate un-measured and measured ions. **Results:** The mean age of patients were 57.2 years and included 33 (78.6%) males and 9 (21.4%) females. Except for sodium, ionized calcium and SIDa, all variables were significantly different between the two groups. Patients with cardiac dysfunctions and arrest were also hyperkalemic, hypochloremic and hyperlactatemic. The anion gap and SIG were also higher in patients with cardiac arrest. Lactate was the strongest determinant of acidemia. **Conclusion:** It was concluded that lactate accounts for only less than 50% of the metabolic acidosis and consequent acidemia seen in such patients and that an increase in unmeasured anions and phosphate also accounts for major portion of acidemia.

## KEY WORDS:

SID = strong ionic difference, SIG = strong ionic gap, hyperlactatemia, anion gap, standard base excess.

## INTRODUCTION:

Metabolic acidosis is the most frequent acid-base disorder in the intensive care and cardiac care<sup>1</sup>. It is reported that critically ill patients sometimes present complex acid-base disorders, even if their pH, PCO<sub>2</sub>, [HCO<sub>3</sub><sup>-</sup>] and base excess levels are normal<sup>2</sup>. Moreover, acidosis caused by increased un-measured anion levels known to occurs after cardiac surgery<sup>3</sup> and some forms of metabolic acidosis (lactate) seem to have worse outcomes than others such as chloride. It has been postulated that hyperlactatemia is not the only cause of acidosis in cardiac dysfunction and there are other factors also that significantly participate in its development<sup>4</sup>. Similarly, it is reported that hyperlactatemia cannot be blamed for the cause of metabolic acidosis in some patients<sup>4-6</sup>. Furthermore, on the contrary, it is known that, metabolic acidosis is common in patients with cardiac arrest and related dysfunctions are conventionally considered to be due essentially to hyperlactatemia<sup>4</sup>.

<sup>10</sup>. In spite of all hypothesis, research and reports, the pathogenesis of the metabolic acidosis in cardiac arrest is not fully understood<sup>11</sup>. Traditional assessment which was the anion gap, bicarbonate and standard base excess have long been useful in understanding acidosis<sup>4,12,13</sup>. However, it provides little information regarding the mechanisms involved and the quantitative contribution of each variable<sup>4,14-17</sup>, especially in the presence of major changes in serum electrolytes and albumin concentration. In recent years a quantitative assessment protocols known as Stewart-Figge methodology<sup>4,18,19</sup> has been recommended and found to be useful in explaining and quantifying acid-base changes in clinical situations in which conventional analysis was deficient<sup>4,20-23</sup>. Therefore the present study is designed to determine different components of metabolic acidosis in cardiac dysfunctions and cardiac arrest patients in order to assess the degree to which lactate (hyperlactaemia) is responsible for the acidosis<sup>24</sup>.

## MATERIALS AND METHODS:

**Research Designs, Patients and Sampling:** A prospective study plan was designed and carried out in Department of Biochemistry Lab services, Liaquat National Hospital and Medical College, Karachi. The patients were recruited prospectively with cardiac dysfunctions and most importantly after cardiac arrest, admitted to the hospital from April 2006 to August 2008. The number of the patients were  $n = 42$ , 33 males (age group 45-59 years) and 9 females (age group 41-60 years). Fifteen patients with minor injuries were also included in the study for comparison purpose. As per description provided earlier<sup>4</sup> cardiac arrest was defined as the absence of both spontaneous respiration and palpable pulse. Data evaluated included age, sex, initial electrocardiographic record, and possible cause. Protocols described and established earlier were followed for proper management of present study<sup>4,24</sup>. As stated earlier to compare the acid-base characteristics of these patients, a comparison group was used comprising of patients with non-fatal or debilitated clinical conditions and for whom the department routinely measured all variables required for the analysis. Arterial samples were collected in heparinized syringes and analyzed within 15 min by a blood-gas analyzer (Nova-Phox-plus, Nova Biomedical, MA, USA) at the time of admission. The data collected from the analyzers output was: pH, partial pressure of carbon dioxide, bicarbonate and standard base excess. Blood samples were also analyzed at the biochemistry laboratory for the measurement of biochemical variables including sodium, potassium, total magnesium, ionized calcium, chloride, albumin, phosphate and lactate (Hitachi 912, Roche Diagnostic, Basil; Nova 4 electrolyte analyzer, Nova Biomedical, MA, USA).

### Quantitative physicochemical analysis:

The results were calculated by Stewart's quantitative biophysical methods<sup>18</sup> as modified by Figge and colleagues<sup>19</sup> including formula for apparent strong ion difference "SIDa", effective strong ion difference "SIDe" and strong ionic gap "SIG" provided earlier<sup>4</sup>. As per description stated<sup>4</sup>, a positive value for SIG must represent unmeasured anions (such as sulfate, oxo acids, citrate, pyruvate, acetate and gluconate) that must be included to account for measured pH. The traditional anion gap was also calculated as anion gap =  $[Na^+] + [K^+] - [Cl^-] - [HCO_3^-]$ , with a reference range of 12-20 mmol/l<sup>25</sup>. Data are expressed as means

$\pm SD$ , or as percentage. Student's *t*-test and Pearson's correlation was used to compare the study group and the comparison group (SPSS ver 13, USA).  $P < 0.05$  was considered statistically significant.

## RESULTS:

Forty two patients with out-of-hospital cardiac dysfunctions and cardiac arrest, admitted to the hospital were included in present study. The details of these patients are presented in Table 1. They had a mean age of 57.2 years and included 33 (78.6%) males and 9 (21.4%) females. Most of the patients had an initial rhythm of a-systolic (54%) or pulse-less electrical activity (38%), and the number of witnessed arrests was 3 (7.10%). The main cause of collapse was cardiogenic (47.6%), followed by trauma (11.9%) and respiratory (14.30%). Forty two patients of cardiac dysfunction were compared with 15 patients with minor injuries as a comparison group (mean age 43.1 years; 11 males and 4 females). The acid-base variables in cardiac arrest and minor injuries are shown in Table 2. Except for sodium, ionized calcium and SIDa, all variables were significantly different between the two groups. In brief, patients with cardiac dysfunctions were acidemic (pH 6.50 versus 7.24;  $P < 0.001$ ), secondary to metabolic acidosis (standard base excess -18.2 versus -1.6 meq/l;  $P < 0.0001$ ) compared with the comparison group. Patients with cardiac dysfunctions and arrest were also hyperkalemic, hypochloremic and hyperlactatemic. The anion gap and SIG were also higher in patients with cardiac arrest. Lactate was the strongest determinant of acidemia.

## DISCUSSION:

It has been well documented that patients with cardiac arrest and dysfunction develops severe metabolic acidosis condition<sup>4, 5-10, 26-28</sup>. This acidosis has been thought to be secondary to hyperlactatemia<sup>8</sup>. However, it has been postulated that the correlation between standard base excess and lactate is poor, suggesting that other factors such as blood anions might participate in the pathogenesis of cardiac arrest acidosis<sup>5</sup>. Previously, several scientists decided to define and quantify acid-base status in such patients by applying the quantitative principles of acid-base analysis described by Stewart, Figge and colleagues<sup>4,18,19</sup>. Using this methodology, they found that the causes of acidosis were much more complex than previously known<sup>4</sup>. The group has reported lactate was found to be the

biggest contributor to metabolic acidosis and the development of acidemia in these patients, which accounted for only about 50% of it, followed by SIG and phosphate contributed an almost equal percentage (about 33% and 13%, respectively)<sup>4</sup>. However, this acidosis condition was associated with strong compensating responses, which attenuated its severity such as hypochloremia, hyperkalemia, hypoalbuminemia and, to a smaller extent, hypermagnesemia and hypercalcemia<sup>4</sup>. A key finding, as in our study, was that patients with cardiac arrest had a disproportionately higher SIG than the comparison group<sup>4,29</sup>. It was also reported that increased SIG in patients has also been associated with major vascular injury<sup>30</sup>. In addition, hyperphosphatemia in patients with cardiac arrest has been underemphasized as a contributor of acidosis, although causes the reasons of this abnormality remain unclear but may attribute to trans-cellular shift, cellular injury and phosphate release<sup>31,34</sup>. In our study, we have quantified acid– base analysis for patients with cardiac dysfunction and arrest. Furthermore, as done in previous studies, since no drug or fluid was administered, it provides a unique opportunity to study the disorders with minimal iatrogenic modifications. For comparison, as described in previous reports, we used patients with minor injuries<sup>4,24,29</sup>. Although they were well enough to be discharged from the hospital within few days, mild hyperlactatemia (2.4 mmol/l) was present in these patients. However, all other variables, including pH and bicarbonate, were near or in the normal ranges<sup>4</sup>.

Previous studies which evaluated the correlation of metabolic acidosis and outcome in the critically ill have focused on either a specific etiology such as high lactate concentration<sup>29,34,35</sup> or a certain degree of acidosis such as base excess<sup>36-38</sup>. However, it was argued that most of these studies had small sample sizes and were, of course, observational in nature<sup>29</sup>. It is a well established fact that hyperlactatemia is marker of poor outcome in critically ill patients<sup>24,39-42</sup>. However, interpretation of high levels of lactate is a demanding to intensive care consultants since its etiology and pathophysiology is not always understood<sup>24</sup>. Until recently, it was common to use the terms "hyperlactatemia" and "lactic acidosis" interchangeably and as synonyms of "tissue hypoperfusion;" however, this is not always the case<sup>24,43</sup>. In a previous study, it has been shown that patients

with hyperlactatemia usually presented with metabolic acidemia<sup>24</sup>. Furthermore, at the time of admission, both lactate and the standard base deficit were significantly different between intensive care survivors and non-survivors, therefore lactate was not primarily responsible for the acidemia; rather it was the unmeasured anions that were primarily responsible<sup>24</sup>. They are known to increase in several distinct clinical situations such as renal and hepatic impairment<sup>44</sup> tissue hypoperfusion<sup>30</sup> and endotoxemia<sup>45</sup>.

In recent years, it has been extensively suggested that in comparison with chloride, acidosis due to lactate or other anions (SIG) was associated with much higher mortality in hospital<sup>29</sup>. This finding, thus noted, that it was not surprising when the causative anion was found to be lactate, because lactic acidosis has been known for some time to be associated with high mortality in this population<sup>4,24,29,34</sup>. However, other anions, determined in several concurrent studies, including the present one, measured by SIG, are not clearly associated with poor outcome in ICU patients<sup>4,24,29,34</sup>. Moreover, some studies have suggested that SIG is associated with increased mortality in critically ill patients<sup>30,46,47</sup>. A previous study also identified a significant difference in SIG between survivors and non-survivors of patients presenting to the accident and emergency unit who required hospital admission<sup>48</sup>. In agreement with our study, a group of researcher noted that lactate level and SIG were the variables most strongly associated with mortality in critically ill patients suspected of having lactic acidosis<sup>29</sup>.

## CONCLUSION:

In present study using the Stewart–Figge methodology, as suggested earlier<sup>4</sup>, we have studied the acid– base status of cardiac dysfunction and cardiac arrest patients. We found that lactate accounts for only less than 50% of the metabolic acidosis and consequent acidemia seen in such patients and that an increase in unmeasured anions and phosphate also accounts for major portion of acidemia. It was also noted that the acidosis was partially attenuated by the alkalinizing effect of hypochloremia, hyperkalemia, hypoalbuminemia, hypermagnesemia and hypercalcemia. However, the diagnostic and prognostic significance of such study associated with metabolic and acid-base alteration needs larger population and further investigation.

## ACKNOWLEDGEMENTS:

The authors wish to thank Prof. Dr. Jun Makino, Tokyo-Japan; Prof Dr. Kyle J Gunnerson and Prof. Dr. John A. Kellum-Richmond USA and Prof. Dr. Alexandre T. Maciel-Sao Paulo, Brazil, for providing valuable articles and published materials for conception and completion of present study and data comparison.

## REFERENCES:

1. Moviat M, van Haren F, van der Hoeven H. Conventional or physicochemical approach in intensive care unit patients with metabolic acidosis. *Crit Care*. 2003; 7 (3): 219-220.
2. Tuhay G, Pein MC, Masevicius FD, Kutscherauer DO, Dubin A. Severe hyperlactatemia with normal base excess: a quantitative analysis using conventional and Stewart approaches. *Crit Care*. 2008; 12 (3).
3. Murray D, Grant D, Murali N, Butt W. Unmeasured anions in children after cardiac surgery. *J Thorac Cardiovasc Surg*. 2007; 133 (1): 235-240.
4. Makino J, Uchino S, Morimatsu H, Bellomo R. A quantitative analysis of the acidosis of cardiac arrest: a prospective observational study. *Crit Care*. 2005; 9:R357-R362.
5. Praise G, Ratzenhofer-Comenda B, Pierer G, Smolle-Juttner F, Glanzer H, Smolle J. Comparison of lactate or BE during out-of hospital cardiac arrest to determine metabolic acidosis. *Resuscitation* 2001, 51:297-300.
6. Cairns CB, Niemann JT, Pelikan PC, Sharma J. Ionized hypocalcemia during prolonged cardiac arrest and closed-chest CPR in a canine model. *Ann Emerg Med* 1991, 20:1178-1182.
7. Tuchschmidt JA, Mecher CE: Predictors of outcome from critical illness. Shock and cardiopulmonary resuscitation. *Crit Care Clin* 1994, 10:170-195.
8. Capparelli EV, Chow MS, Kluger J, Fieldman A: Differences in systemic and myocardial blood acid-base status during cardiopulmonary resuscitation. *Crit Care Med* 1989, 17:442-446.
9. Leavy JA, Weil MH, Rackow EC: Lactate washout following circulatory arrest. *J Am Med Assoc* 1988, 260:662-664.
10. Sato S, Kimura T, Okubo N, Naganuma T, Tanaka M: End-tidal CO<sub>2</sub> and plasma lactate level: a comparison of their use as parameters for evaluating successful CPR. *Resuscitation* 1993, 26:133-139
11. Hayhoe M, Bellomo R, Liu G, McNicol L, Buxton B. The etiology and pathogenesis of cardiopulmonary bypass-associated metabolic acidosis using polygeline pump prime. *Crit Care*. 1999; 25 (7): 680-685.
12. Astrup PJK, Jorgensen K, Andersen OS, Engel K: The acid-base metabolism – a new approach. *Lancet* 1960, 1:1035-1039.
13. Siggaard-Andersen O, Fogh-Andersen N: Base excess or buffer base (strong ion difference) as measure of a non-respiratory acid-base disturbance. *Acta Anaesthesiol Scand Suppl* 1995, 107:123-128.
14. Figge J, Rossing TH, Fencl V: The role of serum proteins in acid-base equilibria. *J Lab Clin Med* 1991, 117:453-467.
15. McAuliffe JJ, Lind LJ, Leith DE, Fencl V: Hypoproteinemic alkalosis. *Am J Med* 1986, 81:86-90.
16. Rossing TH, Maffeo N, Fencl V: Acid-base effects of altering plasma protein concentration in human blood in vitro. *J Appl Physiol* 1986, 61:2260-2265.
17. Gilfix BM, Bique M, Magder S: A physical chemical approach to the analysis of acid-base balance in the clinical setting. *J Crit Care* 1993, 8:187-197.
18. Stewart PA: Modern quantitative acid-base chemistry. *Can J Physiol Pharmacol* 1983, 61:1444-1461
19. Figge J, Mydosh T, Fencl V: Serum proteins and acid-base equilibria: a follow-up. *J Lab Clin Med* 1992, 120:713-719.
20. Liskaser FJ, Bellomo R, Hayhoe M, Story D, Poustie S, Smith B, Letis A, Bennett M: Role of pump prime in the etiology and pathogenesis of cardiopulmonary bypass-associated acidosis. *Anesthesiology* 2000, 93:1170-1173.
21. Story D, Poustie S, Bellomo R: Quantitative physical chemistry analysis of acid-base disorders in critically ill patients. *Anaesthesia* 2001, 56:530-533.
22. Wilkes P: Hypoproteinemia strong-ion difference, and acid-base status in critically ill patients. *J Appl Physiol* 1998, 84:1740-1748.
23. Fencl V, Jabor A, Kazda A, Figge J: Diagnosis of metabolic acid-base disturbances in critically ill patients. *Am J Respir Crit Care Med* 2000, 162: 2246-2251.

24. Maciel AT, Park M. Unmeasured Anions Account For Most Of The Metabolic Acidosis In Patients With Hyperlactatemia. *Clinics* 2007;62(1):55-62
25. Shapiro BA, Peruzzi WT: Interpretation of blood gasses. In *Textbook of Critical Care* 3rd edition. Edited by: Shoemaker WC, Ayres SM, Grenik A, Holbrook P. Philadelphia: WB Saunders Company; 1995:274-290.
26. Stewart JS, Stewart WK, Gillies HG: Cardiac arrest and acidosis. *Lancet* 1962, ii:964-967.
27. Edmonds-Seal J: acid-base studies after cardiac arrest. A report on 64 cases. *Acta Anaesthesiol Scand* 1966;235-241.
28. Chazan JA, Stenson R, Kurland GS: The acidosis of cardiac arrest. *N Engl J Med* 1968, 278:360-364.
29. Gunnerson KJ, Saul M, He S, Kellum JA. Lactate versus non-lactate metabolic acidosis: a retrospective outcome evaluation of critically ill patients. *Critical Care* 2006, 10:R22 (doi:10.1186/cc3987)
30. Kaplan LJ, Kellum JA: Initial pH, base deficit, lactate, anion gap, strong ion difference, and strong ion gap predict outcome from major vascular injury. *Crit Care Med* 2004, 32:1120-1124.
31. Oster JR, Alpert HC, Vaamonde CA: Effect of acid-base status on plasma phosphorus response to lactate. *Can J Physiol Pharmacol* 1984, 62:939-942.
32. Barsotti G, Lazzeri M, Cristofano C, Cerri M, Lupetti S, Giovannetti S: The role of metabolic acidosis in causing uremic hyperphosphatemia. *Miner Electrolyte Metab* 1986, 12:103-106.
33. Wang F, Butler T, Rabbani GH, Jones PK: The acidosis of cholera. Contributions of hyperproteinemia, lactic acidemia, and hyperphosphatemia to an increased serum anion gap. *N Engl J Med* 1986, 315:1591-1595.
34. Kirschbaum B: The acidosis of exogenous phosphate intoxication. *Arch Intern Med* 1998, 158:405-408.
35. Vincent JL, Dufaye P, Berre J, Leeman M, Degaute JP, Kahn RJ: Serial lactate determinations during circulatory shock. *Crit Care Med* 1983, 11:449-451.
36. Davis JW, Parks SN, Kaups KL, Gladen HE, O'Donnell-Nicol S: Admission base deficit predicts transfusion requirements and risk of complications. *J Trauma* 1996, 41:769-77
37. Rutherford EJ, Morris JA Jr, Reed GW, Hall KS: Base deficit stratifies mortality and determines therapy. *J Trauma* 1992, 33:417-423.
38. Siegel JH, Rivkind AI, Dalal S, Goodarzi S: Early physiologic predictors of injury severity and death in blunt multiple trauma. *Arch Surg* 1990, 125:498-508
39. Smith I, Kumar P, Molloy S, Rhodes A, Newman PJ, Grounds RM, Bennett ED. Base excess and lactate as prognostic indicators for patients admitted to intensive care. *Intensive Care Med*. 2001;27:74-83.
40. Marecaux G, Pinsky MR, Dupont E, Kahn RJ, Vincent JL. Blood lactate levels are better prognostic indicators than TNF and IL-6 levels in patients with septic shock. *Intensive Care Med*. 1996;22:404-8.
41. Bakker J, Coffernils M, Leon M, Gris P, Vincent JL. Blood lactate levels are superior to oxygen-derived variables in predicting outcome in human septic shock. *Chest*. 1991;99:956-62.
42. Bernardin G, Pradier C, Tiger F, Delooffre P, Mattei M. Blood pressure and arterial lactate level are early indicators of short-term survival in human septic shock. *Intensive Care Med*. 1996;22:17-25.
43. Handy JM, Soni NC. Lactic acidosis: theory and practice uncoupled? In *Yearbook of Intensive Care and Emergency Medicine*. Edited by Vincent JL. Berlin: Springer-Verlag; 2004, p 675-82.
44. Kellum JA. Closing the gap on unmeasured anions. *Critical Care*. 2003;7:219-220.
45. Kellum JA, Bellomo R, Kramer DJ, Pinsky MR. Hepatic anion flux during acute endotoxemia. *J Appl Physiol*. 1995;78:2212-7.
46. Balasubramanyan N, Havens PL, Hoffman GM: Unmeasured anions identified by the Fencl-Stewart method predict mortality better than base excess, anion gap, and lactate in patients in the pediatric intensive care unit. *Crit Care Med* 1999, 27:1577-1581.
47. Dondorp AM, Chau TT, Phu NH, Mai NT, Loc PP, Chuong LV, Sinh DX, Taylor A, Hien TT, White NJ, Day NP: Unidentified acids of strong prognostic significance in severe malaria. *Crit Care Med* 2004, 32:1683-1688.
48. Hucker TR, Mitchell GP, Blake LD, Cheek E, Bewick V, Grocott M, Forni LG, Venn RM: Identifying the sick: can biochemical measurements be used to aid decision making on presentation to the accident and emergency department. *Br J Anaesth* 2005, 94:735-741.

**Table 1: Demographics of patients with cardiac dysfunctions**

Parameters	N (%)
Age (years)	57.2 ± 12.6
Male (%)	33 (78.6%)
Female (%)	09 (21.4%)
Cause of dysfunctions (%)	
Cardiogenic	20 (47.6%)
Trauma	05 (11.9%)
Respiratory	06 (14.3%)
Neurological	04 (9.52%)
Other	07 (16.7%)

**Table 2: Biochemical and acid-base components in patients with cardiac dysfunctions and minor injuries**

Variable	Cardiac dysfunction/arrest	Minor Injury	P
pH	6.5 ± 0.11	7.24 ± 0.05	0.01
PCO <sub>2</sub>	76.1 ± 22.1	34.5 ± 6.9	0.002
Bicarbonate (mmol/l)	12.1 ± 2.3	24.3 ± 2.1	0.001
Standard base excess (mmol/l)	-18.2 ± 3.1	-1.6 ± 0.9	0.0001
Sodium (mmol/l)	152.1 ± 6.4	134.2 ± 5.2	0.1
Potassium (mmol/l)	5.5 ± 1.8	3.5 ± 0.6	0.01
Ionized calcium (mmol/l)	1.24 ± 0.11	1.19 ± 0.09	0.1
Total magnesium (mmol/l)	1.18 ± 0.20	0.89 ± 0.11	0.002
Chloride (mmol/l)	94.5 ± 6.1	105.0 ± 2.3	0.002
Lactate (mmol/l)	18.1 ± 4.6	2.4 ± 1.4	0.001
Albumin (g/dl)	3.3 ± 0.9	3.7 ± 0.6	0.01
Phosphate (mmol/l)	2.81 ± 1.11	1.02 ± 0.42	0.001
Anion gap (meq/l)	40.4 ± 11.2	8.5 ± 4.1	0.002
SIDA (meq/l)	48.2 ± 7.2	30.5 ± 2.4	0.29
SIDE (meq/l)	16.2 ± 4.5	10.5 ± 3.0	0.01
SIG-Strong ion gap (meq/l)	35.3 ± 5.7	23.6 ± 4.7	0.001

SIDA = apparent strong ionic difference

SIDE = effective strong ionic difference;

SIG = strong ionic gap