DETERMINATION OF HYPERLACTATEMIA AND ACIDOSIS IN ADULT PATIENTS WITH CARDIAC DISEASES AND DYSFUNCTIONS

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Abstract

It has been postulated that acidosis, which is co-morbid in cardiac dysfunctions usually not occurs only due to high lactate concentration in blood (hyperlactatemia), but some other components such as un-measured anions are known to significantly induce characteristic acidemia in patients also contribute to it. The present study describes the determination of different components of metabolic acidosis in cardiac dysfunction and cardiac arrest patients in order to assess the degree to which lactate is responsible for the acidosis. Fifty five adult patients with cardiac dysfunctions and cardiac arrest who were brought to the hospital for treatment or admitted to the hospital were included in present study. All biochemical, blood gases and related parameters were determined by standard methods using auto-analyzers. Stewart's (1983) quantitative biophysical methods and formula were used for apparent strong ion difference "SIDa" and strong ionic gap "SIG", to evaluate un-measured and measured ions. The average age of the patients was 58.4 years, including 39 (70.90%) males and 16 (29.09%) females. All assessed variables were found significantly different between the two groups, except the concentration of sodium, ionized calcium and SIDa. Cardiac dysfunction patients also showed low potassium (hyperkalemia) and chloride (hypochloremia) and elevated lactate concentration (hyperlactatemia) in blood, whereas higher anion gap and SIG were also noted to be manifested. Lactate as an independent component was observed to be a notable assessor of acidemia. It was concluded that although lactate accounts for only less than 50% of acidemia it did influence the occurrence of metabolic acidosis and subsequent acidemia in patients. Moreover, amplification in unmeasured anions (SIG) and phosphate is also related to the major portion of acidemia.

Introduction

The most profound acid-base disarray is metabolic acidosis and is known to occur in patients being treated at the intensive care units and cardiac care specialty (Moviat *et al.,* 2003). It is a well known fact that patients being treated for critical ailments sometimes exhibits multipart acid-base syndrome, although their pH, PCO2, bicarbonate and base excess status level tends to show normal biochemical picture (Tuhay *et al.,* 2008). Furthermore, acidosis caused by increase in un-measured anions has known to occur after cardiac surgery and some forms of metabolic acidosis, induced by the presence of lactate which seems to have worse outcomes than other anions, such as chloride (Murray *et al.,* 2007). However, it has been argued that high lactate concentration in blood is not the only basis of acidosis in cardiac dysfunction and there are several other components related to metabolism that radically induce acidemia (Makino *et al.*, 2005). Similarly, it was stated that hyperlactatemia as an individual component cannot be held responsible for the cause of generalized metabolic acidosis in some patients (Cairns *et al.,* 1991; Makino *et al.,* 2005; Prause *et al.,* 2001). Nonetheless, it was argued and a observational or tested fact that, metabolic acidosis is common in patients with cardiac arrest and its related dysfunctions are conventionally considered to be due to high lactate level in blood (Cairns *et al.,* 1991; Caparelli *et al.,* 1989; Leavy *et al.,* 1988; Makino *et al.,* 2005; Prause *et al.,* 2001; Sato *et al.,* 1993; Tuchschmidt and Mecher, 1994). Beside all these reasons, hypothesis, research and reports, the causes of metabolic acidosis in cardiac arrest is still not fully comprehend (Hayhoe *et al.,* 1999). Customary assessment of anion gap, bicarbonate and standard base excess has long been useful in understanding acidosis and its consequent physiological anomalies (Astrup *et al.,* 1960; Makino *et al.,* 2005; Siggaard-Anderson and Fogh-Anderson, 1995). However, till date it provides modest information regarding the involvement of various mechanisms and actual amount of each variable that might have been contributing to it, especially when significant alterations taking place in serum electrolytes and albumin levels (Fench *et al.,* 2000; Figge *et al.,* 1991; Gilfix *et al.,* 1993; Makino *et al.,* 2005; MacAuliffe *et al.,* 1986; Rossing *et al.,* 1986; Wilkes *et al.,* 1998). In recent years a

quantitative assessment protocols known as Stewart–Figge methodology (Figge *et al.,* 1992; Makino *et al.,* 2005; Stewart, 1983) has been recommended and found to be useful in explaining and quantifying acid–base changes in clinical situations in which conventional analysis seems to fail in evaluating all variables (Fench *et al*., 2000; Liskaser *et al*., 2000; Makino *et al*., 2005; Story *et al*., 2001; Wilkes *et al.,* 1998). In this regard, the present study describes the determination of different components of metabolic acidosis in adult patients of cardiac dysfunctions and cardiac diseases in order to assess the degree to which elevated blood of lactate (hyperlactaemia) or of any other similar contributing anions are responsible for the resultant acidosis (Maciel and Park, 2007).

Materials and Methods

Protocols and Patients: A prospective study plan was designed and carried out in Department of Biochemistry Lab services, Liaquat National Hospital and Medical College, Karachi and Department of Pathology, Govt. Layri General Hospital, Karachi. The patients were selected prospectively with known cardiac dysfunctions and most importantly those under treatment after cardiac arrest, admitted to the hospital from January 2007 to Dec 2010. The number of the patients were n = 55, 39 males (age group 47-61 years) and 16 females (age group 49-63 years). Twenty patients with minor injuries were also included in the study for comparison purpose. As per description provided earlier (Makino *et al.,* 2005) cardiac arrest was defined as the absence of both spontaneous respiration and palpable pulse. Data that were considered for inclusion were age, gender, initial electrocardiographic record, and cause of cardiac problem. Protocols described and established earlier were followed for standardization of processes and procedures used in the present study (Maceil and Park, 2007; Makino *et al.*, 2005). As stated earlier, to establish comparison among the acid–base profile of the patients, another group was inducted that comprises of patients with non-fatal or debilitated clinical conditions and for whom the department services routinely measured all variables required for the analysis.

Blood Sampling and Biochemical 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 in hospital. The data collected from the analyzers output was: pH, partial pressure of carbon dioxide, bicarbonate and standard base excess. Blood samples were also processed at the biochemistry laboratory for the determination of biochemical components 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 data was obtained by employing Stewart's Quantitative Biophysical Methods (Stewart, 1983) as modified by Figge *et al.,* (1992) using formula for apparent strong ion difference "SIDa", effective strong ion difference "SIDe" and strong ionic gap "SIG" following Makino *et al.,* (2005). Makino *et al.,* (2005) also described the definitions regarding meanings of positive value for SIG that signify un-measured anions (such as sulfate, oxo acids, citrate, pyruvate, acetate and gluconate) which should be incorporated to account for measured pH. The traditional anion gap was also calculated as anion gap with a reference range of 12–20 mmol/l (Shapiro and Peruzzi, 1995). Data are expressed as means ± 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

Fifty five (n = 55) patients with cardiac dysfunctions, diseases and cardiac arrest which occurred outside the hospital and then were admitted to the hospital were included in the present study. The details of these patients are shown in Fig.1 while blood analysis was presented in Table 1. They had a mean age of 58.4 years, including 39 (70.90%) males and 16 (29.09%) females. Initial rhythm of most of the patients recorded as a-systolic (n = 21, 38.18%) or pulse-less electrical activity (n = 15, 27.27%), and the number of cardiac arrests in the presence of an acquaintance was 6 (10.90%). The main cause of collapse was noted to be cardiac-related (n = 27; 49.09%), followed by trauma (n=8, 14.54%) and respiratory reasons (n = 8, 14.54% while un-identified were n = 9 or 12.72%. Fifty five patients of cardiac dysfunction and twenty patients of minor injuries (mean age 45.20 years; 15 males and 5 females) were compared with each other. The result of acid–base components in cardiac arrest and minor injuries are shown in Table 1. All components were noted to be different between the two groups, except for sodium, ionized calcium and SIDa. Asserting the results, it was found that the patients with cardiac dysfunctions were acidemia (pH 6.30 versus 7.20; $P < 0.001$), thus derivative of metabolic acidosis (standard base excess -18.3 versus -1.7 meq/l; $P < 0.0001$) when compared with the other group. The patients also display elated potassium (hyperkalemic), lactate (hyperlactatemia), anion gap and SIG whereas low

chloride (hypochloremic) levels. Being an independent anionic component, lactate was noted to be the most important assessor of acidemia.

Table 1. Biochemical and acid-base components in patients with cardiac dysfunctions, cardiac arrest and minor injuries

Variable	Cardiac dysfunction/ arrest	Minor injury	*P*
pH	6.3 ± 0.13	7.20 ± 0.05	0.01
pCO_2	75.2 ± 18.68	35.40 ± 7.0	0.002
Bicarbonate (mmol/L)	12.4 ± 3.2	26.8 ± 3.4	0.001
Standard base excess (mmol/L)	-18.3 ± 4.5	-1.7 ± 0.9	0.0001
Sodium (mmol/L)	150.4 ± 8.5	137.3 ± 6.7	0.1
Potassium (mmol/L)	5.4 ± 1.2	3.7 ± 0.8	0.011
Ionized calcium (mmol/L)	1.28 ± 0.12	1.19 ± 0.09	0.1
Total magnesium (mmol/L)	1.20 ± 0.10	0.90 ± 0.12	0.002
Chloride (mmol/L)	96.1 ± 5.6	107.10 ± 3.0	0.002
Lactate (mmol/L)	19.2 ± 6.6	2.5 ± 1.0	0.001
Albumin (g/dL)	3.0 ± 0.6	3.8 ± 0.7	0.01
Phosphate (mmol/L)	2.90 ± 1.22	1.04 ± 0.16	0.001
Anion gap (meq/L)	40.6 ± 11.80	8.9 ± 5.10	0.002
SIDa (meq/L)	49.02 ± 6.10	31.06 ± 2.8	0.29
SIDe (meq/L)	16.80 ± 4.8	10.25 ± 32.8	0.01
SIG-Strong ion gap (meq/L)	36.25 ± 5.8	24.10 ± 4.6	0.001

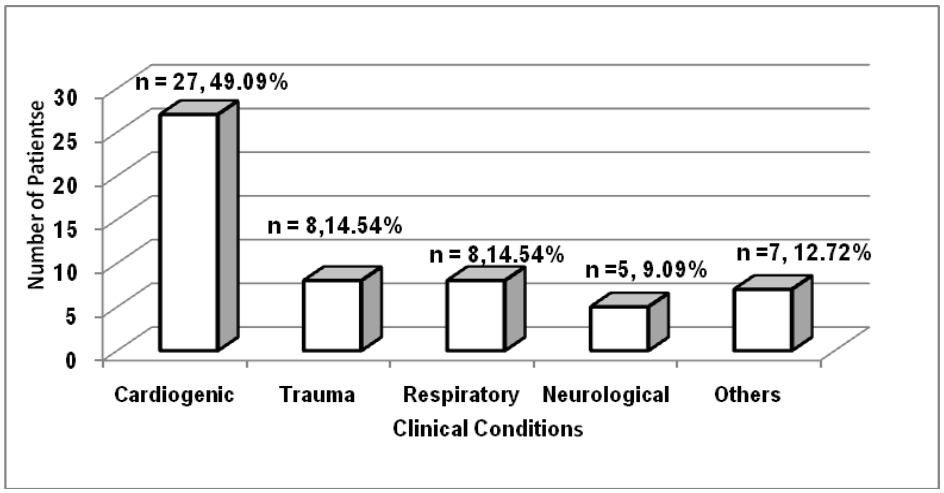

Fig 1. Various causes of cardiac dysfunctions in adult patients n = 55 studied in the present study

Discussion

In this present study, we have quantified acid– base analysis for patients with cardiac dysfunction and arrest. The patients were suffering from either clinical condition outside the hospital and/or admitted to hospital for treatments. Furthermore, in previous studies, no acidemia-inducing drug or fluid administration was done at the time of arrival, therefore it offers distinctive prospect to study the syndrome with nominal modified clinical conditions (Maciel and Park, 2007; Makino *et al.,* 2005). For comparison purpose, we used patients with minor injuries, that were hospitalized for treatments as done by various workers *i.e.* (Gunnerson *et al.,* 2006; Maciel and Park, 2007; Makino *et al.,* 2005). Although they were treated fairly and discharged from the hospital within a few days, minor elevation of blood lactate [hyperlactatemia (2.5 mmol/l)] was noted in these patients. However, all other components, such as pH and bicarbonate, were close to or in the standard range (Makino *et al.,* 2005). It has been well documented for three decades that patients with cardiac arrest and dysfunction develop marked metabolic acidosis (Cairns *et al.,* 1991; Caparelli *et al.,* 1989; Chazan *et al.,* 1968; Edmonds-Seal, 1966; Leavy *et al.,* 1988; Makino *et al.,* 2005; Prause *et al.,* 2001; Sato *et al.,* 1993; Stewart *et al.,* 1962; Tuchschmidt and Mecher, 1994). This acidosis has been considered to be the result of hyperlactatemia (Capparelli *et al.,* 1989). However, it has been postulated that the direct proportional association between standard base excess and lactate is not very significant, suggesting that other acidic factors such as blood anions

may be responsible in the pathogenesis of acidosis pertaining to cardiac arrest (Prause *et al*., 2001). Previously several researchers decided to outline and enumerate acid–base status in cardiac patients by applying the quantitative principles of acid–base analysis (Figge *et al.,* 1992; Makino *et al.,* 2005; Stewart, 1983). Exercising the techniques and route of acid-base analysis, the team recounts that the sources for acidosis were intricate as compared to the opinions reported earlier (Makino *et al.,* 2005). The group has reported that lactate was found to be the prevalent independent contributor for the development of acidemia and thus subsequent metabolic acidosis for the patients. Furthermore lactate accounts for less than 50% of the acidosis assessed so far, followed by cumulative sum of SIG and phosphate (Makino *et al.,* 2005). Concomitantly, the academic condition was coupled with strong balancing responses that reduced its gravity by inducing low chloride (hypochloremia) and albumin and elevated potassium (hyperkalemia). In addition, to a smaller extent, high magnesium (hypermagnesemia) and calcium (hypercalcemia) as reported by Makino *et al.,* (2005) also facilitates in the balancing act for diminishing acidosis severity. A key finding, similarly noted in our study as well, was the presence of higher SIG levels in patients with cardiac arrest anomaly when compared with other groups (Gunnerson *et al.,* 2006). It was also reported that increased SIG when occurs in patients has also been associated with major vascular injury (Kaplan *et al.,* 2004). In addition, hyperphosphatemia in patients with cardiac arrest has not been emphasized as a purveyor of acidosis. Additionally the grounds for this aberration remains undecided but high phosphate levels may attribute to trans-cellular shift, cellular injury and more phosphate liberation (Kirschbaum, 1998; Oster *et al.,* 1984).

Previous studies which showed the correlation between metabolic acidosis and a possible inauspicious effect in the critically ill patients have focused on either a specific etiology such as high lactate concentration (Gunnerson *et al.,* 2006; Kirschbaum, 1998; Vincent *et al.,* 1983) or a certain extent of acidosis such as base excess (Davis *et al.,* 1996; Rutherford *et al.,* 1992; Siegel *et al.,* 1990). However, it was argued that most of these studies were un-conclusive because of insignificant population sizes and were, most of the time, observational in functioning (Gunnerson *et al.,* 2006). However, regardless of all unfavorable and un-conclusive notion, it is a well established fact that hyperlactatemia is marker of poor outcome in critically ill patients (Bakker *et al.,* 1991; Bernardin *et al.,* 1996; Maciel and Park, 2007; Marecaux *et al.,* 1996). In a previous study, considering the fact that patients with high lactate levels usually shows metabolic acidemia, observed that at the time of the admission in hospital care, lactate and the standard base deficit were assessed to be significantly different between patients in intensive care and those who didn't survive cardiac dysfunctions (Maciel and Park, 2007). Therefore after thoroughly assessing the biochemical attributes and causes, it was suggested that lactate was not primarily responsible for that acidemia; rather it was the unmeasured anions that were primarily responsible (Maciel and Park, 2007). Arguably, as previously defined the unmeasured anions are also known to increase in several distinct clinical situations such as renal and hepatic impairment (Kellum, 2003) tissue hypo-perfusion (Kaplan and Kellum, 2004) and endo-toxemia (Kellum *et al.,* 1995).

In recent years, it has been extensively suggested that, when compared to chloride, acidosis occurring because of high level of lactate or other anions (SIG) was related to an increase in incidence of mortality in hospitals (Gunnerson *et al.,* 2006). The findings, thus observed and suggested that causative agent was lactate, as this lactic-acidosis has been identified as a factor for incidence of high mortality in cardiogenic and/or hospital admitted patients in intensive cardiac care (Gunnerson *et al.,* 2006; Kirschbaum, 1998; Maciel and Park, 2007; Makino *et al.,* 2007). However, other anions assessed as SIG, determined in several concurrent studies, including the present one, are not proportionally linked with untoward consequences in ICU patients. Moreover, few researches recommended that SIG may have contributed to the increase in mortality levels of critically ill patients (Balasubramanyan *et al.,* 1999; Dandorp *et al.,* 2004; Kaplan and Kellum, 2004). A previous study conducted on patients admitted to hospitals, both who responded to treatment and those who did not identified a notable dissimilarity in SIG levels (Hucker *et al.,* 2005). Like our study, a group of researcher noted that the components sturdily coupled with increased incidence of mortality in critically ill patients are notably lactate and SIG (Gunnerson *et al.,* 2006).

Conclusion: It may be concluded that lactate may be responsible for only less than 50% of the existing metabolic acidosis and that an enhancement in unmeasured anions, known as SIG as well as phosphate also contributes in the major portion to acidemia. However, as an individual component, lactate was a significantly independent indicator of academia. It was also concluded that the acidosis ascertained in present study in cardiac arrest/dysfunction groups of patients was partially conciliate by the alkalinizing effects of low chloride and albumin and high potassium, magnesium and calcium in blood as compared to patients with minor injuries. However it is apparent that due to diagnostic and prognostic significance of such studies require larger population of patients.

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