

Metabolic Acidosis in the Surgical Intensive Care Unit: Risk Factors, Clinical Correlates and Outcome. Findings from a High Dependency Heart and Vascular Surgical Center in Nigeria

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How to cite this paper: Uduagbamen, P.K., Sanusi, M., Udom, O.B., Salami, O.F., Adebajo, A.D. and Alao, O.J. (2020) Metabolic Acidosis in the Surgical Intensive Care Unit: Risk Factors, Clinical Correlates and Outcome. Findings from a High Dependency Heart and Vascular Surgical Center in Nigeria. *World Journal of Cardiovascular Surgery*, 10, 226-241.

<https://doi.org/10.4236/wjcs.2020.1011025>

Received: September 14, 2020

Accepted: November 27, 2020

Published: November 30, 2020

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Abstract

Background: Metabolic acidosis (MA) is a common finding on the surgical ward, more so in the intensive care unit. Diseases affecting the major organ systems of the body and higher grades of surgery are common risk factors for MA. It is associated with poor treatment outcome. **Aim:** To determine the risk factors and clinical correlates of metabolic acidosis and assess its relationship with treatment outcome. **Methodology:** A retrospective study at the “Tristate Heart and vascular Center” in Ilishan-Remo South west Nigeria, on patients that had cardiac and vascular surgeries from January 2015 to December 2019. Three hundred and forty two participants took part in the study. The demographic, clinical and laboratory findings were entered. Statistical analysis was with Student’s t-test and Chi square. **Results:** Two hundred and six males and 136 females were studied. The incidences of metabolic acidosis prior to induction, on post-operative day one (POD¹) and on POD²⁸ were 20.7%, 39.8% and 14.1% respectively. Nine (2.6%) participants died during admission, of this, 6 (66.7%) had MA at presentation but all (100%) had MA on POD¹. The Risk factors for MA were advanced age, comorbidities, open heart surgery, elevated systolic blood pressure and low eGFR. Metabolic acidosis was a risk factor for prolonged hospital stay, perioperative death and declining kidney function which was commoner among participants with preexisting kidney dysfunction. **Conclusion:** The incidence of metabolic acidosis was 20.7% at induction of anesthesia, rose to 39.8% on POD¹ and by POD²⁸, it has significantly reduced to 14.1%. While advancing age and com-

orbidities were risk factors for MA, the occurrence of MA increased the risk of declining kidney function, prolonged hospital stay and death.

Keywords

Metabolic Acidosis, Perioperative, Anesthetic Induction, Post-Operative Day, Open Heart, Vascular, Comorbidities, Kidney Function

1. Introduction

Metabolic acidosis (MA), defined as elevated hydrogen ions (H^+) concentration in the blood, is a common finding in most illnesses, particularly those affecting the major organ systems of the body [1]. It is reported to be a risk factor for poor treatment outcome in many medical and surgical conditions, more so in highly dependent intensive care units dedicated for managing patients with advance cardiac and vascular procedures, due to greater incidence of perioperative comorbidities and complications [2]. The body in normal state balances the net acid production (NAP) with the net acid excretion (NAE) through tubular generation of ammonium salt (NH_4) and excretion of an acidic urine [3]. Metabolic acidosis would therefore result from net acid over production, reduced NH_4 generation and subsequent low NAE or in primary dysfunctional tubular NH_4 generation. The activation of the renin angiotensin aldosterone pathway (RAAS), with the sympathetic nervous system inhibits the renal excretion of (H^+) ions that occurs through the activation of the atrial natriuretic peptides (ANP) induced by increased atrial pressures [4]. Angiotensin II is also a potent stimulator of the NADPH oxidase for the release of reactive oxygen species, cytokines and hydrogen ions with resultant lowering of the blood PH [5].

Metabolic acidosis is most commonly assessed by determining the serum bicarbonate (HCO_3^{2-}) level either by the total carbon dioxide concentration or by arterial blood gases (ABG) using the Henderson-Hasselbach equation with the PH of blood and the partial pressure of carbon dioxide [6]. A good correlation is reported between these measures while another study reported wide differences in findings from the two methods [7] [8]. The differences could however, be as a result of the differences in timing and in sample compartments. [8] Locally analyzed samples are reported to give lower bicarbonate values compared with pooled samples assessed in large central laboratories due to gas leakage that results from changes in atmospheric pressure during flights, in addition to sample exposure in larger carriage tubes [9] [10].

The incidence of preoperative MA is reported to be 17% [11]. Metabolic acidosis arising from acute inflammatory conditions presents with worse prognosis in males whereas in chronic inflammatory conditions, females fare worse. The ability of females to mount greater inflammatory response, with higher erythrocyte sedimentation rate (ESR), C-reactive protein and neutrophil count, in acute settings, most likely accounts for the better outcome for females. However, in

chronic inflammatory states, with the exception of connective tissue disease, males have less morbidity and mortality [12].

Aging is associated with lowering of serum bicarbonate which is reported to be directly related to the glomerular filtration rate (GFR) in health and in chronic kidney disease (CKD) [13]. Individuals with cardiac and vascular diseases needing surgical corrections commonly present with diminished GFR, either from relative renal hypoperfusion as a result of reduced cardiac output, or as part of a wider spectrum of diseases of the organ systems particularly the kidneys, heart and the brain. The aging process is commonly associated with poor urine concentration, reduced total body water (TBW) and reduced excretion of water, sodium and potassium [14]. The elderly commonly have elevated antidiuretic hormone coupled with massively elevated atrial natriuretic peptide hence the higher prevalence of hyponatremia in them [15].

Aging is associated with reductions in kidney sizes and function, with a relatively greater affectation of the renal cortex than the medulla [16]. Between 30 and 85 years, there is a 20% - 25% reduction in the GFR hence the need for compensatory mechanisms when MA occurs. A common compensatory mechanism in MA is pulmonary hyperventilation, developed to reduce the carbon dioxide load of the blood by stimulating the brain stem respiratory pathway. The presence of respiratory diseases which are more common in the elderly population therefore, makes this population group more vulnerable to and to suffer more deleterious effects of metabolic acidosis [17]. This also contributes to the higher prevalence of MA in the obese population due to the compromised ventilation in them. This obesity related problem is made worse in the supine position due to some degree of closure of the terminal airway, a condition that could impact negatively during surgeries under general anesthesia [18].

The serum albumin is reported to be lower in the elderly [19]. This could be multifactorial in origin, from lower intake, The fluid shift noticed with surgeries of the pancreatic, cardiac and biliary tree further worsens the effects of metabolic acidosis by causing fluid shift, electrolyte and acid-base derangement. The alteration of the pressure gradient between compartments from fluid shift during surgeries has a cause and effect relationship with changes in membrane potential [20]. The restoration of normal acid base balance in acidosis could be partly achieved by the loss of calcium from bone to buffer the excess acid and this results in hypercalcemia. The demineralization of bone could precipitate the formation of kidney stones, fractures, osteolytic lesions and the development of the CKD bone mineral disease (CKD-BMD), a common finding in patients with CKD, and with hyperparathyroidism [21].

Perioperative metabolic acidosis is reported to be a risk factor for poor treatment outcome on the surgical ward more so in the intensive care units due to greater incidence of perioperative comorbidities and complications. Highly dependent surgical units dedicated for advance cardiac and vascular procedures are still very few in Nigeria and many low income countries hence the paucity of literature on the relationship between perioperative biochemical state and treat-

ment outcome. In our clime, we are not aware of any work on perioperative metabolic acidosis and treatment outcome in this population. We therefore studied perioperative metabolic acidosis in this population and determined its risk factors, relationship with post-operative events and treatment outcome.

2. Patients and Methods

This was a cohort retrospective study carried in the “Tristate Heart and vascular Center” a high dependency cardiovascular surgical unit of a tertiary health institution in Ilishan-Remo, South west Nigeria dedicated to managing patients requiring heart and vascular surgical procedures. Case notes and perioperative charts of patients treated in the center from January 2015 to December 2019 were retrieved. Variables obtained from the case files included age, gender, type and cause of cardiovascular disease, duration of disease, previous surgical procedure related to disease, class of surgery, body mass index (BMI), percentage oxygen saturation, pulse rate, blood pressures (BP), heart rate, duration of hospital stay till discharge or death and comorbidities (heart failure, chronic liver disease, chronic kidney disease, stroke or cancer). Also retrieved from the case files were the preoperative, post-operative day 1 (POD¹) and post-operative day 28 (POD²⁸), urinalysis, serum electrolyte, urea and creatinine, full blood count (FBC), blood glucose, fasting lipids, arterial blood gases and liver function test results and erythrocyte sedimentation rate (ESR).

Participants less than 16 years or those that had previous surgery within 30 days prior to the index surgery or had repeat surgeries for the same condition and those whose data were missing were excluded.

According to the unit protocol, blood samples for arterial blood gases, serum electrolytes, albumin, fasting lipids, full blood count (FBC) and blood glucose were taken before incision, with participants awake, and samples for serum electrolytes, FBC and blood glucose were taken 24 hours post-surgery, POD 7 and on POD 28 whether patient was on admission or had been discharged, as unit protocol demanded a review of all patients, with laboratory tests on POD 28. Where infection occurred, type and site were documented. The types of infusions and inotropes used were documented, and including the charted urinary output.

For the purpose of this study, the following definitions were used:

Metabolic acidosis—serum bicarbonate (HCO_3) < 20 mmol/l [1].

Kidney dysfunction—GFR < 60 ml/min [22].

Hypertension—BP \geq 140/90 mmHg [23].

Diabetes—FBS > 7.0 mmol [24].

Anemia—packed cell volume (PCV) —30% [25].

Standard base excess (SBE)—< -2 mEq l^{-1} [11].

Anion gap (AN)—Na + K - Cl - HCO_3 [11].

Data obtained were analyzed using IBM SPSS software version 22 (IBM Inc, NY, USA). Continuous variables were expressed as means with standard deviations and compared using Student t-test. Categorical variables were expressed as

frequencies and percentages and compared using Chi square test. Where 3 or more variables were compared, analysis of variance (ANOVA) was used. The level of $P < 0.05$ was considered statistically significant. The research followed the tents of the Declaration of Helsinki. The Ethics Committee of Babcock University approved this study. The institutional ethical committee of Babcock University approved the study (BUHREC558/19, NHREC/24/01/2018).

3. Results

Five hundred and thirty six patients had surgeries in the center during the period studied. After applying the exclusion criteria, 342 participants took part in the study and of this, 128 (37.4) had open heart surgery, 101 (29.5) had major vascular surgery and 113 (33.1) had intermediate/minor surgeries. Two hundred and six (60.2%) were males and 136 (39.8%) were females. The mean age of the participants was 53.2 ± 14.3 years, with males 51.9 ± 8.4 and females, 55.1 ± 4.5 . The demographic and clinical characteristics of the participants is shown in **Table 1**. A greater proportion of participants, 198 (57.9%), were 50 years or more. Difficulty with breathing 182 (53.2%) was the commonest presenting complaint followed by chest pain 171 (50.0%). Majority of participants had low or normal BMI. One hundred and four (30.4%) participants had comorbidities, 77 (74.0%) of these were males with 27 (26.0%) females.

Table 1. Preoperative sociodemographic and clinical characteristics of the participants.

Variables	Frequency	Percentage
Gender		
Male	206	39.8
Female	136	60.2
Age, years		
16.0 - 49.9	144	42.1
≥ 50	198	57.9
BMI, kg/m ²		
<25.0	179	52.3
≥ 25.0	163	47.7
SBP, mmHg		
<140	147	43.0
>140	195	57.0
DBP, mmHg		
<90	143	41.8
≥ 90	199	58.2
SPO ₂ , %		
<95	103	30.1
>95	239	69.9

BMI—body mass index, SBP—systolic blood pressure, DBP—diastolic blood pressure, SPO₂—percentage oxygen saturation.

At presentation, 70 (20.5%) participants had metabolic acidosis as against 272 (79.5%) that had normal serum bicarbonate. On POD¹ 136 (39.8%) participants had MA compared to 206 (60.2%) with normobicarbonemia. On POD²⁸, forty seven (14.1) had MA compared to 286 (85.9%) with normal serum bicarbonate, $P < 0.001$.

The mean serum bicarbonate, pre surgery, on POD¹ and on POD²⁸ were 19.3 ± 2.7 mmol, 18.1 ± 2.8 mmol and 21.6 ± 5.3 respectively, $P < 0.001$. The laboratory results of participants is shown in **Table 2**. The mean eGFR, pre-op, on POD¹ and on POD²⁸ were 73.6 ± 9.7 ml/min, 56.4 ± 17.9 ml/min and 86.5 ± 21.8 ml/min respectively, $P < 0.001$. There were significant differences in the mean neutrophil count, platelet count and serum creatinine, at presentation, on POD¹ and on POD²⁸, $P < 0.001$, $P = 0.04$ and $P < 0.001$ respectively. There were no significant difference in the serum albumin and ESR at presentation and on POD²⁸, $P = 0.05$ and $P = 0.9$ respectively.

Table 3 shows that males have the larger proportion of metabolic acidosis at all stages of the study though the proportion of females with MA increased on POD¹, $P = 0.001$. MA was commoner among participants 50 years and upwards compared with those less than 50 years, $P, 0.001$ As the BMI increased, the proportion of participants with MA increased, the difference was further widen on POD¹, $P < 0.001$. Metabolic acidosis was more common among participants who had open heart surgery and even more so, on POD¹, $P < 0.001$.

Table 2. Laboratory results of the study population.

Variables	Preoperative	POD ¹	POD ²⁸	P-value
	N = 342	N = 342	N = 333	ANOVA
Sodium, mmol	132.3 ± 3.5	130.6 ± 9.4	138.2 ± 11.6	0.001
Potassium, mmol	4.2 ± 1.5	4.8 ± 1.4	$3.8.2 \pm 1.1$	0.03
Chloride, mmol	102.3 ± 1.5	111.8 ± 1.4	99.2 ± 1.1	0.03
Bicarbonate, mmol	19.3 ± 2.7	18.1 ± 2.8	21.6 ± 5.3	<0.001
Anion gap, mEq/l	5.2 ± 1.2	1.4 ± 0.7	8.9 ± 4.5	<0.001
Urea, mmol	8.8 ± 2.6	11.3 ± 3.7	9.0 ± 3.1	0.001
Creatinine, umol	114.5 ± 14.2	143.8 ± 7.7	99.1 ± 15.8	<0.001
GFR, ml/min (CKD-EPI)	73.6 ± 9.7	143.8 ± 7.7	86.5 ± 21.8	<0.001
Total WBC, $\times 10^9/l$	5.6 ± 8.3	6.3 ± 4.9	5.2 ± 4.1	0.003
Neutrophils, $\times 10^9/l$	2.9 ± 3.3	3.9 ± 2.7	2.4 ± 1.8	<0.001
PCV, %	36.8 ± 3.6	36.2 ± 2.3	37.5 ± 4.2	0.05
Glucose, mmol	5.8 ± 2.1	5.9 ± 4.1	5.1 ± 1.9	0.1
Platelets, $\times 10^9/l$	235.8 ± 12.4	276.4 ± 32.4	243.6 ± 5.4	0.04
Albumin, g/l	38.7 ± 5.9		39.8 ± 9.4	0.05
ESR, mm/hr	11.8 ± 5.2		11.3 ± 3.2	0.9

POD—post operative day, GFR—glomerular filtration rate, CKD-EPI—chronic kidney disease epidemiology collaboration, WBC—white cell count, PCV—packed cell volume, ESR—erythrocyte sedimentation rate.

Table 3. Relationship between pre-op metabolic acidosis and participants' characteristics.

Variables	Frequency	Pre-opHCO ₃	POD ¹ HCO ₃	POD ²⁸ HCO ₃	P-value
	N = 342 (%)	N = 70 (%)	N = 136 (%)	N = 47 (%)	ANOVA
		<20	<20	<20	
Gender					
Males	206 (60.2%)	43 (61.4%)	72 (52.9%)	28 (66.1%)	0.001
Female	136 (39.8%)	27 (38.3%)	64 (47.1%)	19 (33.9%)	
Age, years					
16 - 49	144 (42.1%)	12 (17.1%)	22 (16.2%)	18 (38.3%)	<0.001
≥50	198 (57.9%)	58 (82.9%)	114 (83.8%)	29 (61.7%)	
BMI, <i>kg/m</i> ²					
<25.0	179 (52.3%)	25 (35.7%)	28 (20.6%)	20 (42.6%)	<0.001
≥25.0	163 (47.7%)	(64.3%)	108 (79.4%)	27 (57.4%)	
SBP, mmHg					
<140	144 (42.1%)	31 (44.3%)	34 (25.0%)	22 (46.8%)	0.003
≥140	198 (58.9%)	39 (55.7%)	102 (75.0%)	25 (53.2%)	
DBP, mmHg					
<90	154 (45.0%)	25 (35.7%)	63 (46.3%)	23 (48.9%)	0.05
≥90	188 (55.0%)	45 (64.3%)	73 (53.7%)	24 (51.1%)	
SPO ₂ , %					
<95	58 (17.0%)	27 (38.6%)	49 (36.0%)	11 (23.4%)	0.04
≥95	294 (83.0%)	43 (61.4%)	87 (64.0%)	36 (76.6%)	
Surgery					
Open heart	128 (37.4%)	49 (70.0%)	97 (71.3%)	28 (59.6%)	<0.001
Vascular	101 (29.5%)	18 (25.7%)	35 (25.7%)	17 (36.2%)	
Intermediate	113 (33.1%)	3 (4.3%)	4 (3.0%)	2 (4.2%)	

BMI—body mass index, SBP—systolic blood pressure, DBP—diastolic blood pressure.

One hundred and four participants had comorbidities, 70 (67.3%) of this, all (100%) and 47 (45.2%) of this had metabolic acidosis prior to surgery, on POD¹, and on POD²⁸ respectively. One hundred and eighty four (53.8%) were on anti-hypertensive drugs and of this, 127 (69.0%) were receiving diuretic for blood pressure control.

One hundred and twenty nine (37.7%) participants had kidney dysfunction (KD) prior to surgery as against 213 (62.3%) who had no kidney dysfunction. Of the participants with preexisting KD, 39 (30.2%) had significant worsening of kidney function within POD⁷. Of the participants without preexisting KD, 49 (23.0%) had acute kidney injury (AKI) within the first POD⁷. Of the eighty eight participants reviewed by the nephrologist, 57 (64.8%) were males, 31 were females (35.2%), 35 participants (39.8%) underwent hemodialysis treatment.

The relationship between preoperative bicarbonate and status of kidney func-

tion is shown in **Table 4**. Fourteen (4.1%) had moderate-to-severe metabolic acidosis, 56 (16.4%) had mild MA and 272 (79.5%) had normal serum bicarbonate.

Forty nine (14.3) participants had infections during admission and all (100.0) had metabolic acidosis. Of the 9 (2.7%) deaths, 6 (66.7%) had metabolic acidosis at presentation and all (100.0%) had MA at POD¹. Two (22.2%) of the nine death were within the first three POD, 5 (55.6%) died between POD³ and POD⁷ while the remaining 2 (22.2%) died after the POD 7. Six of the 206 (2.9%) male participants in the study died on admission compared to 3, out of the 136 (2.2%) female participants that died, $P = 0.002$. Two of the 144 (1.4%) participants less than 50 years died during admission compared to 7 of the 198 (3.5%) participants that were up to 50 years, $P < 0.001$. Comorbidities were more in males. Twenty one percent of all participants but eighty six of the participants with metabolic acidosis had comorbidities, $P = 0.003$. The relationship between the preoperative MA and treatment outcome is showed in **Table 5**. There was an inverse relationship between serum bicarbonate level and duration of admission. A higher percentage of those that were on admission for up to 28 days had severe MA while a higher percentage of those on admission 3 - 7 days had normal serum bicarbonate. The difference was statistically significant, $P < 0.001$. There was an inverse relationship between the number of comorbidities and the serum bicarbonate. The highest percentage of participants without comorbidity had normal bicarbonate whereas the largest percentage of participants with 3 or more comorbidities had severe MA. The difference was statistically significant, $P < 0.001$.

Multivariate regression analysis in **Table 6** showed advancing age (OR-7.82, CI-5.63 - 8.47, $P = 0.02$), longer duration of hospital stay (OR-1.23, CI-1.14 - 2.91, $P = 0.001$), type of surgery (OR-0.048, CI-0.012 - 0.153, $P < 0.001$), Comorbidities (OR-2.62, CI-1.44 - 7.67, $P < 0.001$), elevated SBP (OR-9.63, CI-7.88 - 10.34, $P = 0.02$), and low eGFR (OR-4.35, CI-2.74 - 5.85, $P = 0.01$) were predictors of perioperative metabolic acidosis.

Table 4. Relationship between Preoperative serum Bicarbonate and status of kidney function.

Variables	All	Bicarbonate	Bicarbonate	Bicarbonate	P-value
	Participants	<18 mmol	18 - 19.9.0	≥20 mmol	
	N = 342 (%)	N = 14 (%)	N = 56 (%)	N = 272 (%)	
GFR.ml/min (CKD-EPI)					
≥90.0	65 (19.0%)	0 (0.0%)	7 (12.5%)	58 (21.3%)	<0.001
60 - 89.9	148 (43.3%)	0 (0.0%)	48 (85.7%)	100 (36.8%)	
45 - 59.9	114 (33.3%)	1 (7.1%)	1 (1.8%)	112 (41.2%)	
30 - 44.9	12 (3.5%)	10 (71.4%)	0 (0.0%)	2 (0.7%)	
15 - 29.9	3 (0.9%)	3 (21.5%)	0 (0.0%)	0 (0.0%)	

GFR—glomerular filtration rate, CKD-EPI—chronic kidney disease epidemiology collaboration.

Table 5. Relationship between Preoperative metabolic acidosis and treatment outcome.

Variables	Frequency N = 342 (%)	Bicarbonate <18.0 N = 14 (%)	Bicarbonate 18.0 - 19.9 N = 56 (%)	Bicarbonate >20.0 N = 272 (%)	P-value ANOVA
Days on admission					
3 - 7	127 (37.2%)	0 (0.0%)	16 (28.6%)	111 (40.8%)	<0.001
8 - 14	128 (37.5%)	2 (20.0%)	8 (14.3%)	118 (43.4%)	
15 - 28	61 (17.8%)	4 (58.6%)	18 (32.1%)	39 (14.3%)	
>28	26 (10.5%)	8 (21.4%)	14 (25.0%)	4 (1.5%)	
Comorbidities					
None	218 (63.8%)	2 (14.3%)	15 (26.8%)	201 (73.9%)	<0.001
1	74 (21.6%)	6 (42.8%)	24 (42.9%)	44 (16.2%)	
2	42 (12.3%)	4 (28.6%)	11 (19.6%)	27 (9.9%)	
3	8 (2.3%)	2 (14.3%)	6 (10.7%)	0 (0.0%)	
Nephrologist review					
No	307 (89.8%)	8 (57.1%)	54 (96.4%)	245 (90.1%)	<0.001
Yes	35 (10.2%)	6 (42.9%)	2 (3.6%)	27 (9.9%)	

*-fisher's exact test.

Table 6. Multivariate regression analysis.

Variables	OR	95% CI	P-value
Sex	1.32	1.26 - 1.46	0.06
Age	7.82	5.63 - 8.47	0.02
Surgery type	0.048	0.012 - 0.153	<0.001
Comorbidities	2.62	1.44 - 7.67	<0.001
Length of admission	1.23	1.14 - 2.91	0.001
BMI	5.56	5.27 - 7.11	0.05
SBP	9.63	7.88 - 10.34	0.02
DBP	2.92	2.74 - 2.99	0.05
SPO2	0.03	0.02 - 0.41	0.06
eGFR	4.35	2.74 - 5.85	0.01

OR—odd ratio, CI—confidence interval, BMI—body mass index, SBP—systolic blood pressure, DBP—diastolic blood pressure, SPO₂—percentage oxygen saturation, eGFR—estimated glomerular filtration rate.

4. Discussion

We found in our assessment of perioperative metabolic acidosis in a high dependency heart and vascular center, a incidence of 20.5% of preoperative MA. This rose to 39.7% on POD¹ and decreased to 14.1% on POD²⁸. This preoperative prevalence is similar to findings by Lawton *et al.* who reported a prevalence of 17% of metabolic acidosis prior to induction which rose to 42% 12 hrs after

surgery. Metabolic acidosis on the surgical intensive could arise from fasting and fluid administration. The rising prevalence of MA between induction and POD¹ found in our study and that of Lawton *et al.* could be attributable to the stress of surgery leading to increased release of catecholamine and diversion of the glycolytic pathway from pyruvate to lactate production [11]. The rising incidence of acidosis can also result from reduced blood flow to the vital organs consequent upon intra operative blood loss, redistribution of fluid and reduced adenosine triphosphate (ATP) secondary to ongoing inflammation [20].

The male dominance in our study is also reported by Joulidi *et al.* in a series on post-operative MA [26]. In Nigeria and many Sub Sahara African countries, cultural, educational and economic bias against women have impacted negatively on their health seeking capacity [27]. Though MA was more prevalent in males, it is worth noting that the incidence of MA increased in women at POD¹. Casimir *et al.* reported a higher incidence of MA in women in acute inflammatory conditions associated with a more profound peripheral polymorphonuclear cell infiltration and reduction in the PH of the blood. The authors concluded that the relative health survival advantage of women in acute inflammatory conditions was secondary to their ability to mount effective inflammatory response during infections and trauma [28].

In fed states, females convert most of the free fatty acids to triglycerides and then to storage tissues, and during fasting and exercise, their energy source are drawn mostly from remaining fatty acids. Males on the other hand oxidizes free fatty acids, therefore, during starvation and exercise, they draw their energy from carbohydrate stores. Males by having less energy reserve are therefore prone to catabolic degradation of protein stores and ketosis in prolonged fasting states often experience in many perioperative patients [28]. The higher prevalence and severity of cardiovascular diseases in males could also be contributory to the higher incidence of MA in males. Miller *et al.* reported that males manifest a heightened response to adrenergic stimulation and in the presence of adrenergic inhibition, males show lesser responsiveness [29]. In addition, the protective role of estrogens in altering serum lipids and mitigating the release of pro-inflammatory cytokines that follows endothelial injury also contribute to the relative survival advantage of women in acute inflammatory states [12].

We found a direct relationship between perioperative MA and age, this mirrors findings by Frassetto *et al.* [30] who found that background MA, particularly if arising from chronic kidney disease, was a risk factor for accelerated aging. Zampieri *et al.* found a positive correlation between cytokines like IL-1 β , IL-6, TNF- α and hydrogen peroxide (H₂O₂) The release of anorexic cytokines, oxidative stress and a tilting of the body metabolic pathway in favor of the catabolic cascade is associated with chronic tissue degradation and apoptosis common in the aging process [30]. Reduced tubular ammonia generation and acid secretion from the Type A intercalated cells are also contributory to the higher incidence of MA with aging [31].

There was an inverse relationship between the body mass index (BMI) and serum bicarbonate, a negative correlate of MA. This mirrors findings by Souto *et al.* who reported that obesity was a risk factor for MA [32]. We also found a surge in the incidence of MA on POD¹ and this is similar to findings by Al-Mulhim *et al.* who reported a high postoperative MA in many surgical procedures involving major organs of the body [33]. Obesity could be associated with a compromised ventilation especially during surgeries. The combined effect of hypoventilation from relative closure of the terminal airways on the operative table (in the supine position) seen with general anesthesia (GA), poor positioning, physiologic response to pneumothorax and pneumoperitoneum all contribute to worsening of metabolic acidosis intraoperative and early postoperative periods [18].

Metabolic acidosis was more common in the hypertensive population than in the normotensive participants. Taylor *et al.* [34] in a nationwide nutritional examination and survey, found in salt sensitive hypertensive in the United states, a direct relationship between elevated blood pressure on one hand and increased renal tubular acid secretion, increased endogenous acid generation and metabolic acidosis. The authors concluded that the positive relationship between MA and hypertension was more dependent on organic acid generation than on net renal acid loss. Metabolic acidosis act a trigger for the release of catecholamine, endothelin-1, thromboxane A and aldosterone hence its role in the development of increased left ventricular mass and abnormal geometry [35].

Our study found oxygen desaturation prior to induction more prevalent than at POD¹. General anesthesia and mechanical ventilation impair pulmonary function resulting in low tissue oxygenation (low SPO₂) [18]. It is therefore expected that the SPO₂ would be positively related to the bicarbonate concentration both in the pre and postoperative periods [36]. We infer that this unexpected finding is most likely due to the concurrent oxygen therapy that most of the participants were receiving 24 hours after surgery particularly those in the ICU.

Metabolic acidosis was most prevalent amongst participants that had open heart surgery than vascular and intermediate surgeries. Filipescus *et al.* found high incidence of MA after open heart surgeries [37]. The increase in the incidence of MA from induction to POD¹ is commonly associated with hyperchloremia (more than hyperlactatemia), increase anion gap and decrease PH. Metabolic acidosis was commonest on POD²⁸ amongst those that had vascular surgery. Choudhury *et al.* found a high incidence of MA in the immediate postoperative period and concluded that respiratory acidosis tend to play a more causative role than metabolic acidosis, with more involvement of the renal compensatory mechanisms [38]. Cassese *et al.* reported a high rate of vascular restenosis in cardiopulmonary bypass surgeries and listed diabetes, small vessel disease, chronic kidney disease as risk factors for restenosis [39]. The author also found a direct relationship between the restenosis and the number of vessels involved in disease process. Restenosis could also be accelerated by ongoing inflammation mediating vasoconstriction, platelet aggregation and release of trans-

forming growth factor β (TGF β) and fibroblast growth factor with suppression of nitric oxide (NO) release.

The prevalence of preoperative kidney dysfunction among the participants was 37.7%. The incidence and severity of MA increased with the stages of KD and this mirrors findings by Stancu *et al.* [40]. CKD is associated with reduced tubular ammonia excretion and reduced tubular (proximal tubules and collecting ducts) ammonia absorption [28]. Though it is known that metabolic acidosis increases the risk of mortality in CKD, it is also reported that vascular calcification is inhibited by chronic acidosis as a result of suppressed collagen synthesis, coupled with the fact that arteriosclerosis is inhibited from concurrent osteoblast inhibition in MA [41].

We found postoperative infection as a risk factor for death in our series and a predominance of males among the dead. The ability of females to mount effective inflammatory response in sepsis, thereby having a survival advantage over males, has been attributed to this response characterized low PH and polymorphonuclear cell infiltration. The relative higher energy store of the X-chromosome, anti-inflammatory actions of estrogens, anti angiogenic actions of estrogens and a greater tendency to lipid peroxidation by females gives them a survival advantage [42]. We found a positive association between MA and death similar to findings by Gunnerson *et al.* [41]. Comorbid conditions, particularly CKD, were associated with higher incidence of MA in the study. Apart of the known fact that males have more severe forms hypertension and cardiovascular disease as possible risk factor or death in them, we also infer that the higher death rate among males in the study could also be explained on the basis of other comorbidities, like CKD. The findings of lower GFR, higher parathyroid hormone and higher cholesterol associated with MA, by Capusa *et al.* further buttress this association [43]. The kidney disease improving global outcome (KDIGO) Clinical Practice Guideline for the evaluation and management of CKD recommended bicarbonate supplementation when HCO_3^- is less than 22 mmol [44]. Though 37.7% of participants had KD prior to induction, we found a rising percentage of participants with MA associated with decreasing renal function that necessitated the nephrologist review in about 25.7% of participants, out of which 10% had hemodialysis. Raji *et al.* [45] reported a 22.5% incidence rate of perioperative AKI at POD⁷, similar to our finding. Kidney disease are commonly associated with cardiovascular disorders with each worsening the outcome of the other when they occur together [21].

Although MA was most prevalent on POD¹, we found a direct relationship between the length of admission and the severity of MA. Metabolic acidosis in the perioperative period could be pointers to ongoing infections as was found in this study. The additive effect of infections to the disease burden often prolong the wound healing time as collagen formation could become dysregulated necessitating longer treatment time [41]. Metabolic acidosis being a proinflammatory condition, it expect that the release of anorexic cytokines could disrupt the ana-

bolic state that is needed for effective wound healing thereby delay it but Tsuji *et al.* reported that hypercapnia, not acidosis cause stimulation of cell proliferation thereby accelerating wound healing [46].

On multivariate logistic regression, advancing age (≥ 50 yrs), duration of admission ($< \text{POD}^2$), surgery type (open heart surgery), systolic BP (≥ 140) independently predicted metabolic acidosis.

There were some limitations encountered in this study. Data on base excess were not available for many intermediate grade surgeries so was not used in defining MA. Though Hartman solution was used in most cases, data on the use of other solution were incomplete. The effect of perioperative blood transfusion was not determined in the study. Urine osmolality was also not assessed.

5. Conclusion

Metabolic acidosis is common in perioperative patients as we found incidence of 20.4%, 39.8% and 14.1% just prior to induction, on POD^1 and POD^{28} respectively. The risk factors for MA were advanced age (≥ 50 yrs), comorbidities (CKD), type of surgery (open heart surgery), systolic blood pressure (≥ 140 mmHg) and $\text{eGFR} < 60$ ml/min. The presence of metabolic acidosis increased the risk for prolonged hospital stay, decline in kidney function and death. Worsening of kidney function from baseline was more common among participants with preexisting kidney dysfunction than in those without preexisting kidney disease. There is therefore need to optimize the acid base balance in patients with advanced age, CKD and comorbidities to achieve more favorable outcome in patients undergoing cardiovascular surgeries. More multicenter and multi-racial studies are needed to standardize management protocols.

Acknowledgements

We express our profound gratitude to the nurses, technical, administrative staff of Tristate Heart and Vascular Center, Ilishan-Remo, Nigeria for their contribution to the success of this study.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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