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## Management of Metabolic Acidosis in the Post-Cardiac Surgical Patient

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### Abstract

The base deficit is the best way to evaluate severity of Metabolic Acidosis (MA). It indicates a value corresponding to the number of mmol/L below 24 of the measured bicarbonate concentration. Base deficit between 0 and 5 mmol/L indicates that the patient is not at risk of immediate harm. Arterial blood gases are typically measured every 2-4 hours following cardiac surgery and there is always a trend in base deficit changes to consider. Where the base deficit is diminishing, this indicates that the patient is improving, whereas when it is worsening, the opposite is true. Base deficits between 5 and 10 indicate that a serious problem is present which requires urgent correction. Where the base deficit is greater than 10, cardiac arrest may occur, and such patients require constant supervision by a doctor if active management is being pursued. Where the base deficit is persistently greater than 15, survival is extremely unlikely. This degree of acidosis is associated with widespread disruption of mitochondria at cellular level. The mitochondria often do not recover even if the precipitating cause of the MA is corrected, in which case the patient develops fatal multisystem organ failure. The management of MA in post-cardiac surgical patients is indivisibly bound up in optimizing circulatory physiology. We have not expounded on how this foundational knowledge should be applied but without it the management of MA in this patient population will be severely hampered.

**Keywords:** Metabolic acidosis, Cardiac surgery, Post-operative.

### Background

The causes of severe metabolic acidosis in the post-cardiac surgical patient fall into two categories-Hypoperfusion and deranged glucose metabolism. Hypoperfusion can also be defined as impaired oxygen delivery [1]. When the tissues have an insufficient oxygen supply, they switch from aerobic (mitochondrial) ATP production to anaerobic ATP production, a much less efficient means of generating ATP and one which generates lactic acid as a by-product. This form of lactic acidosis is Type A [2]. Lactic and pyruvic acids are important normal precursors for the synthesis of glucose by the liver [3].

Where severe liver disease is present, inadequate glucose synthesis may occur, resulting in low blood glucose levels and high levels of these acidic gluconeogenic precursor molecules. This type of lactic acidosis is called Type B. It may occur in the absence of hypoperfusion but often hypoperfusion is an added complication in the clinical context [1]. Furthermore, certain catecholamines, principally adrenaline but also isoprenaline, accelerate hepatic glycogenolysis and switch off hepatic gluconeogenesis thus promoting high blood sugar levels and high levels of lactic acid [4]. They also have a direct effect on cells in general to activate glycolytic energy production. This may also occur in the absence of hypoperfusion [5].

Unchecked, the high blood sugar levels that may ensue would result in greatly increased blood viscosity and subsequent impaired oxygen delivery due to increased capillary transit time [6]. Hypoperfusion can be cardiac, macro circulatory or microcirculatory in nature. Often there are combinations of aetiologies in any one patient [7]. The various causes of hypoperfusion in the cardiac surgical patient are worth considering in some detail but before doing so it will first be necessary to review some elementary cardiovascular physiology.

### Objective

To investigate and identify mechanisms which are conducive to metabolic acidosis in post-heart surgery patients. Study the consequences of postoperative metabolic acidosis and how this can be corrected.

### Methods

A comprehensive search of electronic databases (PubMed, Science Direct and Google scholar) using the key words "metabolic acidosis", "heart surgery", "post-operative" was used.

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The references in the identified articles were hand-searched for additional studies which were missed by the search strategy. Evidence from these data were critically analysed and summarised to produce this article. The studies consisted of non-randomised retrospective studies, case reports, and review articles.

## Results

### Circulatory Physiology

The circulation of blood is analogous to the movement of electricity. The latter is governed by Ohm's law which states that  $V=IR$  [8]. The equivalent equation for blood circulation is the following: mean blood driving pressure is equal to the product of blood flow (cardiac output) and systemic vascular resistance ( $MAPs-CVP=CO \times SVR$  or for the pulmonary circulation  $MAPp-LAP=CO \times PVR$ ). CVP is central venous pressure and LAP is left atrial pressure. Since it is the MAP, CVP, LAP and CO that can be directly measured, the resistances are always derived values [8]. If the pressure measurements are in mmHg and the CO is in litres per minute, then the resistance units are called Wood units after the famous British pioneer of invasive Cardiology, Paul Wood. The more commonly used unit is when International units are obtained by multiplying the value in Wood units by 80. For blood to flow through the capillary bed a driving pressure from arteriole to venule of at least 25 mmHg is required [9].

Normal circulating blood volume is 5 litres of which red cells constitute around 40% and plasma 60% [10]. Blood volume is principally held in the venous system [11]. Venous channels outnumber arterial channels in a ratio of at least 5 to 1 in all tissues. When general vasodilation occurs the storage capacity of the venous system increases [12]. The pressure exerted by the blood returning to the heart is important and is designated the preload. Optimal cardiac function occurs with filling pressures in the range 5-15 mmHg. Within this pressure range, increasing the filling pressure increases cardiac output [13]. The pressure against which the heart has to eject blood is also an important variable which is called the afterload [14].

When severe hypertension is present or there is some other increased resistance to outflow of blood from the ventricle cardiac output is diminished [15]. During passage of blood through the capillary bed around 10% of the plasma leaks through pores in the capillary wall into the extravascular extracellular space. Most of this fluid is reabsorbed into the circulation by venules but some returns to the central veins via the lymphatic system [16]. The resistance to flow of fluid in a tubular conduit is given by Poiseuille's equation:  $R=(k \times \text{length of tubing} \times \text{viscosity})/\text{radius}^4$ . It is to be noted that vascular resistance is inversely proportional to the fourth power of the radius of the vessel and that it is directly proportional to viscosity [17]. Both blood viscosity and arteriolar tone show considerable variation in the post cardiac surgical patient and need to be considered in the management of hypoperfusion [18].

### Hypoperfusion

Hypoperfusion could be due to severely impaired systolic or diastolic cardiac function. Where the heart is unable to sustain a cardiac output sufficient for life, progressive lactic acidosis occurs due to inadequate oxygen delivery. Severely impaired systolic function may exist pre-operatively or may be a new feature of an operation that has been unsuccessful or where serious complications have occurred. The lactic acidosis in these cases is countered with catecholamines to try and boost cardiac output and systemic vascular resistance. Secondary hyperglycaemia is treated with an intravenous infusion of insulin [19]. Sodium bicarbonate solution can also be given to directly buffer the acids, but this has the limiting factor of increasing plasma sodium level [20]. Usually after using  $\text{NaHCO}_3$  for 24 hours the plasma sodium level has increased noticeably. When it exceeds 145 mmol/L it is generally considered unacceptable to continue using it to treat metabolic acidosis. Severe hyponatremia can have serious

neurological consequences and must be avoided [21]. Intra-aortic balloon pumping is also used in the presence of severely impaired systolic cardiac function. A sausage shaped balloon is inserted through a delivery system into the descending thoracic aorta, usually via the femoral artery. This allows a helium bladder to drive sequential inflation and deflation cycles of the balloon in the aorta.

The cyclical (diastolic) volume displacement that balloon inflation causes acts as an auxiliary pump and usually supplements cardiac output by around 30%. Severely impaired diastolic cardiac function usually indicates the presence of a pathological collection of blood in the pericardial sac, a condition called cardiac tamponade [22]. The clinical features usually include raised CVP, decreased blood pressure, impaired urine output, increasing oxygen requirements and metabolic acidosis. It is treated by immediate re-opening of the chest and the release of the pressurized collection of blood. It is the collection of blood and clot around the heart which prevents the chambers of the heart from filling adequately during diastole.

There is a linear relationship between oxygen delivery and haemoglobin concentration. In the event that non-fatal massive post-operative haemorrhage occurs, hypoperfusion could occur due to lack of circulating blood volume and a low haemoglobin concentration [23]. Such situations are treated with blood transfusion and measures to correct the cause of the haemorrhage which usually means re-opening the chest in the operating theatre. Hypoperfusion is an invariable ramification of being on cardiopulmonary bypass if maintained for a long enough duration. [2]. This is because of activation of a systemic inflammatory response to the extracorporeal circulation wherein blood is directly exposed to the foreign surfaces of the cardiopulmonary bypass machine [24]. Such inflammatory activation results in an opening up of pores in the capillaries of the body such that plasma proteins change their volume of distribution and become distributed in the entire extracellular space, a space that is many times larger than plasma volume [25].

The plasma protein that is routinely measured is albumin. Its concentration day by day following cardiac surgery is inversely proportional to the degree of capillary leak present [26]. Capillary leakage expands the extravascular extracellular space which leads to increased inter-capillary gap at tissue level which in turn results in microcirculatory hypoperfusion. Microcirculatory hypoperfusion is also contributed to by inflammatory mediators and cellular elements of the blood adhering to the inner lining of microcirculatory blood vessels thus reducing their calibre. In patients with diabetes glycosylated haemoglobin gives an indication of average blood glucose levels over the preceding 3 months [27].

Glycosylated haemoglobin cannot carry oxygen. When expressed as a percentage of total haemoglobin the value gives a measure of the average blood glucose concentration over the preceding 3 months. In normal patients and well-controlled diabetics, levels will be below 7g%. Levels above 12g% pre-operatively can be associated with metabolic acidosis due to inadequate oxygen carrying capacity of the blood. Whilst glycosylated haemoglobin is a convenient marker for systemic protein glycosylation, all the body proteins are glycosylated to some extent in diabetic patients which means that glucose has become covalently bonded to them. It is likely that this process affects basement membranes of capillaries and could impair oxygen diffusion between cells thus contributing to hypoperfusion at the molecular level.

Capillary architecture is also relevant to microcirculatory hypoperfusion [28]. Capillaries branch off from arterioles at a range of angles from acute to perpendicular to obtuse. Acutely branching capillaries give rise to antegrade flow (in the same general direction as the systolic arterial blood flow) whilst obtusely angled capillaries give rise to retrograde flow, i.e., blood flows into them preferentially during diastole [29]. It is believed that the acute and perpendicularly angled capillaries continue to be perfused during non-pulsatile



cardiopulmonary bypass but the retrograde capillaries, which are normally perfused during diastole are relatively under-perfused during CPB as there is then no diastolic flow phase. At a macroscopic level the coronary arteries are examples of blood vessels in which flow occurs principally in diastole [30]. Patients cannot be maintained on cardiopulmonary bypass for prolonged periods of time. Due to the above mechanisms, irreversible and terminal decline would occur if a healthy adult was placed on conventional cardiopulmonary bypass for 48 hours. In clinical practice the limit for a bypass run would be 24 hours in the average adult cardiac surgical patient although times of 1-3 hours are the normal duration for the vast majority. Longer periods on CPB can be sustained by using special extracorporeal life support systems which are not routinely used in clinical cardiac surgery.

Sepsis is another form of hypoperfusion. Its characteristic is the release of lipid soluble bacterial endotoxins into the bloodstream [31]. As the liver normally filters lipid soluble toxins from the blood, it is usually affected early on in the clinical picture of sepsis. As noted earlier, liver dysfunction itself is a potent cause of type B lactic acidosis [28]. Adequate perfusion of the tissues requires a driving pressure between the heart and the capillaries. The driving pressure is provided by the heart contracting but also by the arterioles maintaining a tone which resists the flow of blood to some extent. In this way normal blood flow is distributed to the tissues that need it most by selective arteriolar vasodilation. The endotoxins in sepsis paralyse the arterioles so that they lose their tone and no longer restrict blood flow into the capillary beds they supply. This causes a severe drop in blood pressure which in turn leads to hypoperfusion. To make matters worse, the endotoxins can have a direct effect on the heart to depress its function.

Where blood pressure falls to dangerously low levels due to endotoxin mediated arteriolar vasodilation, we call the clinical picture septic shock. It can be present without any impairment of cardiac function. Severe allergic reactions can cause a very similar clinical picture of circulatory shock in which case it is generally called anaphylactic shock [32]. It is distinguished from septic shock by its sudden onset associated with drug administration. When sepsis is suspected it is treated with antibiotics directed against the known or likely infecting bacterium and with vasoconstrictor medication, most commonly noradrenaline, by intravenous infusion. In cardiac surgery we deal with septic patients either because they have had endocarditis pre-operatively or they become septic following routine cardiac surgery, for instance due to infarction of the intestines.

In the latter condition metabolic acidosis is a usual feature. The gravity of the situation can be gauged by whether or not renal failure has supervened as well [33]. Where there is a metabolic acidosis and the patient continues to pass satisfactory volumes of urine he will likely survive. Where the urine output tails off or stops in MA survival become much more of an issue and concerned vigilance in optimizing all aspects of care needs to be strictly enforced. Even when that is done the likelihood of mortality for this type of patient is at least 50% [33]. Mesenteric infarction is one of the more common causes of death following cardiac surgery and occurs as a result of thrombotic or embolic occlusion of mesenteric arteries. In patients who remain in the ITU for several weeks following surgery, other causes of sepsis are often seen typically in the form of pneumonia, sternal wound infection and central line sepsis.

### Correction of Metabolic Acidosis

In metabolic acidosis, there is an excess of hydrogen ions in the blood which is reflected in the base deficit. In order to get early warning of the direction of travel, the MA can be temporarily corrected by administering 8.4% sodium bicarbonate. Each millilitre of this solution contains 1meq of hydroxyl ions. The dose (in mls) required to correct a MA is given by the formula: (Body weight x BD)/6. After the corrective dose is administered the BD will rise to a new level in keeping with the speed of recovery. In the favorable situation it will not rise back to the level it was at before administering bicarbonate. Where

the outcome is going to be fatal the BD keeps rising back to its previous level or higher despite multiple attempts at correction. The only exception to this is in the case of catecholamine induced metabolic acidosis which generally responds to high dose IV insulin by infusion along with minimisation or withdrawal of intravenous adrenaline.

### Other Causes of Metabolic Acidosis

Acute or chronic renal failure is associated with the build-up of fixed acids in the blood such as sulphate, phosphate chloride and urate [34]. The hydrogen salts of these anions are acidic to a variable degree and may contribute to MA where cardiac surgical patients have co-existing renal failure. The healthy kidneys are able to secrete hydrogen ions in exchange for re-absorbing potassium into the blood stream so that the hydrogen salts are excreted in the urine while those in the bloodstream are generally potassium or sodium salts [34]. Normal urine is acidic in reaction [35].

### Anion Gap

Biochemistry textbooks are keen on the idea of the anion gap as a measure of MA. It is given by formula:  $AG=[Na] - [(Cl) + (HCO_3)]$  [36]. It can be useful in non-surgical settings such as in the evaluation of a variety of types of poisoning, such as with salicylic acid but is of very little use in clinical cardiac surgery [36].

### Conclusion

In clinical cardiac surgery, severe metabolic acidosis (defined as a base deficit of 6 mmol/L or more) is invariably a finding which demands serious consideration and attention. The magnitude of base deficit is a good marker of the severity of metabolic derangement and can help to prioritise the need for urgent senior medical input when the base deficit exceeds 10 mmol/L [37]. Lactic acidosis is the principal cause of MA in post cardiac surgical patients [28]. Type A lactic acidosis is treated by attending to the underlying cause of hypoperfusion. Type B lactic acidosis is treated with supportive measures including repeated correction of the MA with sodium bicarbonate [38]. When due to liver failure, the outcome is unfortunately frequently fatal. Catecholamine induced lactic acidosis always responds well to withdrawal of adrenaline or substitution with noradrenaline coupled with intravenous insulin by infusion [4].

### References

1. Anderson LW, Mackenhauer J, Roberts JC, Berg KM, Cocchi MN, et al. Etiology and therapeutic approach to elevated lactate levels (2013) *Mayo Clin Proc* 88: 1127-1140. <https://doi.org/10.1016/j.mayocp.2013.06.012>
2. Naik R, George G, Karuppiah S and Philip MA. Hyperlactatemia in patients undergoing adult cardiac surgery under cardiopulmonary bypass: Causative factors and its effect on surgical outcome (2016) *Ann Card Anaesth* 19: 668-675. <https://doi.org/10.4103/0971-9784.191579>
3. Silverstein DC and Hopper K. Small animal critical care medicine (2009) Elsevier 2009: 254-257. <https://doi.org/10.1016/B978-1-4160-2591-7.X1000-4>
4. Schade DS. The role of catecholamines in metabolic acidosis (1982) *Ciba Found Symp* 87: 235-253. <https://doi.org/10.1002/9780470720691.ch13>
5. Mizock BA and Falk JL. Lactic acidosis in critical illness (1992) *Crit Care Med* 20: 80-93. <https://doi.org/10.1097/00003246-199201000-00020>
6. Cho YI, Mooney MP and Cho DJ. Hemorheological disorders in diabetes mellitus (2008) *J Diabetes Sci Technol* 2: 1130-1138. <https://doi.org/10.1177/193229680800200622>
7. Kara A, Akin S and Ince C. The response of the microcirculation to cardiac surgery (2016) *Curr Opin Anaesthesiol* 29: 85-93. <https://doi.org/10.1097/ACO.0000000000000280>

**Citation:** Francis J, Prothasis S, Varghese R, Jomon M, Roy R, et al. Management of metabolic acidosis in the post-cardiac surgical patient (2020) *Clinical Cardiol Cardiovascular Med* 4: 12-15.



8. Lai YC, Potoka KC, Champion HC, Mora AL and Gladwin MT. Pulmonary arterial hypertension: the clinical syndrome (2014) *Circ Res* 115: 115-130. <https://doi.org/10.1161/CIRCRESAHA.115.301146>
9. Yuan S and Rigor R. In Regulation of Endothelial Barrier Function (2011) *Morgan & Claypool Life Sciences* 3: 1-146. <https://doi.org/10.4199/C00025ED1V01Y201101ISP013>
10. Cotter SM. Hematology (2001) *Teton New Media* 2001: 3.
11. Chaudhry R, Miao JH and Rehman A. Physiology, Cardiovascular (2020) *StatPearls Publishing*.
12. Young DB. Control of Cardiac Output (2010) *Morgan & Claypool Life Sciences*.
13. Russell RO Jr, Rackley CE, Pombo J, Hunt D, Potanin C, et al. Effects of increasing left ventricular filling. Pressure in patients with acute myocardial infarction (1970) *J Clin Invest* 49: 1539-1550. <https://doi.org/10.1172/JCI106371>
14. Tarazi RC and Levy MN. Cardiac responses to increased afterload (1982) *Hypertension* 4: 8-18.
15. Lund-Johansen P. Haemodynamics in essential hypertension (1980) *Clin Sci (Lond)* 6: 343s-354s. <https://doi.org/10.1042/cs059343s>
16. Breslin JW, Yang Y, Scallan JP, Sweat RS, Adderley SP, et al. Lymphatic Vessel Network Structure and Physiology (2018) *Compr Physiol* 9: 207-299. <https://doi.org/10.1002/cphy.c180015>
17. Klabunde R. Cardiovascular Physiology Concepts (2<sup>nd</sup> Edn) (2012) *Lippincott Williams & Wilkins* pp: 98-99.
18. Vercaemst L. Hemolysis in cardiac surgery patients undergoing cardiopulmonary bypass: a review in search of a treatment algorithm (2008) *J Extra Corpor Technol* 40: 257-267.
19. Najmaï S, Redford D and Larson DF. Hyperglycemia as an effect of cardiopulmonary bypass: intra-operative glucose management (2006) *J Extra Corpor Technol* 38: 168-173.
20. Boldt J, Knothe C, Zickmann B, Andres P, Dapper F, et al. Influence of different intravascular volume therapies on platelet function in patients undergoing cardiopulmonary bypass (1993) *Anesth Analg* 76: 1185-1190. <https://doi.org/10.1213/00000539-199376060-00002>
21. Singh S and Hutton P. Cerebral effects of cardiopulmonary bypass in adults (2003) *BJA CEPD Reviews* 3: 115-119. <https://doi.org/10.1093/bjacepd/mkg115>
22. Stashko E and Meer JM. Cardiac Tamponade (2019) *StatPearls*.
23. Spiess BD. Critical oxygen delivery: the crux of bypass with a special look at the microcirculation (2011) *J Extra Corpor Technol* 43: 10-16.
24. Paparella D, Yau TM and Young E. Cardiopulmonary bypass induced inflammation: pathophysiology and treatment. *An Update* (2002) *Eur J Cardiothorac Surg* 21: 232-244. [https://doi.org/10.1016/s1010-7940\(01\)01099-5](https://doi.org/10.1016/s1010-7940(01)01099-5)
25. Machin D and Allsager C. Principles of cardiopulmonary bypass (2006) *BJA Educ* 6: 176-181. <https://doi.org/10.1093/bjaceaccp/mki043>
26. Kapoor PM, Narula J, Chowdhury UK, Kiran U and Taneja S. Serum albumin perturbations in cyanotics after cardiac surgery: Patterns and predictions (2016) *Ann Card Anaesth* 19: 300-305. <https://doi.org/10.4103/0971-9784.179633>
27. Klein R, Klein BE, Moss SE, Davis MD and DeMets DL. Glycosylated hemoglobin predicts the incidence and progression of diabetic retinopathy (1988) *JAMA* 260: 2864-2871.
28. Minton J and Sidebotham DA. Hyperlactatemia and Cardiac Surgery (2017) *J Extra Corpor Technol* 49: 7-15.
29. Bates RJ, Toscano M, Balderman SC and Anagnostopoulos CE. The cardiac veins and retrograde coronary venous perfusion (1977) *Ann Thorac Surg* 23: 83-90. [https://doi.org/10.1016/s0003-4975\(10\)64076-3](https://doi.org/10.1016/s0003-4975(10)64076-3)
30. Ramanathan T and Skinner H. Coronary blood flow (2005) *BJ Educ* 5: 61-64. <https://doi.org/10.1093/bjaceaccp/mki012>
31. Michalopoulos A, Stavridis G and Geroulanos S. Severe sepsis in cardiac surgical patients (1998) *Eur J Surg* 164: 217-222. <https://doi.org/10.1080/110241598750004670>
32. Levy JH. Anaphylactic reactions in cardiac surgical patients: Et tu, brute? (2001) *J Cardiothorac Vasc Anesth* 15: 677-679. <https://doi.org/10.1053/jcan.2001.28306>
33. Howitt SH, Herring M, Malagon I, McCollum CN and Grant SW. Incidence and outcomes of sepsis after cardiac surgery as defined by the Sepsis-3 guidelines (2018) *Br J Anaesth* 120: 509-516. <https://doi.org/10.1016/j.bja.2017.10.018>
34. Dhondup T and Qian Q. Acid-Base and Electrolyte Disorders in Patients with and without Chronic Kidney Disease: An Update (2017) *Kidney Dis* 3: 136-148. <https://doi.org/10.1159/000479968>
35. Smith D, Spaněl P, Holland TA, al Singari W and Elder JB. Selected ion flow tube mass spectrometry of urine headspace (1999) *Rapid Commun Mass Spectrom* 13: 724-729. [https://doi.org/10.1002/\(sici\)1097-0231\(19990430\)13:8724::aid-rcm548>3.0.co;2-e](https://doi.org/10.1002/(sici)1097-0231(19990430)13:8724::aid-rcm548>3.0.co;2-e)
36. Arieff AI. Pathogenesis of Metabolic Acidosis with Hypoxia (1992) *Hypoxia, Metabolic Acidosis and the Circulation* 1992: 116-138. [https://doi.org/10.1007/978-1-4614-7542-2\\_7](https://doi.org/10.1007/978-1-4614-7542-2_7)
37. Chawla LS, Nader A, Nelson T, Govindji T, Wilson R, et al. Utilization of base deficit and reliability of base deficit as a surrogate for serum lactate in the peri-operative setting (2010) *BMC Anesthesiol* 2010: 10. <https://doi.org/10.1186/1471-2253-10-16>
38. Luft FC. Lactic acidosis update for critical care clinicians (2001) *J Am Soc Nephrol* 17: S15-S19.