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The importance of arterial blood gas analysis as a systemic diagnosis approach in assessing and preventing chronic diseases, from emergency medicine to the daily practice

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Abstract. – Blood gas analysis is a diagnostic tool to evaluate the partial pressures of gas in blood and acid-base content. The use of blood gas analysis enables a clear understanding of respiratory, circulatory, and metabolic disorders. The arterial blood gas (ABG) explicitly analyzes blood taken from an artery, assessing the patient's partial pressure of oxygen (PaO_2) and carbon dioxide ($PaCO_2$) pH (acid/base). PaO_2 indicates the oxygenation status, and $PaCO_2$ indicates the ventilation status (chronic or acute respiratory failure). PaO_2 is affected by hyperventilation, characterized by rapid or deep breathing, and hypoventilation, characterized by slow or shallow breathing. The acid-base balance tested by the ABG procedure measures the pH and $PaCO_2$ directly, while the use of the Hasselbach equation gives the serum bicarbonate (HCO_3) and base deficit or excess. The measured HCO_3 is based on a strong alkali that frees all CO_2 in serum, including dissolved CO_2, carbamino compounds, and carbonic acid. The calculation uses a standard chemistry analysis, giving the amount of "total CO_2"; the difference will amount to around 1.2 mmol/L. Though ABG is frequently ordered in emergency medicine contests for acute conditions, it may also be needed in other clinical settings. The ABG analysis shows to be an exceptional diagnostic tool, including the group of diseases known as acid-base diseases (ABDs), which include a great variety of conditions such as severe sepsis, septic shock, hypovolemic shock, diabetic ketoacidosis, renal tubular acidosis, chronic respiratory failure, chronic heart failure, and diverse metabolic diseases.

Key Words:
Arterial blood gas analysis (ABG), Partial pressure of oxygen (PaO_2), Partial pressure $PaCO_2$ ($PaCO_2$), Serum bicarbonate (HCO_3), Hasselbach, Acid/base.

Introduction

Low oxygen levels and impaired alveolar gas exchange may indicate a non-pulmonary medical condition. Acid-base diseases (ABDs) indicate a wide group of diseases that are encountered in critically chronic metabolic conditions such as chronic kidney disease (CKD), diabetes, chronic respiratory failure (COPD), and chronic heart failure. There are four simple ABDs generally indicated as: (1) metabolic acidosis, (2) respiratory acidosis, (3) metabolic alkalosis, and (4) respiratory alkalosis. The use of arterial blood gas (ABG) analysis in all these cases was revealed to be a highly precise tool in diagnosis and prognosis, including the typology of disorders evaluated as single or primary disorder or mixed ABDs[1].

The ABD may be of simple or primary type with a secondary compensatory response or

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may be of mixed type- occurrence of two or more independently existing primary ABDs in the same patient[1,2]. Nevertheless, the laboratory diagnosis should always need comparative data from clinical details. The cause of individual acidemia or alkalaemia should be explored in each single case that allows the unveiling of a complete picture made of complications and co-morbidities leading to proper condition management[1,2].

Complex or mixed acid-base disturbances involve more than one primary process. In these mixed disorders, values may be deceptively normal or between the normal ranges for years to the point the system cannot compensate anymore[3-6]. It is crucial to identify whether changes in partial pressure of carbon dioxide ($PaCO_2$) and HCO_3 when evaluating acid-base disorders are indicative of expected compensation or suggestive of unnoticed, minimal fluctuations that may accumulate over time and worsen with age, ultimately leading to the development of a disease (as shown in Figure 1)[5]. If not, the second primary process should be suspected of causing the abnormal compensation. The overall interpretation must thus consider the clinical conditions as a direct consequence of disturbed compensatory mechanisms (e.g., chronic lung disease, chronic renal failure, osteoporosis, osteopenia, arthritis...)[3-5,7-9].

A steady, well-balanced acid-base level is based on the assonance between all acids produced equal to all acid excreted. The renal, skeleton, and lungs are key actors in the clearance of acid anions by replacing them with anion base and bicarbonates; the whole process takes place on multiple levels in order to reach the systemic acid/base equilibrium, in which the full reabsorption of filtered bicarbonate and the formation of buffered urine with ammonia produced by the kidney and excreted as ammonium, with filtered phosphate and chloride. The alveolar ventilation works using a similar mechanism to reach the full carbon dioxide clearance to avoid respiratory disorders and acid overloading. Equally, through different mechanisms, the long-term level of bicarbonate concentration is constantly monitored and performed by the skeleton. In fact, the skeleton starts decaying following the persistent net acid retention and bicarbonate loss from bone mineral breakdown to keep tissues and organs acid/base in constant balance[8,10,11].

The body's response to the hypoxemic state is characterized by an increase in minute ven-

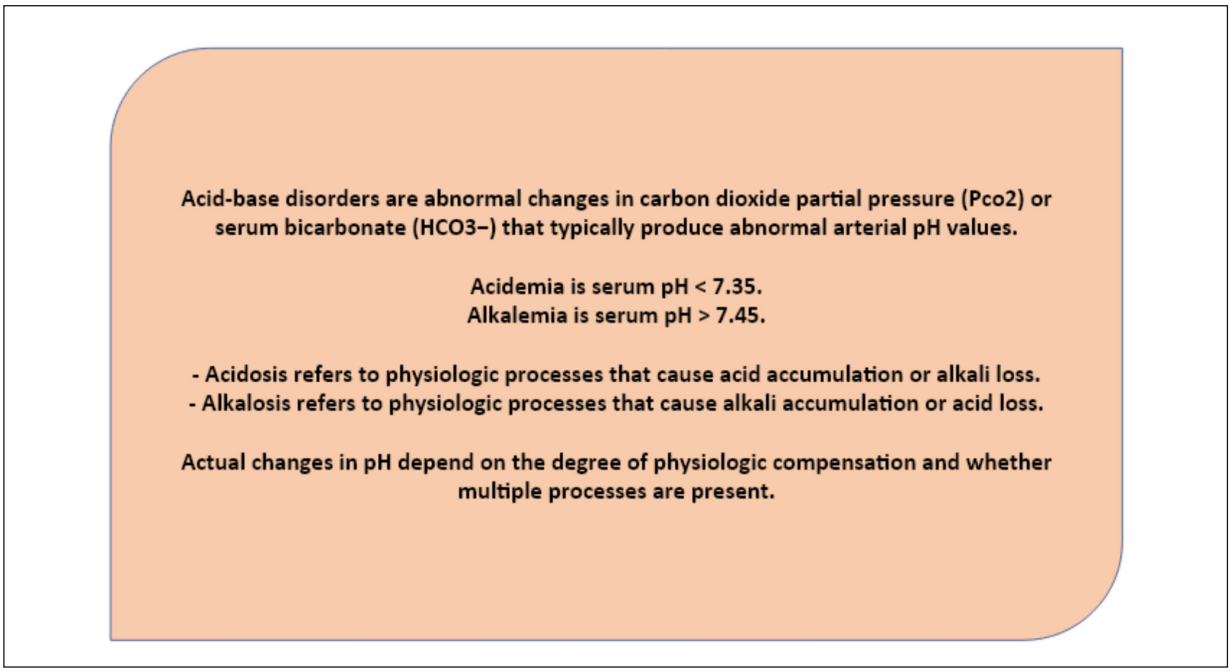

Figure 1. Acid/base disorders are classified according to their cause and pH change into respiratory acidosis, metabolic acidosis, respiratory alkalosis, or metabolic alkalosis. Any deviation of the acid/base balance requires compensatory changes in an attempt to restore homeostasis. For instance, acidosis due to respiratory and metabolic failure leads to compensatory renal and skeleton changes, which lead to increased reclamation of HCO_3 and Ca++.

tilation that may drive to either unrestrainable hypocapnia or hypercapnia (acidosis or alkalosis, respectively) as the CO_2 diffuses through tissues about 20 times faster than O_2. Though the pathoanatomical and pathophysiological basis of ABG validity in assessing long-term systemic deficits still has to be fully clarified, the presence of progressive damages remains the key point[5,7,8,10-15].

Our team proved this in the COVID-19 pandemic during the year 2021-2022[16]. The first period of the pandemic was very particular as a large number of patients were admitted, manifesting only mild symptoms that unexpectedly worsened shortly afterward with clear signs of acute respiratory distress syndrome. Most of these patients were necessarily hospitalized, some of them deceased, and all of them were affected by pre-existing metabolic diseases such as diabetes, overweight, and hypertension[16].

Thus, the perception that acid-base imbalance in metabolic disorders is only confined to metabolic acidosis was challenged by our results. In fact, the most common observed disturbances were suggestive of acid-base balance mixed disorders that were present in almost the totality of the admitted patients. The ABG parameters, together with patients' clinical history and symptoms, were extremely useful in depicting the SARS-CoV-2 infection and its progression. The obtained results indicated that the majority of tested individuals (33 patients out of 46) were confirmed to be affected by COVID-19. COVID-19-affected patients revealed a quite unusual scenario made of respiratory disturbance predominantly characterized by alkalosis accompanied by hypocapnia (during the early phase of the infection) followed by hypercapnia (during the late stage of infection) and hypoxia (pH > 7.45; low PaO_2 < 75; low $PaCO_2$ < 35). These patients were those who showed to be positive either to RT-PCR or thoracic CT-scan that confirmed a bilateral interstitial pneumonia characterized by ground glass opacities (46 patients out of 46) later on, whereas only a few patients suffered from respiratory acidosis, exactly those ones resulted negative to both RT-PCR and thoracic CT scan[15,17].

Why medium/severe COVID-19 patients suffer from respiratory alkalosis rather than acidosis has been associated with the hyperventilation mode, which evolves from hypoxemic causes, pulmonary diseases, and central diseases. In lung diseases, hypoxic stimulation usually causes hyperventilation in trying to resolve a hypoxic state at the expense of CO_2 loss[4,18-24]. Similarly, in COVID-19, despite the fact that some patients did not exhibit severe external hypoxic signs, the ABG analysis was able to show a respiratory alkalosis, considered as a transient compensatory hyperventilation effort that without any prompt medical intervention, often worsened in a matter of few hours[16].

Therefore, since respiratory alkalosis is caused mostly by hypoxia-induced hyperventilation, while respiratory acidosis is caused by hypercapnic respiratory failure, these two ABG markers were the main indicators (in the absence of RT-PCR and CT scan) of the two phases of SARS-CoV-2 infection, the early and the late phases often narrowly close to each other (Figure 2)[20-22,25].

Of note, the ABG analysis was also a life-saver tool in those cases found with COVID-19 symptoms, albeit negative to RT-PCR. This variant, defined later as a COVID-like infection, showed the same clinical signs with look-like COVID-19 ABG's parameters, accompanied by typical bilateral lung pneumonia. Both forms, COVID-19 and COVID-like, were thus considered clinically as the same respiratory disease with multi-organ involvement and unpredictable disease progression characterized by sudden worsening clinical manifestation and unexpected death[15,17].

Extracellular Acidosis and the Immunity, Clinical and Physiologic Implications

It is widely accepted that metabolic acidosis works as the fertile soil of most physical, bone, nervous, and mental degenerative diseases, the main traits of which are deficits in the cellular respiration mechanism. The degenerative patterns are observed with chronic inflammatory processes, food intolerances, high toxic loading linked with the active presence of opportunist micro-organisms, and heavy systemic dysbiosis[4,5,7,8,10-14,17-20].

Metabolic acidosis is a silent progressive condition. During a long-term metabolic acidosis, urine calcium excretion is continuously present without a compensatory phase managed by the intestines *via* calcium absorption with a consequent net loss of bone minerals. The metabolic acidosis pathway induces bone calcium efflux initially due to biochemical dissolution and subsequently by cell-mediated mechanisms that involve a strong inhibition of mesenchymal stem cells (MSCs) differentiation to osteoblasts with a strong stimulation of osteoclasts on one side and neuro cells on the other side. The inhibitory effect on the MSCs differentiation process takes place

Prehospital emergency care of suspected COVID-19 patient with acute respiratory failure (low to medium grade of severity)

The main objective
Ensure the patient classified as a suspected or full-blown case with an initial clinical picture of acute respiratory failure and/or shock the appropriate and continued emergency therapeutic support during the phases of protected transport and temporary management pending the taking charge of the dedicated hospital units.

Methodology
At home and in a mobile station (ambulance) SET-118 → acute respiratory failure → therapeutic protocol as follow:

Oxygen therapy, as needed (SpO_2 > 90%):

low flow (P/F > 300 mmHg): with nasal cannula: 2-4 L/min

high flow (P/F < 300 mmHg): with face mask with reservoir: 15 L/min

Non Invasive Mechanical Ventilation (SpO_2 < 90% or P/F < 200 mmHg + severe dyspnoea, use of accessory respiratory muscles - sternocleidomastoid and scalene, performing paradoxical breathing-, RR > 35 breaths/min, pH < 7.35, pH > 7.2, Kelly 1-2) → CPAP: 5-10 cm H_2O, with FiO_2 of 60-90%

In more severe cases
In the presence of severe hypercapnia, altered mental status, hemodynamic instability, invasive mechanical ventilation IMV → ETI is indicated.

Therapy
If the clinical picture compatible with bilateral interstitial pneumonia: dexamethasone: 6 mg iv (associated with gastroprotection with pantoprazole 40 mg iv) acetylcysteine fl300 mg iv: 2 flev in 250 ml of saline enoxaparinafl: 1 fl4000 IU sc (in the absence of specific contraindications)

Intravenous drip with 5% glucose solution → for nutritional purposes, in case of prolonged hospitalization.

Figure 2. The 118 ABG adopted procedure during the COVID-19 pandemic.

only within a pH-acidic environment mediated by prostaglandins (PGs). Different studies[4,21,22,26] confirmed the strict correlation between calcium flux, medium prostaglandin E2 (PGE_2), and metabolic acidosis that alters the RANKL pathway considered the major osteoclastogenic factor, which is a PGs-dependent response.

Furthermore, in metabolic acidosis, the sympathetic nervous system and corticosteroids tend to increase, accompanied by an increase in leukocytes and hypercatabolic rate. The low bicarbonate and acidic pH stimulate peripheral chemosensors, which induce the medullary center to increase ventilation. This results in increased energy consumption by respiratory muscles. Patients with chronic metabolic acidosis typically show, in different degrees, the Kussmaul breathing sign characterized by a deep, rapid breathing pattern, suggestive that the body or organs have accumulated high levels of acidic compounds. This can be interpreted as the body's attempt to expel carbon dioxide, an acidic compound in the blood, through faster and deeper breaths. In acute cases such as infections or sepsis, physicians may observe a clear inspiratory retraction of the intercostal muscles[8,10-14].

In chronic conditions, once the breathing rate is increased, the trade-off will settle in due to an incomplete compensation, which in turn induces the pH to rise enough to maintain survival rates; the inhibition of a full compensation is necessary at this stage to preserve energy consumption whilst keeping the system active for a longer period of time. This event could be seen in both hypoventilated and hyperventilated patients with chronic obstructive pulmonary disease in which a hypercapnic patient shows less muscle energy while the emphysematous hyperventilates to keep oxygen tension (Figure 3). The Henderson-Hasselbalch equation explains this mechanism: $pH = pK_a + \log([A^-]/[HA])$ decreasing $PaCO_2$ increases the pH. Paradoxically, the acidosis tends to reflect a compensatory effect towards respiratory alkalosis, which in turn affects respiration so that it rises, making the acidosis respiratory compensation[27].

The chemical buffers resist changes in plasma pH by binding H+ ions when they are in excess and dissociating to form H+ ions when the [H+] falls. The respiratory system adjusts plasma pH by adjusting the $PaCO_2$. During acidosis, respiration is stimulated, resulting in decreased $PaCO_2$.

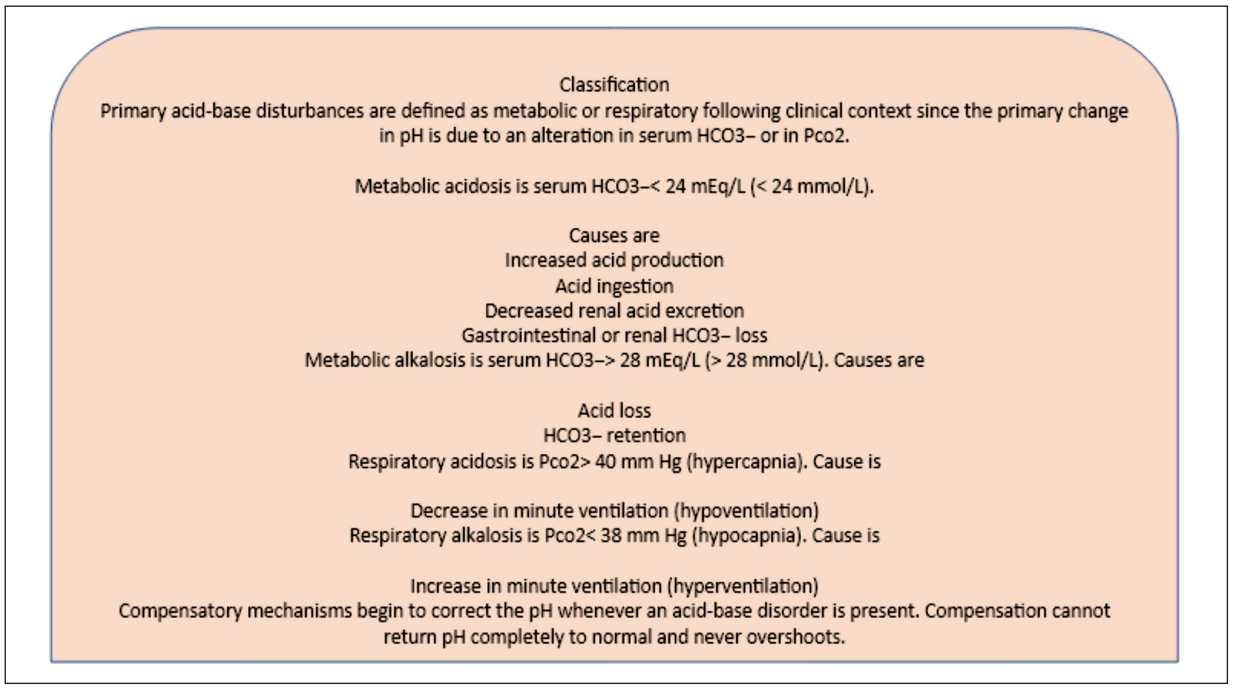

Figure 3. Responses to acid/base imbalance are accomplished by the chemical buffers of the blood, the respiratory system, the renal system, and bones. Acidosis due to either respiratory or metabolic failures leads to compensatory skeleton and renal changes, and both lead to an increased need for HCO_3 in the system.

Therefore, abnormalities in systemic acid/base balance may either affect the CO_2-O_2 micro-exchange process and both in turn affect the ventilation-associated mechanism of organs and tissues generating injuries that are characterized by an increased systemic inflammation. The body's response to the hypoxemic state either acute or chronic, is linked to an increase in minute ventilation leading to a steady increase of hypocapnia, as the CO_2 diffuses through tissues faster than O_2. Though the clinical significance of this loop still remains to clarify, the whole scenario suggests that this condition may generate a steady immune dysfunction due to a subtle inflammatory process that progress over the years almost unnoticed, typical patterns that vividly recall the ABDs[28-30].

Interesting, the ABDs follow a similar process of those of acute condition characterized by a steady and silent respiratory failure over the years. The presence of an unspecific inflammatory state often seen as part of progressive and diffuse tissues, veins and arteria damages with interstitial thickening and gas exchange impairments seems to be the reasonable mechanism able to clarify ABDs degenerative patterns[30,31].

Furthermore, evidences suggest that this atypical hypoxic/hypocapnic-hypercapnic condition enhance the formation of cholesterol oxidation products, known as oxysterols, and 4-hydroxy-2-nonenal (HNE), otherwise considered the major proatherogenic components of oxidized low density hypoproteins (oxLDLs). These components significantly contribute to build up atherosclerotic plaques weakening arteria and vein walls leading to easy breakage. These oxidized lipids are active promoters of inflammatory processes, oxidative stress, and tissue degeneration *via* unrecovered cell apoptosis. As a matter of fact, the distinctive traits of ABDs are well characterized by the release of inflammatory mediators, such as tumor necrosis factor (TNF), nitric oxide (NO), macrophages, and peripheral lymphocyte subset alteration that often pass without being noticed. The level of sub-set cells T-lymphocytes, macrophages (M1 and M2), and B-lymphocytes could be thus used as an independent predictor for ABDs severity and treatment efficacy[30-32].

Studies conducted in resident macrophages or macrophage-like cell lines used acid lactic Hcl to provide a pH environment not less than 6.0 showed clear proinflammatory effects triggering nuclear factor-κB (NF-κB) DNA binding or TNF synthesis. These outcomes were then confirmed *in vivo* in periodontal patients. Similarly,

our outcomes showed a noticeable increase of macrophage polarization M1 and M2 with a significant difference between healthy individuals versus periodontal disease groups. The periodontics patients showed higher inflammatory marker expression with a significant pH difference compared to the healthy group, pH 5.5 *vs.* pH 7. The periodontal individuals showed a lower differentiation of M2-like macrophages with a higher M1-like phenotype. The agonist/antagonist interaction was especially seen in the higher expression of pro-inflammatory cytokines, like IL-1β, interferon-gamma (IFNγ), tumor necrosis factor alpha (TNF-α) and IL-6, linked to M1 activity, and lower expression of immune-regulatory cytokines, such as the IL-10 and transforming growth factor beta (TGF-β) that on the contrary modulate M1 by promoting the healing and regenerative mechanism driven by M2[33-35].

Of note, *in vitro* experiments[36] showed that in the acidic conditions of pH 6.5, nitric oxide (NO) release decreased in response to LPS and was again similar to pH 7.4. At pH 6.5, the release of both IL-6 and IL-10 was significantly less than at pH 7.0 or 7.4. However, IL-10 release was reduced to a far greater extent than IL-6, and thus, the ratio of IL-6 to IL-10 increased significantly from 5:1 at pH 7.4 to 55:1 at pH 6.5. These findings showed that the base/acid balance and pH interpretation should analyze specific patterns in conformity with time and clinical settings. In addition, all forms of metabolic acidosis appear to be associated with prolonged length of mild metabolic condition[36].

The Clinical Effectiveness of ABG Procedure in Preventing Long-Term Consequences Derived from Metabolic Unbalances

Though the concept of performing prehospital ABG analysis is not yet generally accepted, and the value of this approach is still a matter of debate, several studies[37] have already suggested the value of ABG in patients with suspected chronic multi-system decay. Clarifying the effects of acid/base balance and the link with inflammatory and persistent degenerative patterns is extremely relevant to clinical and preventive medicine. The rise of an inflammatory state is always a matter of a long-term silent and unnoticed loading of acid/base disorders that will eventually manifest later on in life. Most clinicians tend to ignore the effects of exogenous acidifying inducers on pH, although many tend to give therapy for mild forms of acidemia[1,5,10-12]. Therefore, an understanding of the physiologic consequences of altered pH by the use of ABG analysis would be imperative in medical assessment (Figure 4)[36-40].

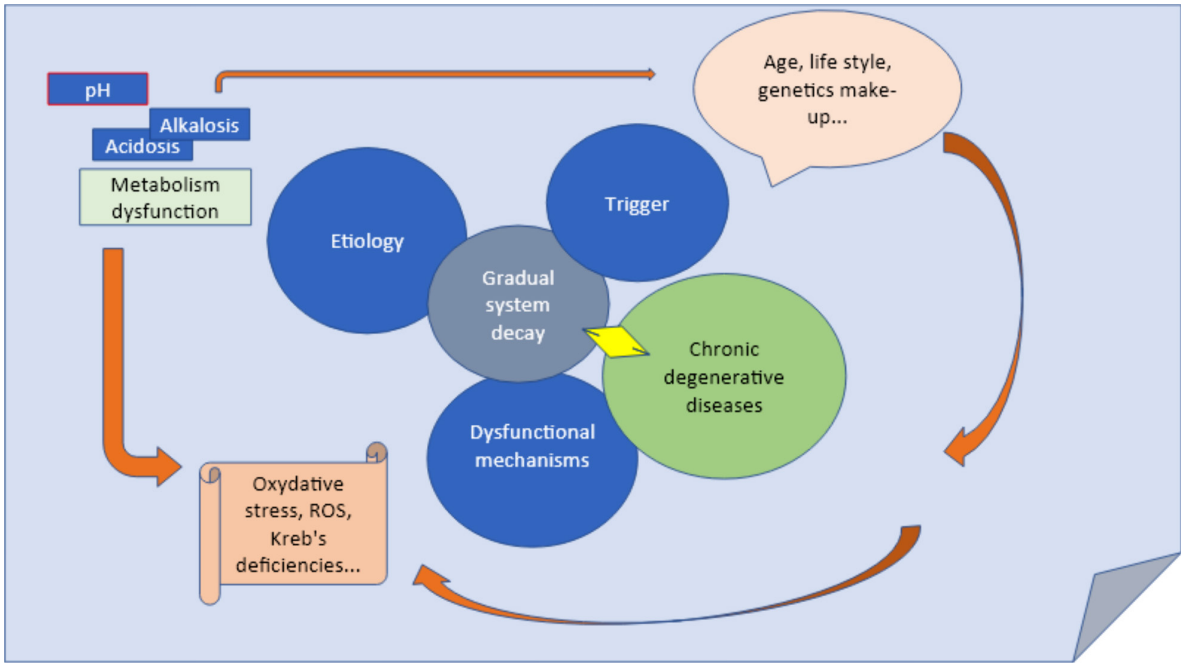

Figure 4. The monitoring of arterial blood gas (ABG) is an essential part of diagnosing and managing severe complications in many disease states, and often the abnormalities may be used in predicting and preventing severe life-threatening risk factor.

For example, in patients with bone degenerative conditions, renal decay, and diabetes, authors examined factors associated with the use of ABG and also assessed whether the measurement in patients was related to hospitalization, ICU treatment, or even death. Following this concept, preventing the extension of metabolic conditions might increase the rate of survival from occasional sepsis or organ failures. Though acidosis/alkalosis has been associated with hemodynamic instability, the underlying mechanisms are not always clear [36-39,41,42].

The fact is that both metabolic acidosis/alkalosis are known to increase inducible NO synthase (iNOS) expression; in animals, the increase of iNOS was seen inducing vasodilation and then shock. Intriguingly, kidney, gut, and lung barrier dysfunction, mucosa permeability, and cardiovascular condition were strictly linked to both acidosis and alkalosis, even in the absence of sepsis or endotoxemia[36-39,43-45]. In addition, acidosis could be considered an important factor that drives oxidative stress due to a steady delocalization of protein-bound iron stored in cells, leading to Fenton-type biochemistry and redox stress[44]. The latter phase is based on the protonation of the peroxynitrite anion (ONOO-) acting like a potent free radical hydroxyl (OH•), which is known to damage cells irreversibly. It is well known that hyperchloremic acidosis tends to increase kidney, gut, lung, and heart injuries in healthy rats[43-46].

Literature reported that it could be rather difficult to obtain arterial blood samples in prehospital patients, and the results would be not accurate due to the analytical equipment's consistent failure rate. However, recent studies[37] have demonstrated that not only has the technology reached a higher standard, but emerging reports have also indicated that the capacity to target patient's conditions has improved.

Therefore, understanding the minimal variation in acid/base balance and minute ventilation over a period of time might be of help for physicians in highlighting important deep and unnoticed changes, correlated to the expression of specific disease patterns, for e.g. abnormal immunology profile [T and B lymphocytes, cytokines and interleukins, toll-like receptor (TLR) 4], abnormal metabolic and endocrine profile (insulin resistance, adiponectin resistance, etc.)[47-50].

Any acute phase of chronic diseases tends to show common progressive patterns that drive to a general system and homeostatic breakdown that are, often if not always, confirmed by the ABG analysis irrespective of the original reason for the disease [47-49]. For patients with chronic cardiac insufficiency, colitis, COPD, kidney age-chronological age difference (KCD), and human immunodeficiency virus (HIV), both pH and hypoxemia values seem to be valuable markers. Increased oxygen consumption in absence of correct compensation and supply generates tissue hypoxia at chronically inflamed sites. Hypoxia drives an increase in HIF activity (a transcription factor known as hypoxia-inducible factor) in both resident and recruited immune cells, which in turns negatively affect immune cells functions and thus increasing the inflammatory activity[51-53].

For instance, the finding of severe metabolic acidosis in these patients has been confirmed to be a helpful tool for prehospital physicians to direct patients to immediate interventional procedures rather than admission to unnecessary wards. The outcomes confirmed that not only are those patients characterized by subtle prolonged hypoventilation and hypoxia status based on their blood gas profiles, but they also have been suffering from long-term uncontrolled inflammatory autoimmune disorders[37,54-59].

The ABG measured at presentation is not only a fast and inexpensive procedure but often offers significant predictions of both short and long-term outcomes in dyspneic patients and has been seen as independent data from other predictive markers associated with mortality, either in patients with pulmonary disorders or other causes of dyspnea[54-56]. It follows that individual ABG data would be essential in either avoiding unintended immunomodulation practice in clinical and laboratory settings or exploring the effectiveness of existing treatments[47-49].

Conclusions

We are aware that there are numerous ways to fall into erroneous conclusions, or oxygen saturation discrepancies may lead to misleading ABG interpretations. Nevertheless, recognizing spurious and apparent "volatile" values will help improve patient evaluation and predictive conclusions by avoiding improper therapies and possible harm arising from a wrong diagnosis. Therefore, with this review, we proposed and discussed the possible advantages of using prehospital ABG measurement as an additional screening procedure that may eventually improve both predictive and diagnostic accuracy of the advancements of

metabolic diseases, which is a fast and inexpensive procedure. ABG parameters may fluctuate with minimal changes during a period of many years and, therefore, are often unrecognized by physicians. The commonest acid-base disorders start early in life and slowly progress, showing minimal audible fluctuations that will become a consolidated disease later in life. For example, cardiac failure, liver failure, renal failure, ventilated patients, and severely and unwell patients from any cause. We therefore suggested that the ABG analysis may enable the prehospital physicians to make the correct diagnosis in a timely manner, thus allowing the appropriate treatment to be initiated before the disease outbreak.

Conflict of Interest
The authors declare that they have no conflict of interests.

Authors' Contribution
Conceptualization, C.G.I. and N.C.D.K.; investigation, C.G.I. and M.G.B., P.D., R.L.; figures, C.G.I. and N.C.D.K.,; data curation, A.P., L.T.H., V.H.P., T.C.T. and S.K.A.; writing, review and editing, C.G.I., S.K.A., R.D.P., and M.G.B.; supervision, K.C.D.N., C.G.I., G.D., and F.I. All authors have read and agreed to the published version of the manuscript.

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Ethics Approval
Ethics approval is not applicable due to the study's design.

Informed Consent
Not applicable.

Data Availability
All data are available upon request from the corresponding author.

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