Hemogasanalysis Point of Care (EPOC) in Pre-Hospital: The Importance of An Early Diagnosis of Silent Hypoxemia in a Context of Scarce Health-Care Resources.

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Abstract

Introduction

Arterial blood gas (ABG) is a useful diagnostic test in the emergency setting. Thanks to the evolution of miniaturized technologies, it was possible to produce a Point of Care ABG analyzer that extended the use of blood gas analysis even in an out-of-hospital context. In the beginning of 2020, the Emergency Medical Service (EMS) of USL Toscana Sud-Est introduced a Point of Care ABG analyzer to characterize respiratory failure in pre-hospital. The onset of SARS-CoV-2 pandemic made the testing ground much more challenging. However, this situation highlighted the potential utility of the hand-held ABG analyzer for a better identification of silent hypoxemia in SARS-CoV-2 patients in pre-hospital setting.

Methods

Primary endpoint

Early identification of cases of silent hypoxemia in pre-hospital setting. In our retrospective observational analysis, we want to understand how many patients with silent hypoxemia the hand-held analyzer detect respect the standard measure of peripheral oxygen saturation (SpO₂) at rest with pulse oximeter or respect the 6 minutes walking test.

Design and setting

We performed a retrospective descriptive analysis of 48 consecutive SARS-CoV-2 patients who activated the territorial Emergency Medical Service of Arezzo (USL Toscana Sud-Est). We included patients between October and November 2020. Age < 18 and pregnancy were considered exclusion criteria. After the telephone triage, the operations center sent the ALS ambulance with a team made up of a physician and a nurse who performed a clinical evaluation of the patient and an arterial blood gas analysis directly at home. Arterial blood was collected from the patient's radial or brachial artery. ALS team directly visualized the result of the exam on EPOC.

Results

A total of 48 SARS-CoV-2 patients were collected, 28 men and 20 women, respectively. Nineteen of the total amounts of 48 SARS-CoV-2 patients had silent hypoxemia identified with the hospital ABG analyzer (gold standard). They didn't refer dyspnea or didn't show increased work of breathing during clinical evaluation. These patients had an arterial blood gas oxygen tension (PaO₂) of less than 60 mmHg. EPOC identified 20 cases of silent hypoxemia instead of the 19 identified with the hospital blood gas analyzer (Sensibility 100%, Specificity 97%, VPP 95%, VPN 100% with 95% CI). The pulse oximeter detected 21 cases of silent hypoxemia (Sensibility 100%, Specificity 94%, VPP 89%, VPN 100% with 95% CI). The 6 minutes walking test detected only 11 of the 19 cases of silent hypoxemia because the test was aborted in 5 cases, and it was not performed in other 3 cases.

Conclusion

From this first descriptive analysis, we conclude that hand-held blood gas analyzer is useful in the early identification of silent hypoxemia in COVID-19 patients. The EPOC system is a handheld and wireless solution that provides accurate results in less than one minute after sample introduction at the patient's side. The portability of this point-of-care tool make it potentially useful in pre-hospital clinical practice.

Introduction

Arterial blood gas (ABG) is a fundamental diagnostic test in many diseases. In the emergency setting, this examination is performed in a few seconds and, if correctly interpreted, provides useful information to the clinician and the staff who assist the patient. ABG is the main guide for the correct diagnosis of respiratory failure, subsequent monitoring, and assessment of the response to treatment. Thanks to the evolution of miniaturized technologies, it was possible to produce a handheld blood gas analyzer. This extended the use of blood gas analysis even in an out-of-hospital context, such as a patient's home, the ambulance, or the family doctor's office.

In the beginning of 2020, the Emergency Medical Service of USL Toscana Sud-Est introduced EPOC (Siemens Healthineers) by launching an experimental phase to evaluate its effectiveness, especially in the characterization of respiratory failure in pre-hospital. The onset of SARS-CoV-2 pandemic made the testing ground for this new Point of Care Test (POCT) much more challenging than expected. In the context of the public health crisis caused by SARS-Cov-2, the rapid transmission of the virus generated a large number of ill patients that exceeds the available health-care resources. We tried to understand whether the information provided by the addition of the blood gas analysis could be useful for a better identification of silent hypoxemia in SARS-CoV-2 patients.

Methods

Primary endpoint

Early identification of cases of silent hypoxemia in pre-hospital setting. Hypoxemia is defined as a decrease (below 60 mmHg) in the partial pressure of oxygen in arterial blood whereas hypoxia is defined by reduced level of tissue oxygenation.

Silent hypoxemia is a hypoxia that is tolerated by patients. Patients with silent hypoxemia do not experience tachypnoea or dyspnea but this condition is related to long-lasting damage of the lungs. In our retrospective observational analysis, we want to understand how many COVID-19 positive patients with silent hypoxemia the hand-held analyzer detect respect the standard measure of peripheral oxygen saturation (SpO_2) at rest with pulse oximeter or respect the 6 minutes walking test.

Design and setting

We performed a retrospective descriptive analysis of 48 consecutive SARS-CoV-2 patients who activated the territorial Emergency Medical Service of Arezzo (USL Toscana Sud-Est). We included patients between October and November 2020, when a second wave of COVID-19 affected Europe. Age < 18 and pregnancy were considered exclusion criteria. After the telephone triage, the operations center sent the ALS ambulance with a team made up of a physician and a nurse who performed a clinical evaluation of the patient and an arterial blood gas analysis directly at home (Fig. 1). Arterial blood was collected from the patient's radial or brachial artery. ALS team directly visualized the result of the exam on EPOC. The blood gas analytical data are subsequently stored on the database of the operations center. All the samples of the handheld system were reprocessed by the hospital blood gas analyzer to verify the accuracy of the results. No discrepancies were noted.

Statistical analysis

The data were analyzed using SPSS V.22 (SPSS, Chicago, Illinois, USA). Continuous variables are expressed as mean $\pm$ standard deviation (SD) while categorical variables are expressed as number (percentage).

Results

A total of 48 SARS-CoV-2 patients were collected, 28 men and 20 women, respectively. The mean age of men was 66.3 ± 17.5 , the mean age of women 69.1 ± 20.1 . In Table 1 we have indicated the characteristics and the laboratory findings of the 48 patients collected (Table 1). All the 48 SARS-CoV-2 patients were evaluated by the ALS team at home. 36 COVID-19 positive patients were centralized for hospital care based on severe comorbidities (immunosuppression, severe COPD, heart disease, etc.) and/or the presence of symptoms such as severe dyspnea, altered vital signs, severe silent hypoxemia, and signs of hypoperfusion (confusion, falls, hypotension, cyanosis, chest pain). The remaining 12 patients continued home care with close monitoring.

Table 1
Presenting patients' characteristics and laboratory findings

	n	COVID-19 positive hospitalized patients	COVID-19 positive home patients
Blood gas characteristics in room air		Median (SD)	Median (SD)
Arterial partial pressure of oxygen (mmHg)		52.7 (12.52)	72.3 (9.42)
Arterial partial pressure of carbon dioxide (mmHg)		37.53 (7.46)	33.65 (5.89)
pH		7.44 (0.08)	7.48 (0.06)
PaO2/FiO2		246.76 (10.71)	341.80 (11.34)
Lactate (mmol/L)		2.2 (0.3)	1.6 (0.4)
Comorbidities		Total	Total
Hypertension		19	5
Diabetes		9	3
Chronic kidney disease		9	0
Cerebrovascular disease		11	2
Cardiovascular disease		15	3
Malignancy		6	0
Autoimmune disease		5	2
Signs and symptoms at disease onset		Total	Total
Fever		32	9
Cough		27	10
Fatigue		20	9
Myalgia		17	8
Dyspnoea		25	3
Diarrhoea		11	2
Vomiting/Nausea		4	0
Syncope		8	0
Vital signs		Total	Total
<i>Respiratory rate (bpm)</i>			

	n	COVID-19 positive hospitalized patients	COVID-19 positive home patients
< 24 breaths per minute	19		12
24–30 breaths per minute	13		0
> 30 breaths per minute	4		0
<i>Systolic arterial pressure (mmHg)</i>			
< 90 mmHg	3		0
90–140 mmHg	22		9
> 140 mmHg	11		3
<i>Heart rate (bpm)</i>			
> 100 beats per minute	19		2
SD: Standard Deviation			

Early detection of silent hypoxemia

Several reports revealed that the prevalence of silent hypoxemia in COVID-19 patients ranges from 20 to 40%, a similar percentage was also identified in our observational study. [1] Nineteen of the total amounts of 48 SARS-CoV-2 patients didn't refer dyspnea or didn't show increased work of breathing during clinical evaluation. These patients had an arterial blood gas oxygen tension (Pa_{O_2}) of less than 60 mmHg and didn't communicate to the ALS team any breathing difficulty. In addition, 14 of the 19 patients had arterial blood gas carbon dioxide tension (Pa_{CO_2}) above 39 mmHg (range 35–42), which would be expected to induce dyspnea; these patients had silent hypoxemia. These data were obtained from the hospital blood gas analyzer, that is considered the gold standard in the identification silent hypoxemia. EPOC identified 20 cases of silent hypoxemia instead of the 19 identified with the hospital blood gas analyzer (Sensibility 100%, Specificity 97%, VPP 95%, VPN 100% with 95% CI).

The pulse oximeter detected 21 cases of silent hypoxemia (Sensibility 100%, Specificity 94%, VPP 89%, VPN 100% with 95% CI). To limit the sources of error, all the measurements has been done indoor and with the patient at rest. Nail polish was removed, and cold extremities have been warmed before the measurement. ALS team considered the most common SpO_2 measured value after an observation of 30–60 seconds.

The 6 minutes walking test detected only 11 of the 19 cases of silent hypoxemia. ALS team took a base line value of SpO_2 with pulse oximeter at rest and after 6 minutes of walking. The test was considered positive when SpO_2 resulted less than 94% or when there was an absolute drop of SpO_2 by 3% or more from baseline. The test was aborted in 5 cases because patients felt unwell. In other 3 cases the test was

not performed due to contraindications like hypomobility, valvular disease and unstable angina in anamnesis.

Discussion

One of the main goals in a general context of lack of ICU beds and overcrowded emergency departments, is to objectively evaluate patients and distinguish those who need hospital care from those who can be assisted at home (Fig. 2). However, in no case this should affect the right standard of care. Generally, severe dyspnea, altered vital signs and symptoms of hypoperfusion (confusion, falls, hypotension, cyanosis, chest pain) are related to patient's hospital admission. The problem related to patients with silent hypoxemia is that they cannot be strictly placed in these categories and in this way, we risk underestimating the disease. In pre-hospital, EPOC could help clinicians to early identify silent hypoxemia.

Mechanism of silent hypoxemia

As the literature data show, even minimal hypoxia can damage several organs. Oxygen limitation impairs mitochondrial respiratory chain and oxidative phosphorylation pathway. The impairment of oxidative phosphorylation pathway inhibits important enzymes' activities and leads to an energy-deprived condition. For this reason, it may be useful to combine patient's clinical evaluation with the use of a hand-held blood gas analyzer that allows early identification of silent hypoxemia. [2] Respiratory distress may occur late in SARS-CoV-2 interstitial pneumonia. [3] This deviation from the typical picture of ARDS is probably due to a set of factors: the severity of the infection, the host's immune response, the patient's comorbidities, the level of response to hypoxia and the patient's respiratory functional reserve. [4] In COVID-19 patients, there are several mechanisms of hypoxia linked to the alteration of the ventilation/perfusion ratio (V/Q) that can be described. [5] First of all, it is possible to observe a deregulation of the normal hypoxia-induced vasoconstriction, due to hyperactivation of inflammatory mechanisms: vasoplegia causes a worsening of the V/Q ratio. [6] In addition, an activation of a cytokine storm and consequent coagulopathy can be observed, which favors thromboembolic events. Microthrombosis in the pulmonary circulation can cause severe hypoxemia and deregulation of V/Q ratio. [7,8]

Unfortunately, it is also possible that SARS-CoV-2 has an idiosyncratic effect on the respiratory control system that reduces the efficacy of this physiologic mechanism. The angiotensin-converting enzyme 2 (ACE-2), which is the cell receptor of COVID-19, is expressed at the level of carotid oxygen chemoreceptors. Probably ACE-2 receptors play an important role in the depressed response to dyspnea in COVID-19 patients. [1]

Therefore, the early assessment of arterial blood gas parameters, such as Pa_{O_2} , Pa_{CO_2} and lactates and derived parameters, such as Pa_{O_2}/Fi_{O_2} and the alveolar-arteriolar oxygen gradient, are essential for early diagnosis of silent hypoxemia, its severity and its classification. [9]

Furthermore, from serial ABG, it is possible to highlight the increase in lactates, which is an early marker of respiratory muscle fatigue and diaphragmatic exhaustion. Our data shows that the median of lactates of COVID-19 hospitalized patients (median 2.2; SD 0.3) is lower than in COVID-19 home patients (median 1.6; SD 0.4). These results may be related to Gattinoni's hypothesis that states that lung compliance is at first greater and should determine a relatively lower Work of breathing (WOB) in the first stage of the disease [10,11]. Furthermore, having a baseline lactate value can be used to highlight its subsequent possible increase in a hospital setting. The increase of lactatemia during hospitalization may represent a useful monitoring tool of insufficient response to therapeutic interventions.

Diagnosis of silent hypoxemia in COVID-19 patients

Early detection of silent hypoxemia and start therapy to prevent further deterioration are crucial to minimize long-term effects as well as mortality rate in SARS-CoV-2 patients. [12]

In pre-hospital setting we have two widely used methods to identify silent hypoxemia: pulse oximetry and the 6 minutes walking test. The pulse oximetry is a common medical device used to measure peripheral oxygen saturation (SpO_2). Although it represents an accessible and hand-held device, it is important to underline that it has low accuracy when patient's SpO_2 is lower than 90%. In this case SpO_2 can differ from true arterial saturation (SaO_2) measured with arterial blood gas analysis by as much as 4–7%. [13] Furthermore, pulse oximetry does not provide any information about adequacy of ventilation, hemoglobin levels, electrolytes or cellular utilization of oxygen and these limitations should be considered when interpreting pulse oximetry findings. In our observational study we were able to find similar data (Fig. 3). Silent hypoxia is also detectable by 6 minutes walking test (peripheral oxygen saturation measured after 6 minutes of walk). In literature was underlined that 6 minutes walking test reported SpO_2 levels significantly reduced in COVID-19 patients in comparison to the control group. [14] Despite that, this test has the disadvantage of not being feasible on all patients, for example in hypomobility syndromes or in patients with contraindications in anamnesis.

It was possible to add arterial blood gas analysis to the two methods previously listed thanks to the introduction of the hand-held ABG analyzer also in pre-hospital setting. This method has the advantage that it can be used to detect silent hypoxemia even in patients with reduced mobility and it has a greater accuracy in defining blood oxygenation values. Recent studies report that also pH level, bicarbonate and electrolyte levels may also be useful in silent hypoxia of COVID-19 patients. [15] Indeed, it has been reported that a lower level of pH, sodium, calcium, and potassium are associated with increased disease severity and lower survival rates of COVID-19 patients. [16, 17] EPOC together with pulse oximeter and 6 minutes walking test could be precious tools for the early detection of silent hypoxia in SARS-CoV-2 positive patients in pre-hospital setting. [15] Therefore it can be an interesting and useful tool to be added to the instrumentation of the ALS team.

Strengths and limitations of this study

ABG was a highly validated tool in in-hospital setting. The study has the advantage of describing the use of the same tool for early identification of silent hypoxemia also in pre-hospital setting.

The study is the result of a first retrospective descriptive analysis of the data collected by EPOC during two months of the second wave of SARS-CoV-2 pandemic. It was a preliminary observational study with a small sample size. Further studies will be necessary to underline its usefulness in this context.

Conclusion

Our understanding of the strategies for the optimal management of SARS-CoV-2 pandemic continues to evolve. The approach described here is based upon our clinical experience in the pre-hospital setting.

From this first descriptive analysis, we conclude that hand-held blood gas analyzer is useful in the early identification of silent hypoxemia in COVID-19 patients. The EPOC system is a handheld and wireless solution that provides accurate results in less than one minute after sample introduction at the patient's side. The handling of this device, make it potentially useful in pre-hospital clinical practice as many other point-of-care tools (Fig. 4). Numerous other studies will be needed to understand how useful this technology can be in leaving the pandemic behind.

List Of Abbreviations

A-a gradient: Alveolar to arterial oxygen gradient

ABG: arterial blood gas

ARDS: acute respiratory distress syndrome

CI: confidence interval

CPAP: continuous positive airway pressure

ED: emergency department

EMS: emergency medical service

ICU: intensive care unit

IOT: orotracheal intubation

Pa_{CO_2} : carbon dioxide partial pressure

Pa_{O_2} : arterial oxygen partial pressure

$\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2}$: arterial oxygen partial pressure/fractional inspired oxygen

PEEP: positive end-expiratory pressure

POCT: point of care tool

SaO₂: arterial oxygen saturation

SD: standard deviation

SpO₂: peripheral oxygen saturation

VPN: negative predictive value

VPP: positive predictive value

V/Q: ventilation/perfusion ratio

WOB: work of breathing

Declarations

Ethics Approval and Consent to participate

This survey did not involve the collection or use of confidential or sensitive personal health information. Ethics approval was not required under the Geneva jurisdiction for reporting the data presented in this study. The present study was conducted in compliance with the Helsinki Declaration of 1975, as revised in October 2013.

Consent for publication

Not applicable.

Availability of supporting data

All data generated or analyzed during this study are included in this publication.

Competing interests

No one.

Founding

This work did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authors' contributions

S.M. and A.U. drafted the primary manuscript, contributed to the conceptualization of the study, and participated to the study selection/data collection; S.C. made the primary contributed to the conceptualization of the study; F.S., G.I. and G.S. revised both the primary manuscript and the study selection/data collection; G.S., T.T., M.M. G.I. and F.S. revised the manuscript and supervised all the work. All authors have read and agreed to the published version of the manuscript.

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Figures

Figure 1

Algorithm of Emergency Medical Service activation.

ITALY: COVID-19 CASES CURVES

- New Infected
- Deceased
- Recovered
- Active

ICU PATIENTS

Number of COVID-19 positive patients in Intensive Care Units in Italy. The orange line show the first alert threshold, the red line the second.

Figure 2

Italy: COVID-19 cases curves and ICU patients.

Figure 3

Scatterplot of the relationship between estimated oxygen saturation from pulse oximetry (SpO2) and SaO2 from hand-held blood gas analysis in 19 COVID-19 patients with silent hypoxemia. Each subject is represented by a point. The solid line is the regression line.

Figure 4

Point of care tools: hand-held blood gas analyzer and portable ultrasound system.