Hypoxemia During Extreme Hyperleukocytosis: How Spurious?

Andry Van de Louw MD PhD, Ruchi J Desai MD, Coursen W Schneider MD, and
David F Claxton MD

BACKGROUND: Spurious hypoxemia has been described in case reports during extreme hyperleukocytosis and has led to recommendations for immediate cooling and analysis of arterial blood gases (ABGs). We sought to determine, in samples processed as recommended, the magnitude of spurious hypoxemia in acute leukemia subjects with hyperleukocytosis. METHODS: A retrospective chart review was conducted of all subjects admitted between 2003 and July 2014 for acute leukemia, who presented with white blood cell (WBC) count $> 50 \times 10^9$ cells/L and had ABGs performed. For each ABG, we collected P_{aO_2}, S_{aO_2}, simultaneous WBC count, and S_{pO_2} when available. Bland and Altman analysis was used to assess the agreement between S_{pO_2} and S_{aO_2}. RESULTS: One-hundred forty-six samples (from 45 subjects) were included, of which 57 samples (from 18 subjects) had data available for Bland and Altman analysis. Mean ($S_{pO_2} - S_{aO_2}$) was 2.5%, and 95% CI for limits of agreement between S_{pO_2} and S_{aO_2} was ($-10.1, 15.1$)%. The mean ($S_{pO_2} - S_{aO_2}$) was significantly higher for WBC count $> 100 \times 10^9$/L as compared with WBC count $< 100 \times 10^9$/L (3.8% vs 0.4%, $P = .04$), and the 95% CIs for limits of agreement were ($-10.3, 18$)% versus ($-7.9, 8.6$)%. S_{pO_2} and S_{aO_2} were poorly correlated ($r^2 = 0.19$), whereas the difference ($S_{pO_2} - S_{aO_2}$) was fairly correlated with WBC count ($r^2 = 0.44$). Overall, 11 of 19 samples with WBC count $> 150 \times 10^9$/L had $P_{aO_2} < 55$ mm Hg whereas S_{pO_2} was $> 94\%$, the proportion being 5 of 62 samples for WBC count $< 150 \times 10^9$/L ($P < .001$). Three subjects with WBC count $> 150 \times 10^9$/L exhibited large S_{pO_2} to S_{aO_2} differences (10–20%) before leukapheresis, which decreased to below 5% afterward. CONCLUSIONS: In subjects with acute leukemia and hyperleukocytosis, despite cooling and quickly analyzing the samples, we observed poor correlation and agreement between S_{pO_2} and S_{aO_2}, unacceptably low for WBC count $> 100 \times 10^9$/L. Our results suggest that current guidelines may not totally prevent the diagnosis of spurious hypoxemia. *Key words: hypoxemia; blood gas analysis; leukocytosis; acute leukemia; oximetry; oxygen.* [Respir Care 0;0(0):1–•. © 0 Daedalus Enterprises]

Introduction

Between 10 and 30% of patients newly diagnosed with acute leukemia present with hyperleukocytosis, usually de-

Dr Van de Louw is affiliated with the Division of Pulmonary and Critical Care Medicine, Drs Desai and Schneider are affiliated with the Department of Internal Medicine, and Dr Claxton is affiliated with the Division of Hematology and Oncology, Penn State Milton S Hershey Medical Center and College of Medicine, Hershey, Pennsylvania.

Correspondence: Andry Van de Louw MD PhD, Division of Pulmonary and Critical Care Medicine, Milton S Hershey Medical Center, 500 University Drive, Hershey, PA 17033. E-mail: avandelouw@hmc.psu.edu.

fined as a white blood cell (WBC) count $> 100 \times 10^9$/L.[1] Hyperleukocytosis not only negatively impacts overall survival but is also associated with increased early mortality, due to cerebral and pulmonary leukostasis.[2] Patients requiring ICU admission and mechanical ventilation for acute respiratory failure have an overall poor survival[3,4]; thus, the respiratory status of acute leukemia patients with hyperleukocytosis is a major concern.

In acute leukemia, early detection of pulmonary compromise may prompt invasive intervention aimed at decreasing WBC count (leukapheresis) or improving gas exchange (mechanical ventilation). As clinical signs and chest x-ray findings may be subtle in immunocompromised hosts, the assessment of patient's oxygenation via arterial blood gas (ABG) measurement and/or pulse oximetry is crucial. The finding of artifactual decrease in P_{aO_2} due to increased

oxygen consumption by WBCs in collected samples, has been described and referred to as spurious hypoxemia.[5] A clinically relevant decay in P_{aO_2} may occur as soon as 2 min in samples with WBC count as low as 55×10^9/L and seems proportional to WBC count.[5] Several case reports have been published,[6-9] but other authors have emphasized that the hypoxemia observed during hyperleukocytosis might actually be real and reflect subtle pulmonary leukostasis.[10] Published data come from small series, but no study has ever systematically investigated the reliability of P_{aO_2} and S_{aO_2} in this setting, probably because of the relative rarity of extreme hyperleukocytosis. Although the American Association for Respiratory Care (AARC) has recommended immediate cooling and analysis of ABG for hyperleukocytic patients,[11] these guidelines rely on limited data, and their effect on the magnitude of spurious hypoxemia has never been evaluated.

Given the limited published data, we included a large series of acute leukemia subjects with hyperleukocytosis in this retrospective study and systematically assessed (1) the relationship between P_{aO_2}, S_{aO_2}, and WBC count and (2) the agreement between S_{aO_2} and S_{pO_2} in cooled and quickly analyzed ABG.

Methods

This retrospective study was approved by the Pennsylvania State University College of Medicine Institutional Review Board (IRB number 00000374), and informed consent was waived.

Subjects

The charts of all subjects admitted to our institution with a newly diagnosed acute leukemia between January 2003 and July 2014 were screened, and all subjects with at least one ABG performed with a concomitant hyperleukocytosis (WBC count $> 50 \times 10^9$/L) were included for further analysis.

Data Collected

Baseline demographic data, significant comorbidities, type of acute leukemia, the use of invasive or noninvasive mechanical ventilation during admission, and 28-d and 6-month survival were collected. Whenever an ABG and a complete blood count were performed simultaneously, we collected P_{aO_2}, S_{aO_2}, and WBC count, along with S_{pO_2} recorded at the same time, when available. Mean arterial pressure, heart rate, and vasopressor requirements (yes/no) at the time of ABG were also recorded. As per hospital policy, ABGs were collected in plastic syringes, stored in ice, and immediately sent (via pneumatic tube system) and processed in the laboratory, in agreement with published

QUICK LOOK

Current knowledge

Patients newly diagnosed with acute leukemia may present with hyperleukocytosis, usually defined as a white blood cell (WBC) count $> 100 \times 10^9$/L. The finding of artifactual decrease in P_{aO_2}, due to increased oxygen consumption by WBCs in collected samples, has been described in this population and referred to as spurious hypoxemia. A clinically relevant decay in P_{aO_2} may occur as soon as 2 min in samples with WBCs as low as 55×10^9/L and seems proportional to WBC count.

What this paper contributes to our knowledge

In a retrospective review of acute leukemia subjects with hyperleukocytosis, despite cooling and quickly analyzing the samples, there was poor correlation and agreement between S_{pO_2} and S_{aO_2}, unacceptably low for WBC count $> 100 \times 10^9$/L. These results suggest that current guidelines may not always prevent the diagnosis of spurious hypoxemia.

recommendations.[12] The type of oxygen or ventilatory support was recorded as follows: no oxygen requirement, oxygen on nasal cannula, high-flow oxygen device (high-flow nasal cannula, Venturi mask), noninvasive mechanical ventilation, invasive mechanical ventilation.

Statistical Analysis

All results were reported as mean $\pm$ SD (SPSS 20, SPSS, Chicago, Illinois). To assess the agreement between S_{aO_2} and S_{pO_2}, we used the method described by Bland and Altman,[13] calculating the mean difference (bias, d) and the SD of the differences (precision, s) between S_{pO_2} and S_{aO_2} and the 95% CIs for limits of agreement between S_{pO_2} and S_{aO_2} (d $\pm$ 2s). We used the 2-tailed Student t test to compare the bias, mean arterial pressure, and heart rate between samples with a WBC count below versus above 100×10^9/L. A 2-tailed Fisher exact test was used to compare the proportion of cases with hypoxemia ($P_{aO_2} < 55$ mm Hg) and vasopressor requirements between samples with WBC below or above 100×10^9/L, respectively. Analysis of variance for repeated measures was used to assess the effect of leukapheresis on ($S_{pO_2} - S_{aO_2}$) differences. $P < .05$ was considered statistically significant.

Results

Subjects

Of 874 patients admitted during the 11½ year period with a newly diagnosed acute leukemia, 45 subjects were

Table 1. Demographic, Clinical, Biological, and Survival Data for the 45 Subjects

Parameters	Values
Age, y	60.0 ± 12.9
Sex, male/female	25/20
Comorbidities, n	
Congestive heart failure	1
Coronary artery disease	7
Hypertension	20
Diabetes	10
Obstructive sleep apnea	5
COPD	3
Chronic liver disease	0
Chronic kidney disease	1
Previous cancer	6
Smoking history	15
Biological data on admission	
Creatinine, mg/dL	1.54 ± 0.71
Bilirubin, mg/dL	0.98 ± 0.47
LDH, units/L	4132 ± 3510
Hemoglobin, g/dL	8.4 ± 1.5
INR	1.99 ± 2.05
Platelets, $\times 10^9$/L	53 ± 73
WBC count, $\times 10^9$/L	133.87 ± 93.52
P_{aO_2}, mm Hg	58.3 ± 18.7
P_{aCO_2}, mm Hg	37.8 ± 11.3
S_{aO_2}, %	90.3 ± 7.8
S_{pO_2}, %	95.3 ± 2.9
Clinical data	
Mean arterial pressure on admission, mm Hg	93 ± 17
Heart rate on admission, beats/min	103 ± 20
Subjects requiring vasopressors within 24 h, n	8/45
Subjects requiring invasive mechanical ventilation during admission, n	27/45
Duration of mechanical ventilation, d	7.3 ± 5.8
Day 28 survival, n	19/45
6-mo survival, n	8/45

Data are presented as mean $\pm$ SD.
LDH = lactate dehydrogenase
INR = international normalized ratio
WBC = white blood cell

included in this analysis. In total, these subjects had 146 simultaneous complete blood counts and ABGs performed. All subjects had acute myeloid leukemia, and 6 had the acute promyelocytic leukemia subtype. None of the 63 patients with hyperleukocytic acute lymphoblastic leukemia had an ABG performed. Baseline demographic, clinical, and biological data as well as survival are detailed in Table 1. ABGs were performed while subjects were breathing room air ($n = 3$), receiving oxygen on nasal cannula ($n = 23$) or high-flow device ($n = 23$), or supported by noninvasive ($n = 4$) or invasive ($n = 93$) mechanical ventilation.
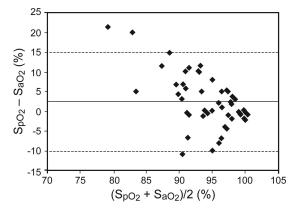

Fig. 1. Bland and Altman representation of the agreement between S_{pO_2} and S_{aO_2}. For the 57 samples (18 subjects), ($S_{pO_2} - S_{aO_2}$) was plotted on the Y axis versus ($S_{pO_2} + S_{aO_2}$)/2 on the X axis. The mean ($S_{pO_2} - S_{aO_2}$) (bias) was 2.5% (center line), and the 95% CI for limits of agreement was ($-10.1,15.1$)% (dotted lines).
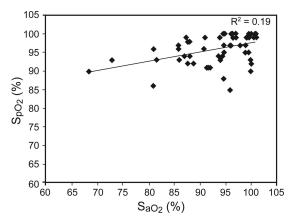

Fig. 2. Correlation between S_{pO_2} and S_{aO_2} for 57 samples (18 subjects). The correlation equation is $S_{pO_2} = 0.243 S_{aO_2} + 73.3$ ($r^2 = 0.19$).

Agreement and Correlation Between S_{aO_2} and S_{pO_2}

Among the 146 ABGs performed in 45 subjects, we were able to collect simultaneous S_{aO_2} and S_{pO_2} and performed Bland and Altman analyses for 57 samples in 18 subjects. The mean ($S_{pO_2} - S_{aO_2}$) was 2.5%, and the 95% CI for limits of agreement between S_{pO_2} and S_{aO_2} were ($-10.1,15.1$)% (Fig. 1). Plotting S_{pO_2} versus S_{aO_2} (Fig. 2), we observed a poor correlation with a coefficient of determination (r^2) of 0.19.

Effect of WBC Count on P_{aO_2} and on the Agreement Between S_{pO_2} and S_{aO_2}

Figures 3 and 4 represent the distributions of P_{aO_2} and ($S_{pO_2} - S_{aO_2}$) versus WBC count, respectively. The coefficient of determination for the correlation between ($S_{pO_2} - S_{aO_2}$) and WBC count was 0.44; thus, 44% of the ($S_{pO_2} - $

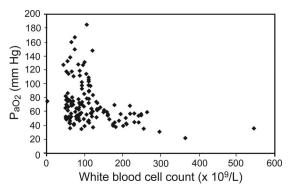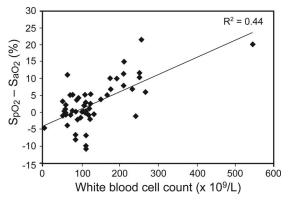Fig. 3. Distribution of P_{aO_2} and white blood cell count for 146 samples (45 subjects).

Fig. 4. Distribution of $(S_{pO_2} - S_{aO_2})$ and white blood cell count for 57 samples (18 subjects). The correlation equation is $S_{pO_2} - S_{aO_2} = 0.05 \times$ white blood cell count $- 4.0$ ($r^2 = 0.44$).
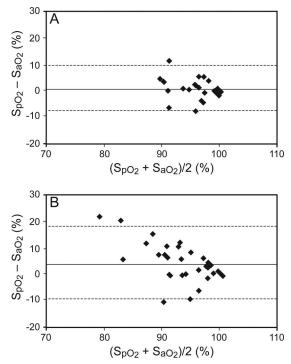

Fig. 5. Bland and Altman representation of the agreement between S_{pO_2} and S_{aO_2} according to white blood cell (WBC) count. ($S_{pO_2} - S_{aO_2}$) was plotted against ($S_{pO_2} + S_{aO_2}$)/2 for the 22 samples with a WBC count $< 100 \times 10^9$/L (A) and for the 35 samples with a WBC count $> 100 \times 10^9$/L (B). The bias was 0.4% for white blood cell count $< 100 \times 10^9$/L versus 3.8% for WBC count $> 100 \times 10^9$/L ($P = .04$) (center lines). The 95% CIs for limits of agreement were ($-7.9, 8.6$)% and ($-10.3, 18.0$)%, respectively (dotted lines).

S_{aO_2}) variance was accounted for by variations in WBC count. Figure 5 displays the effect of WBC count on the agreement between S_{pO_2} and S_{aO_2}. The mean ($S_{pO_2} - S_{aO_2}$) was significantly higher for WBC count $> 100 \times 10^9$/L as compared with WBC count $< 100 \times 10^9$/L (3.8% vs 0.4%, $P = .04$). Likewise, the 95% CIs for limits of agreement were ($-10.3, 18.0$)% for WBC count $> 100 \times 10^9$/L versus ($-7.9, 8.6$)% for WBC count $< 100 \times 10^9$/L. There was no difference between the 2 groups in terms of vasopressor requirements (11 of 35 samples with WBC count $> 100 \times 10^9$/L vs 11 of 22 samples with WBC count $< 100 \times 10^9$/L, $P = .28$) or heart rate (96 $\pm$ 22 beats/min for samples with WBC count $> 100 \times 10^9$/L vs 93 $\pm$ 20 beats/min for samples with WBC count $< 100 \times 10^9$/L, $P = .60$). Mean arterial pressure at the time of ABG was higher for WBC count $> 100 \times 10^9$/L as compared with WBC count $< 100 \times 10^9$/L (90 $\pm$ 22 mm Hg vs 77 $\pm$ 14 mm Hg, $P = .002$). Including only the 10 samples with WBC count $> 200 \times 10^9$/L, the bias and 95% CI for limits of agreement were 11.0% and ($-2.4, 24.5$)%, respectively.

Among 44 samples with WBC count $> 100 \times 10^9$/L, 18 (10 subjects) exhibited a $P_{aO_2} < 55$ mm Hg, whereas

S_{pO_2} was > 88%, the proportion being only 4 of 36 samples for WBC count $< 100 \times 10^9$/L ($P = .003$). Similarly, 11 of 19 samples with WBC count $> 150 \times 10^9$/L had $P_{aO_2} < 55$ mm Hg, whereas S_{pO_2} was > 94%, the proportion being only 5 of 62 samples for WBC count $< 150 \times 10^9$/L ($P < .001$). The lowest P_{aO_2} observed was 22 mm Hg in a subject with a WBC count of 365 $\times 10^9$/L, breathing O_2 4 L/min via nasal cannula with a S_{pO_2} of 96% and no clinical sign of respiratory distress.

Comparison of ($S_{pO_2} - S_{aO_2}$) Differences Before/After Leukapheresis

Six subjects who underwent leukapheresis to quickly decrease their WBC count had ABGs performed before and after the procedure. ($S_{pO_2} - S_{aO_2}$) was 9.4 $\pm$ 9.2% before leukapheresis versus 0.5 $\pm$ 3.8% afterward ($P = .055$). Three subjects with very high WBC count ($> 150 \times 10^9$/L) all exhibited large S_{pO_2} to S_{aO_2} differences (10–20%) before leukapheresis, which decreased to < 5% after the procedure (Fig. 6).
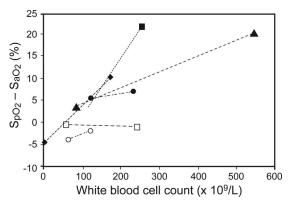
Fig. 6. Effect of leukapheresis on white blood cell count and (S_{pO_2} – S_{aO_2}) in 6 subjects who had arterial blood gas analysis performed before (shapes on the right) and after (shapes on the left) leukapheresis. For the 3 subjects with large S_{pO_2} to S_{aO_2} differences (10–20%) before leukapheresis, (S_{pO_2} – S_{aO_2}) decreased to below 5% after the procedure. The 6 different shapes represent the 6 individual subjects.

Discussion

The main findings of this study are the large bias and limits of agreement and the poor correlation between S_{aO_2} and S_{pO_2} in hyperleukocytic acute myeloid leukemia. This poor agreement seems directly related to the severity of hyperleukocytosis, as it worsened with increasing WBC count and disappeared after leukapheresis in some subjects. It is clinically relevant especially for very high WBC count ($> 150 \times 10^9$/L), as 50% of ABGs suggested severe hypoxemia ($P_{O_2} < 55$ mm Hg), whereas subjects were probably not hypoxic ($S_{pO_2} > 94\%$).

Spurious hypoxemia (or leukocyte larceny) was first described in 1979,[5,14] and a few small series have been published since, mostly in subjects with chronic myeloid or lymphocytic leukemias[6,7,9,14,15] and severe hyperleukocytosis, but no study thus far had investigated the magnitude and clinical relevance of this phenomenon. The pathophysiology of spurious hypoxemia has been thought to involve oxygen consumption by increased numbers of leukocytes inside the syringes (leukocyte larceny) before analysis.[5] This hypothesis was supported by an in vitro study using continuous P_{O_2} measurement in blood samples from 5 hyperleukocytic leukemia subjects and also from granulocyte donors, where authors observed a progressive decrease in P_{O_2} in hyperleukocytic samples, reaching values as low as 20 mm Hg within 10 min.[16] This progressive decline was grossly proportional to WBC count and was not subsequently observed in the same subjects after cytoreductive therapy or in whole blood from the granulocyte donors.[16] These results are also consistent with the decrease in P_{O_2} expected when applying Henry's law to hyperleukocytic samples, using known data on in vitro oxygen consumption by leukocytes[17]; assuming, for in-

stance, that the oxygen consumption of leukocytes is about 0.1 μl O_2/10^6 cells/h,[18] one would expect a drop in P_{O_2} of about 50 mm Hg within 10 min for a WBC count of 100×10^9/L at ambient temperature. This P_{aO_2} decay could be related not only to the WBC count but also to the type of cells, as immature leukocytes seem to have higher metabolic rates than normal cells.[19]

Although scattered case reports or small series of spurious hypoxemia have been published,[5-8] our study is the first to systematically investigate the magnitude of spurious hypoxemia in a large population of acute leukemia subjects with hyperleukocytosis. Other authors have challenged the magnitude of spurious hypoxemia and suggested that part of the observed hypoxemia might actually be real and related to either unrecognized leukostasis or increased methemoglobinemia.[10] Indeed, increased methemoglobinemia described during acute leukemia[20] is associated with false S_{pO_2} readings and was also proposed to account for low S_{aO_2} in hyperleukocytic subjects.[10] However, methemoglobinemia is unlikely to explain spurious hypoxemia, as it is associated with normal P_{aO_2}[21] and could not account for the extremely low P_{aO_2} observed in the present study and others.[5,9,22,23]

Overall, we described a poor correlation between S_{aO_2} and S_{pO_2} in the presence of a WBC count $> 50 \times 10^9$/L, as attested by the low coefficient of determination ($r^2 = 0.19$) observed when plotting S_{pO_2} versus S_{aO_2}. Although correlation analysis may not be the best approach to compare S_{aO_2} and S_{pO_2}, a large meta-analysis of 74 studies reported an r^2 of 0.8 between S_{aO_2} and S_{pO_2},[24] much higher than the r^2 of 0.19 that we observed for subjects with WBC count $> 50 \times 10^9$/L. The bias and 95% CI for limits of agreement in our whole population (2.5% and ($-10.1,15.1$)%) were also larger than those reported by most studies in non-hyperleukocytic subjects[24-26] but were probably negatively affected by samples with extreme WBC count. Indeed, the bias and 95% CI for limits of agreement that we observed in subjects with WBC count $< 100 \times 10^9$/L (0.4% and ($-7.9,8.6$)%) are similar to those reported in studies in critically ill[27] and COPD[26] populations. Conversely, the bias and 95% CI for limits of agreement were 3.8% and ($-10.3,18.0$)% for WBC count $> 100 \times 10^9$/L, whereas one of the largest studies on 102 general ICU subjects reported a bias of only 0.02% with 95% CI for limits of agreement of ($-4.2,4.2$)%.[25] Although peripheral vasoconstriction can cause false S_{pO_2} readings,[28] the large (S_{aO_2} – S_{pO_2}) differences for WBC count $> 100 \times 10^9$/L are unlikely to be explained by a worse hemodynamic status associated with hyperleukocytosis, as we found no difference in heart rate or vasopressor requirements between the 2 groups, and if anything, mean arterial pressure was higher for those with WBC count $> 100 \times 10^9$/L. As expected, bias and 95% CI for limits of agreement were even poorer for WBC count $> 200 \times 10^9$/L (11.0% and ($-2.4,24.5$)%,

respectively). The relationship between ($S_{pO_2} - S_{aO_2}$) and WBC count was reinforced by the correlation observed when plotting the difference ($S_{pO_2} - S_{aO_2}$) versus WBC count ($r^2 = 0.44$).

Following the publication of several case reports[6-8] and of in vitro studies,[5] recent clinical practice guidelines from the AARC recommend immediate cooling and analysis of ABGs for patients with very high leukocyte counts.[11] Although our ABGs were processed according to these recommendations (immediately cooled and analyzed without delay), we still observed clinically important spurious hypoxemia. Some authors have described a blunted P_{aO_2} decay in samples placed on ice,[5,10] but others have argued that immediate cooling is not sufficient to eliminate spurious hypoxemia, because the oxygen consumption by leukocytes continues during the time (as short as a few minutes) required by samples to gradually reach ice water temperature.[23] As in the present study, Loke et al[22] observed a significant P_{aO_2} decay even in samples stored on ice and analyzed immediately. The addition of potassium cyanide appears to be the best way to stop the P_{aO_2} decay,[5] but it is more difficult to implement in daily practice. Rapid processing of the samples alone is certainly not sufficient to prevent spurious hypoxemia, as elegantly shown by Fox et al[5]; performing in vitro studies of blood samples using a tonometer, they observed a drop in P_{O_2} from 130 to 55 mm Hg within 2 min only for a WBC count of 276×10^9/L at ambient temperature. Our results reinforce the AARC recommendations[11] but suggest that they may not be sufficient to prevent spurious hypoxemia.

Spurious hypoxemia may have deleterious consequences if not adequately recognized. First, P_{aO_2} may be used as a criterion to initiate mechanical ventilation in patients with hematological malignancies,[29] along with clinical signs of respiratory distress. Coexisting conditions (pain, anxiety, cerebral leukostasis) may also cause tachypnea, reinforcing the pivotal role of P_{aO_2} in the clinical decision making. Second, during mechanical ventilation, unrecognized spurious hypoxemia may trigger inappropriate increase in F_{IO_2} and expose patients who are already prone to respiratory complications to additional pulmonary oxygen toxicity.[30] Third, P_{aO_2} is part of severity scores widely used in critically ill patients (APACHE [Acute Physiology and Chronic Health Evaluation] and SOFA [Sequential Organ Failure Assessment]),[31] and low recorded P_{aO_2} may falsely increase those scores. Finally, initial P_{aO_2} has been shown to be an independent predictor of mortality in immunocompromised populations with pulmonary infiltrates.[32] In summary, assessment of oxygenation is crucial in acute leukemia patients but is particularly challenging in the presence of extreme hyperleukocytosis.

Interestingly, most if not all cases of spurious hypoxemia published involved myeloid leukemias, acute or chronic.[5-8,10] In agreement with the literature, all of our subjects had acute myeloid leukemia. The most probable explanations for the lineage specificity of this observation are: (1) acute myeloid leukemia is the most frequent acute leukemia in adults[33] and (2) symptomatic pulmonary leukostasis is more frequent in acute myeloid leukemia subjects,[34] who are therefore more likely to have ABGs performed. Indeed, among 874 patients admitted for acute leukemia in the present study, only 63 had acute lymphoblastic leukemia, and none of them had ABGs performed during their admission.

The main limitation of this study is its retrospective design and the inherent concern about the reliability of the data collected. Pulse oximetry is subject to plethysmography artifacts,[28] and we were not able to account for some factors affecting its reliability (methemoglobinemia); thus, S_{pO_2} recorded in the charts could be false. We tried to minimize this bias by ensuring that consistent S_{pO_2} values were recorded around the time of ABG, but we cannot rule out, despite all of our precautions, the possibility of false S_{pO_2} readings. However, extreme hyperleukocytosis in acute leukemia is so infrequent that a study prospectively recording S_{pO_2} and S_{aO_2} would be difficult to perform. Although our hospital policy requires all ABGs to be stored on ice and immediately processed, we could not control for the exact time elapsed between ABG collection and analysis. Because of the irreducible time required for transport to the laboratory, receipt, labeling, and accessioning of the samples, we estimate this delay at about 10–15 min. As discussed above, however, even a few minutes may be enough to cause P_{aO_2} decay, and the only way to prevent that delay would be to use portable gas analyzers at bedside. Another limitation is the lack of a control group with normal WBC count; however, the bias and 95% CI for limits of agreement that we observed for WBC count between 50 and 100×10^9/L were similar to those reported in general ICU subjects,[25,26] so that the poor agreement observed for WBC count $> 100 \times 10^9$/L can probably be ascribed to hyperleukocytosis. Our choice to include subjects with WBC count $> 50 \times 10^9$/L is also arguable, but it was based on a study reporting a rapid decay in P_{aO_2} in blood samples with a WBC count of 55×10^9/L.[5] Although these results were obtained by in vitro studies using tonometry in a few samples, our data actually suggest that spurious hypoxemia is clinically unacceptable for WBC count $> 100 \times 10^9$/L. Finally, oxygen supplementation may have altered the relationship between P_{aO_2} and WBC count, as presented in Figure 3. We were not able to present data with uniform F_{IO_2} (due to the small number of subjects for a given F_{IO_2}) or P_{aO_2}/F_{IO_2} ratios, as accurate computation of F_{IO_2} is challenging for patients receiving oxygen via nasal cannula or face mask. Notwithstanding this limitation, the relationship between P_{aO_2} and WBC count as depicted in Figure 3 remains convincing. Indeed, one would expect the subjects with higher WBC count to

have presented more severe respiratory symptoms and to have received more oxygen, which could have artificially increased their P_{aO_2} as compared with subjects with lower WBC count. The fact that we observed, on the contrary, extremely low P_{aO_2} in subjects with higher WBC count suggests that supplemental oxygen did not distort the overall relationship between P_{aO_2} and WBC count and, if anything, strengthens our results.

Conclusions

In acute leukemia subjects with hyperleukocytosis, even cooled and quickly analyzed ABGs exhibited unacceptably poor agreement and correlation between S_{pO_2} and S_{aO_2} for WBC count $> 100 \times 10^9$/L. This spurious hypoxemia seems grossly proportional to WBC count and may lead to significant misinterpretation of the subject's oxygenation status. The clinical practice guidelines for immediate cooling and analysis of ABG for very high WBC count are reinforced but may not be sufficient to prevent spurious hypoxemia.

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