Explanation for Apparent Hypoxemia Associated With Extreme Leukocytosis: Leukocytic Oxygen Consumption

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We investigated the hypoxemia associated with extreme leukocytosis in leukemic patients. In vitro experiments showed that the rate of decrease in the partial pressure of oxygen in the blood samples from such patients was proportional to the white cell count. In the presence of normal white cell count no drop in \( P_o \) was observed. We conclude that a low arterial oxygen tension in the presence of extreme leukocytosis reflects oxygen consumption by leukocytes rather than true hypoxemia. Both normal as well as leukemic leukocytes appear to exhibit this phenomenon.

Severe hypoxemia is encountered frequently in patients with leukemia and high leukocytic counts. Since many of these patients are acutely ill with sepsis and pneumonia, and since thrombocytopenia precludes frequent arterial punctures, hypoxemia is commonly attributed to pulmonary pathology. Therefore, no accurate data are available to predict the frequency and severity of hypoxemia in leukemic patients.

We have observed several patients with leukemia and extreme leukocytosis (<100 x 10^9/liter) who exhibited severe hypoxemia despite immediate cooling of samples in the absence of any obvious pulmonary pathology. Upon reduction of the leukocyte count to <50 x 10^9/liter, the arterial oxygen tension (P_{O_2}) promptly returned to normal. Since these patients did not exhibit any significant respiratory distress or acid-base disturbance and seemed to tolerate the hypoxemia without discomfort, we proceeded to explore the nature of this "hypoxemia." After the completion of these studies, a recent report has also appeared on this subject, confirming our earlier observations.

Materials and Methods

Patients with acute and chronic leukemia having leukocyte counts in excess of 100 x 10^9/liter were chosen for the initial study. Informed consent was obtained and, whenever the platelet count was in an acceptable range (>50 x 10^9/liter), arterial blood samples were drawn for arterial blood gas measurements and in vitro studies. If thrombocytopenia was severe (<50 x 10^9/liter), only venous blood samples were obtained. Three milliliters of blood was equilibrated with a gas mixture consisting of 12% O_2, 5% CO_2, with the balance being nitrogen. An oxygen electrode was immersed in the blood sample to measure in situ P_{O_2} on a continuous basis in an air-tight system. The flask was agitated in a 37° Celsius water bath (Fig. 1). A blood sample from a healthy volunteer was also treated in an identical manner.

After the P_{O_2} reading had stabilized for 1 min, flow of the gas mixture was stopped, and the P_{O_2} value was recorded at 37°C every 30 sec for a period of 10 min. Whenever possible, blood from the patient after cytoreductive therapy was studied in the same manner. Granulocyte-rich fractions were also studied along with the whole blood sample from the same donors in order to measure the oxygen consumption of normal granulocytes in the same system.

Results

The initial P_{O_2} in 5 healthy volunteers was 85 ± 3.5 mm Hg (mean ± SD) and did not change appreciably during serial measurements over 10 min, as shown in Fig. 2. However, each sample with a leukocyte count greater than 100 x 10^9/liter, whether lymphocytic or granulocytic, showed a rapid and progressive drop in P_{O_2} in proportion to the degree of leukocytosis. This change was evident within 30 sec after discontinuing the flow of gas mixture. It was of interest that the presence of immature cells seemed to accelerate this phenomenon.

When blood samples were studied from patients during the course of their therapy, declining white count seemed to ameliorate this effect. The results on two such patients' blood are shown in Fig. 3. After the white count has been reduced from 452 x 10^9/liter to 59 x 10^9/liter in one patient, only a minimal drop in P_{O_2} was evident. The blood sample from another patient whose posttherapy white count was 3 x 10^9/liter did not exhibit any abnormality in P_{O_2}. Similarly, reduction of white cells with filtration of such blood samples through a mixture of microcrystalline cellulose and alpha cellulose eliminates this phenomenon (Fig. 4).

In order to test the characteristics of normal granulocytes in this experimental setting, blood samples from healthy granulocyte donors were studied. Data on two such studies are shown in Fig. 5. As is evident, granulocyte-rich fractions showed a rapid drop in the P_{O_2} in proportion to the leukocyte count, whereas no such drop was evident in corresponding whole blood samples from these volunteers with normal white cell counts.
count. The hemoglobin concentration and the platelet counts in these two samples, however, were not comparable and could be responsible for some of the differences.

DISCUSSION

Our results indicate that the blood samples from patients with extreme leukocytosis, when studied in vitro, show a swift and progressive decline in $P_O_2$ as a consequence of rapid oxygen consumption by the leukocytes in these samples. This decline in $P_O_2$ is apparent within seconds of stoppage of oxygenation, and the degree of decline is proportional to the number and immaturity of leukocytes. This phenomenon is exhibited by normal as well as abnormal leukocytes. Reduction in the leukocyte count with therapy or with artificial means diminishes this $P_O_2$ decline on such a sample proportionally. Almost complete removal of the leukocytes eliminates this phenomenon entirely, suggesting that leukocytes are indeed the elements responsible for the observed drop in partial pressure of oxygen in blood samples with high leukocyte counts.

Leukocytes of lymphocytic or granulocytic lineage are known to possess active metabolic processes and their oxygen consumption rates are almost identical. Our experiments document the extremely rapid nature of the leukocytic oxygen consumption in blood samples from patients with extreme leukocytosis. It is therefore not surprising to see the rapid in vitro "oxygen steal" in our experiments. Since it takes several minutes for actual blood gas analysis, some leukocytic oxygen consumption probably continues despite immediate placing of samples in ice. As the temperature of a blood sample at 37°C is gradually approaching that of ice-water, the process of leukocytic oxygen consumption is slowed, but rapid $O_2$ consumption probably resumes as the sample is rewarmed to 37°C in the gas analyzer during the process of actual $P_A_2$ measurements. This is probably responsible for the low $P_A_2$,
readings observed by us and by Hess et al. during the blood gas analysis of samples with extremely high white cell counts. However, these authors failed to recognize the rapid nature of this phenomenon and erroneously attributed this initial "hypoxemia" in their patients to the underlying conditions. We believe the starting \( \text{Pa}_2 \) readings in their leukemic samples were probably in the normal range and immediate cooling of these samples was effective in preventing only the subsequent oxygen consumption by the leukocytes.

Because of this fictitious hypoxemia in a clinical setting of extreme leukemic leukocytosis, \( \text{Pa}_2 \) readings on such blood samples are unreliable. We believe the \( \text{O}_2 \) consumption by the white cells in these samples occurs with such rapidity that conventional cooling of arterial blood samples in ice-water may not be sufficient to arrest this phenomenon entirely. The diagnosis of hypoxemia in such patients without obvious respiratory symptoms and pulmonary pathology needs caution. Failure to recognize this process in patients with extreme leukocytosis could lead to the erroneous diagnosis of severe hypoxemia, which might appear reversible with cytoreductive therapy. An isolated report of "alveolar capillary block syndrome" in the presence of extreme leukemic leukocytosis did not take into account the in vitro \( \text{O}_2 \) consumption by the leukocytes. A major component of the apparent hypoxemia therefore could have been spurious.

REFERENCES

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