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ORIGINAL ARTICLES

THE UNRELIABILITY OF CYANOSIS IN THE RECOGNITION OF ARTERIAL ANOXEMIA

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In 1919 Stadie\(^7\) first correlated arterial oxygen saturations with clinical impressions of cyanosis in patients with pneumonia. His data show that lower arterial oxygen saturations were usually associated with more intense cyanosis but that the arterial saturations corresponding to impressions of slight, moderate, marked and intense cyanosis varied widely in different patients. In 12 patients with "moderate cyanosis," the arterial oxygen saturations ranged from 65 to 91% while in 12 instances of "marked cyanosis," the saturations varied from 56 to 86%. A few years later, Lundsgaard and Van Slyke,\(^5\) in their monograph, "Cyanosis," summarized the factors which contribute to the presence of cyanosis and concluded that approximately 5 gm. of reduced hemoglobin must be present in 100 cc. of capillary blood to produce visible cyanosis in an individual otherwise normal; this could correspond to an arterial oxygen saturation of 80% and a venous saturation of 55% (assuming a peripheral A-V oxygen difference of 5 vols. per 100 cc.). An arterial oxygen saturation of 80% is equivalent to that produced by inhalation of 10 to 12% oxygen instead of the normal 21% present in room air.

Despite these 2 careful studies which indicated that serious arterial anoxemia may exist before even moderate cyanosis is visible, most physicians have continued to regard cyanosis as the most characteristic sign of anoxemia and the most reliable guide for intelligent oxygen therapy.\(^2\) It has been our impression for some years that excellent diagnosticians differ widely in their ability to recognize visually the presence of arterial anoxemia. The development of the oximeter by Millikan\(^6\) provided us with a new method with which we could repeat and extend earlier studies\(^7\) using large numbers of observers and subjects. It became evident early in these studies (a) that the detection of cyanosis depends not only upon variables in the patient,\(^1,5\) but also upon variables in observers and (b) that cyanosis is a poor guide for the detection of arterial anoxemia of slight to moderate degrees.

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Method. These experiments were designed to measure the highest arterial oxygen saturation at which observers could detect cyanosis. The arterial oxygen saturation of normal subjects was varied by the inhalation of low oxygen mixtures while observers attempted to estimate the existence and degree of cyanosis present. The arterial oxygen saturation was measured continuously by an oximeter. This instrument is essentially a miniature photo-electric colorimeter which may be placed on the ear; it measures arterial oxygen saturation with an average accuracy of 3% (as compared with values obtained by direct determinations on arterial blood). A total of 20 subjects (normal white males between the ages of 19 and 25, all accustomed to laboratory procedures) and 127 observers (105 medical students and 22 physicians) participated in the study.

A typical experiment was conducted as follows: An oximeter was attached to the subject's left ear. His nose was occluded by a clip. He then breathed through a mouthpiece, an inspiratory demand valve, and an expiratory flutter valve. Arrangements were made so that he might inhale room air, 100% oxygen, or 12, 10, or 8% oxygen (the remainder of the gas mixture in the latter 3 instances being nitrogen) in random sequence; precautions were taken that no one except the recorder knew the gas mixture being inhaled or the oximeter readings until the experiment was concluded. Five 6000 liter high pressure tanks containing the gas mixtures were connected to a 5 outlet manifold; the oximeter recorder, the gas tanks and all manipulations of these were obscured from the observers and subject by a screen. The subject was given room air to breathe, and the observers were informed that the subject's color at that moment represented his "normal" color.

From this time on the observers, in groups of 4 to 10, were instructed to note the color of the subject's face, right ear, hands, fingers or nail-beds every ½ minute and independently record it as "normal," "slightly or questionably cyanotic" or "definitely cyanotic." Since each experiment lasted approximately 30 minutes, each observer made about 60 color estimations. During this time the subject was given high and some of the low oxygen atmospheres to breathe for variable periods of time. Each subject was made anoxic at least twice in each experiment. Each low oxygen mixture was breathed for a minimum of 2 minutes after the oximeter had reached its lowest level.

The conditions under which the experiments were conducted were unusually favorable for early detection of cyanosis by the observer for several reasons: (a) the experimental room was lighted by daylight or by artificial tungsten filament lamps; (b) the subject's normal color was observed as a control with which ensuing color changes could be compared; (c) the observers were informed that periods of low and high arterial oxygen saturation in the subject could be expected during the ensuing 30 minute period; and (d) all subjects were white males.

The studies were conducted in a warm room, free from draughts, to minimize the occurrence of peripheral vasoconstriction and local cyanosis due to cold. Total hemoglobin was determined upon venous blood in 16 of 20 subjects; hemoglobin varied from 13.5 to 16.5 gm. per 100 cc.

Results. In Table 1 are recorded the levels of arterial oxygen saturation corresponding to estimations of "normal color," "slight or questionable cyanosis" and "definite cyanosis." This shows that the visual impressions of cyanosis are not necessarily accurate indications of anoxemia. Of the 3673 observations made when the subjects were breathing room air or oxygen and had oximeter readings of 96 to 100%, 26% stated that slight cyanosis existed. Furthermore only 49% of the students and 53% of the staff observations indicated "definite cyanosis" at the times when the oximeter registered 81 to 85% saturation (the level found by Stadie in severe lobar pneumonia). Even at 71 to 75% saturation, 25% of the student and 15% of the staff observations recorded only "slight cyanosis."

The highest level of arterial oxygen

* When the medical students acted as observers, a trial experiment was conducted first: The subject breathed 8 or 10% oxygen and the observers watched the development of cyanosis while the recorder called out the oximeter readings. When all observers recognized definite cyanosis, the subject breathed 100% oxygen and the observers were thus permitted to observe the abrupt color change from blue to pink.
saturation at which each observer noted definite cyanosis is recorded in Table 2. Because of the marked inconsistencies that occurred in the records of many observers, data from consistent “series” only are included in this table.* The median in both the student and staff groups noted definite cyanosis at 85 to 81% saturation. For example, 1 physician first noted definite cyanosis at levels of 84, 77, 94 and 82% in 4 consecutive trials upon the same subject within a period of 40 minutes. There were 35 cases in which observers noted definite cyanosis (in consistent series) 2 to 5 times in the same subject. In 11 instances (31%) the highest and lowest levels at which the observer first noted cyanosis varied by 5% saturation or less, and in 13 of the other 24 instances the variation was 10% saturation or more. The highest and lowest levels at which definite cyanosis was first noted could not be determined accurately in all of the experiments. However, 20 observers (see Table 2) did not detect definite cyanosis until the oximeter readings fell below 75% saturation. On the other hand, 11 observers noted (in “consistent series”) definite cyanosis at saturations above 90%. The validity of the observations at the higher levels may be questioned since none of the sudden “switchbacks” to 100% O2 occurred when the saturations were above 90%; hence these observations were not so rigidly controlled as those in the 70 to 90% range, in which the ability to

<p>| Table 1.—Percentages of Total Observations at Various Arterial Oxygen Saturation Levels Noted as Normal Color, Slight Cyanosis or Definite Cyanosis |
| No. observations at each arterial O2 level | Normal color | Slight cyanosis | Definite cyanosis |</p>
<table>
<thead>
<tr>
<th>(arterial O2 level)</th>
<th>Students (%)</th>
<th>Staff (%</th>
<th>Total (%)</th>
<th>Students (%)</th>
<th>Staff (%)</th>
<th>Total (%)</th>
<th>Students (%)</th>
<th>Staff (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oximeter reading</td>
<td>100-96</td>
<td>2865</td>
<td>808</td>
<td>3673</td>
<td>67</td>
<td>70</td>
<td>68</td>
<td>27</td>
<td>22</td>
</tr>
<tr>
<td>(arterial O2 reading)</td>
<td>95-91</td>
<td>711</td>
<td>203</td>
<td>914</td>
<td>42</td>
<td>48</td>
<td>43</td>
<td>42</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>90-86</td>
<td>712</td>
<td>162</td>
<td>874</td>
<td>33</td>
<td>25</td>
<td>32</td>
<td>36</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>85-81</td>
<td>799</td>
<td>244</td>
<td>1043</td>
<td>15</td>
<td>10</td>
<td>14</td>
<td>36</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>80-76</td>
<td>418</td>
<td>76</td>
<td>494</td>
<td>10</td>
<td>4</td>
<td>10</td>
<td>43</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>75-71</td>
<td>139</td>
<td>47</td>
<td>186</td>
<td>4</td>
<td>0</td>
<td>4</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>5644</td>
<td>1560</td>
<td>7204</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

It must be remembered that the data in Table 2 represent the highest saturations at which observers detected definite cyanosis. An observer often noted cyanosis at a high level in 1 series of observations and 10 to 20 minutes later was unable to detect cyanosis in the same subject until a much lower oximeter reading was reached.

* A “series” is defined as the observations during a consecutive sequence of high oxygen, low oxygen and high oxygen inhalation. “Consistency” of an observer for a series was judged by the following criteria: (a) the observer must have noted “normal color” throughout the period that the subject was breathing room air or 100% O2; (b) if the observer recorded slight or definite cyanosis at some time after the subject inhaled a low oxygen mixture and the oximeter reading started to fall, he must have consistently recorded cyanosis until the subject breathed a mixture richer in oxygen and the oximeter readings rose; and (c) the observer must have noted later in the same experiment an abrupt change from “cyanosis” to “normal color” within 1 minute after the subject suddenly breathed 100% O2 (following 12, 10, or 8% oxygen) and the oximeter readings rose to 95% or more.
note a sudden change from cyanosis to normal color aided in determining the "consistency" of each series.

There were also marked variations in the ability of different observers to detect cyanosis in any one subject. One observer noted definite cyanosis at a level of 94% saturation while a second physician, observing the same subject simultaneously, could not detect definite cyanosis until the oximeter fell to 71%, a difference of 23%. Differences of this type were noted in observations made upon each of the 20 subjects; these ranged from 3 to 23% (median 12%).

Though all the subjects were white males, cyanosis was not detected at the same level in all. It is impossible to state the average level at which cyanosis was observed in the different subjects, since some observers did not detect cyanosis at the lowest level of oxygen saturation reached in each series. It was evident though that the majority of observers could detect cyanosis at a level of 85% saturation or more in some subjects, but not until a level of 75% saturation or less in others. More quantitative information is available from an analysis of the number of "consistent series" noted in each subject. Upon 1 subject, no consistent observations were made by 7 observers (2 series each); in another, 11 "consistent series" were recorded by 7 observers out of a total of 14 series. In 4 subjects, 25% or less of the series were consistent; in 3, more than 50% of the series were "consistent." Our data indicate that few physicians make consistent observations on every trial. Of those observers who participated in only 2 series, 23% were consistent in both, of those in 3 series, 20% were consistent in all 3, in 4, only 13% were consistent throughout, while of those who had 5 trials, no observer was consistent in all.

The value of the notation "slightly cyanotic" is questionable for the following reason: 55% of 255 series of observations by medical students and 53% of 89 series by physicians were "inconsistent." The most frequent inconsistency was in cri-

terion "a" (see page 3); when the subjects were breathing room air or 100% O2, observers noted slight (usually) or definite cyanosis in 44% of the series.

Repeated practice by 1 individual in observing cyanosis over a period of 1 month did not enable her to detect definite cyanosis at higher levels of oxygen saturation or to become more consistent in her observations. Furthermore, those observers who participated in many trials were not significantly more consistent than those who participated in only 2, and the physicians as a group were no more consistent or able observers than were the inexperienced students.

There was no correlation in these experiments between the subject's total hemoglobin and the ability of observers to detect cyanosis early or consistently. However, no anemic or polycythemic subjects were included in this study (all the hemoglobins were above 13.5 and below 16.5 gm. per 100 cc.).

Discussion. Lundsgaard and Van Slyke defined cyanosis as the blueness of the skin, mucous membranes or organs caused by changes in capillary blood (usually the presence of unusual amounts of reduced hemoglobin). In their opinion the most important factors which modify the perception of cyanosis are; (a) the thickness, color and opacity of the skin or membrane overlying the capillaries, (b) the number and length of blood filled capillaries in a given surface area, and the state of dilatation or constriction of the arterioles, capillaries or venules under observation, (c) variations in plasma color caused by dyes or drugs, and (d) variations in the type, color and amount of hemoglobin (presence of methemoglobin, sulfhemoglobin or carboxyhemoglobin).

The factors mentioned by Lundsgaard and Van Slyke are concerned with variables in the patient. We believe that an equally important variable is the wide range in the abilities of observers to detect cyanosis in any one patient. On the basis of our experiments, we can infer that very few physicians are capable of detecting slight degrees of arterial anox-
emias by the perception of surface blueness. It is probable that an extremely small percentage of physicians could be expected to diagnose early cyanosis in every case. In the majority of cases, arterial anoxemia is probably unrecognized until the saturation of hemoglobin with oxygen has fallen below 85%; in some it is unrecognized even at the 70 to 75% level.

It may be argued by those physicians who consider themselves highly skilled in the detection of cyanosis that most of our observers were relatively inexperienced medical students. It should be emphasized that the students had a preliminary trial in order to acquaint them with the color to be expected at each level of oxygen saturation in the particular subject under observation. Actually the students were only slightly less consistent in their estimations than was the physician group, which included physician anesthesiologists, and cardiologists who had wide experience in the detection of cyanosis. Furthermore the median observers noted definite cyanosis at the same level in both groups. In addition, conditions were particularly favorable for the recognition and recording of cyanosis at high levels of arterial oxygen saturation: the presence of good lighting, the opportunity to observe normal control color in each subject, the use of all young white male subjects, the awareness that a color change was imminent, and the use of a continuous method of measuring oxygen saturation, so that better correlation was obtained.

Another possible criticism of these experiments is that oximeter readings were employed instead of actual figures obtained by direct analysis of arterial blood. The oximeter has an average error of 3%; in the saturation range 75 to 100%, the limit of error is 5% and in the range 50 to 75% it is 8%. However, this error is not a systematically high or low one and should cancel out in a large series of observations. The oximeter has the advantage of continuous recording so that the saturation of arterial blood can be known at the instant that cyanosis is recorded; this favors the recording of cyanosis at higher levels of arterial saturation.

It should be emphasized that not only is cyanosis frequently an unreliable guide to slight to moderate arterial anoxemia, but also other commonly used signs, such as rapid pulse and hyperpnea are not trustworthy. Dripps and Comroe studied the effects of breathing low oxygen mixtures for 8 minutes upon the circulation and respiration of normal subjects. They found that the inhalation of 18% O₂ led to an average increase in pulse rate of only 4%, 16% O₂ to 8% increase, 14% O₂ to 6% increase, 12% O₂ to 16% increase and 10% O₂ to 30% increase. These low oxygen mixtures corresponded to average arterial oxygen saturations of 94, 91, 89, 81 and 73% respectively. In the same experiments respiration was not increased measurable by arterial anoxemia until 10% O₂ was inhaled. At this point, respiratory minute volume increased only 16% (average arterial saturation 73%). Although data obtained from such brief exposures to low oxygen concentrations do not necessarily apply to clinical anoxemia, they suggest that slight anoxemia produces effects upon circulation and respiration which could escape even careful clinical observations. In some individuals the respiratory and circulatory responses are absent or poor even with moderate degrees of anoxemia.

Although other signs (mental confusion, delirium) have been suggested as indications for oxygen therapy, they do not represent early changes. In our experience, the extent of arterial anoxemia can be determined accurately in patients only by direct analyses of arterial blood.*

* The oximeter at present cannot be employed to indicate the level of arterial oxygen saturation in cyanotic individuals since the instrument must be "set" for each individual at a known value. In an individual known to be normal, the oximeter is "set" at 95 to 99% if the individual is breathing room air or at 100% if breathing oxygen. In a cyanotic patient, an arterial puncture can be performed, a determination of oxygen saturation can be done quickly by the method of the Van Slyke and Neill,* and the oximeter can then be "set" to this figure. An evaluation of therapy can then be made easily by noting oximeter changes in response to the employment of oxygen by oropharyngeal catheter, tent, mask or by pressure breathing.
Furthermore, our data indicate that this is the only way in which slight to moderate degree of anoxemia can be detected.

In present practice of medicine, every effort is being made to place therapy upon a scientific basis. It is often essential to know blood sulfonamide, penicillin and salicylate levels in order properly to evaluate therapy. Yet in the evaluation of arterial anoxemia, the clinician still uses a relatively insensitive and unreliable guide, namely cyanosis. The methods for determining arterial oxygen concentration are well established. Arterial puncture is neither dangerous nor painful if done carefully. It is suggested that oxygen therapy be put upon a more quantitative basis by measuring arterial saturation in patients suspected of being anoxicemic and by employing doses or concentrations of oxygen sufficient to increase arterial saturation to normal levels. More frequent measurements of arterial oxygen saturation by direct means (in patients suspected of being anoxicemic) should result in the elimination of much unnecessary oxygen therapy. It will also result frequently in the correction of concentrations of oxygen being given to those in need of oxygen.

Oxygen therapy is of value in many cases of anoxemia. The patient who is chronically anoxicemic usually develops certain compensatory changes which permit a relatively normal existence at rest without the need for oxygen administration. However, the recovery of an acutely anoxicemic patient (who often has fever and accelerated metabolism) can be hastened by maintaining normal amounts of oxygen in the blood. It is doubtful if oxygen therapy per se cures disease processes. However, it is of great value as supportive therapy in anoxemia and there it should be used more quantitatively. When oxygen is given in high concentrations in the treatment of conditions unassociated with anoxemia (e.g., in coronary occlusion, etc.), determinations of arterial oxygen saturation are unnecessary since the arterial blood is almost completely saturated before oxygen inhalation is begun.

Summary and Conclusions. 1. The ability of observers to detect cyanosis was evaluated by comparing their color estimations with known arterial oxygen saturations (oximeter).

2. The majority of 127 observers were unable to detect the presence of definite cyanosis until the arterial oxygen saturation fell to approximately 80%; 25% of observers did not note definite cyanosis even at arterial saturation levels of 71 to 75%.

3. There were marked variations in the ability of an observer to note cyanosis in different subjects or even in the same subject at different times. There were wide variations in color estimations when 5 to 10 observers watched cyanosis develop in the same subject at the same time.

4. The detection of cyanosis is dependent not only upon variable factors in the patient but also upon the ability of individual observers to note color changes.

5. Visual impressions of cyanosis are unreliable. Serious grades of arterial anoxemia may be unrecognized by many physicians unless arterial blood is obtained and analyzed for oxygen content and capacity.

REFERENCES

5. Lundsgaard, C., and Van Slyke, D. D.: Medicine, 2, 1, 1923.