JCI The Journal of Clinical Investigation

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Minerva Morse, … , Florence Numajiri, Edna O'Connell

J Clin Invest. 1950;29(8):1098-1103. https://doi.org/10.1172/JCI102342.

Research Article

THE POSITION OF THE OXYGEN DISSOCIATION CURVE OF THE BLOOD IN CYANOTIC CONGENITAL HEART DISEASE[1]

By MINERVA MORSE, DONALD E. CASSELS, AND MELBA HOLDER WITH THE TECHNICAL ASSISTANCE OF FLORENCE NUMAJIRI AND EDNA O'CONNELL

(From the Department of Pediatrics, University of Chicago Clinics, Chicago)

(Submitted for publication April 14, 1950; accepted, May 22, 1950)

The similarity of the blood picture in patients with cyanotic congenital heart disease and in residents at high altitudes suggested the investigation of the position of the oxygen dissociation curve as a possible compensatory mechanism for reducing tissue hypoxia.

In studies by the International High Altitude Expedition to Chile in 1935, Keys, Hall and Barron (1) found a small and questionably significant displacement of the curve to the right in the blood of residents at 5.34 km., in contrast to a displacement to the left as reported by Barcroft and his collaborators (2) from observations at 4.33 km. in 1922. With one exception, other expeditions to higher altitudes have found no changes in the position of the dissociation curve with decreasing barometric pressures (3, 4). However, a displacement of the curve to the right was given added confirmation by the finding by Aste-Salazar and Hurtado (5) that ten of the 12 native residents at altitudes of 4.5 km. had pO_2 values at 50 per cent saturation which were higher than the corresponding mean level for a group of residents at sea level.[2] Such a displacement, even though slight, would have advantage in that it would increase the capacity for oxygen transport by decreasing the venous saturation level for a given pO_2 level.

The present report describes the results of a study of the positions of the dissociation curve of the blood in 29 patients with cyanotic congenital heart disease[3] as compared with those of 43 normal individuals.

METHODS

The *in vitro* tonometer method was employed, essentially as described by Dill in the high altitude report of Keys, Hall and Barron (1). Details are given in the preceding report (6) in which the oxygen dissociation curves of normal children and adults are compared.

The oxygen and carbon dioxide contents of the arterial blood samples, which were obtained when possible, were determined by the manometric method of Van Slyke and Neill (7). The oxygen and carbon dioxide contents were also determined after equilibration in tonometers containing carbon dioxide and oxygen at approximate tensions of 40 mm. and 185 mm. Hg, respectively. From these data and the gas contents of the tonometers, determined by Haldane analysis, the percentage oxygen saturation, carbon dioxide combining power (T_{co}) of the blood and plasma, and the pH_s were calculated by methods described by Dill and his coworkers (8).

RESULTS

Because the blood of children tends to have a higher oxygen tension than the blood of adults at a given percentage saturation and since the great majority of the patients with cyanotic congenital heart disease who were studied were children, the four adults were omitted in calculating the averages which were used to prepare the curves of Figure 1 and the data of Table I. For purposes of analysis the patients with cyanotic congenital heart disease were divided into three groups, the separation depending first upon the presence or absence of a pulmonary stenosis, and, in the presence of a stenosis, upon whether or not pulmonary blood flow had been increased by the creation of an artificial ductus.

The differences between the groups, which are apparent in Figures 1 and 2, were checked for statistical significance (Table I). The slight difference of approximately 1 mm. Hg between the average curve for the group with cyanotic congenital heart disease but without pulmonary stenosis and the normal curve is significant at the 5 per cent level or lower for all points along the curve except at 80 per cent saturation. At this point the range of variation was higher for normal children than at lower points on the curve.

The oxygen dissociation curve of the blood of children with pulmonary stenosis is displaced to

[1] This work was conducted under a grant from the Douglas Smith Foundation at the University of Chicago.

[2] It is probable that the discrepancies in the reports prior to 1935 were due to faulty techniques.

[3] We are indebted to Dr. Stanley Gibson of The Children's Memorial Hospital in Chicago who made several cases available for study.

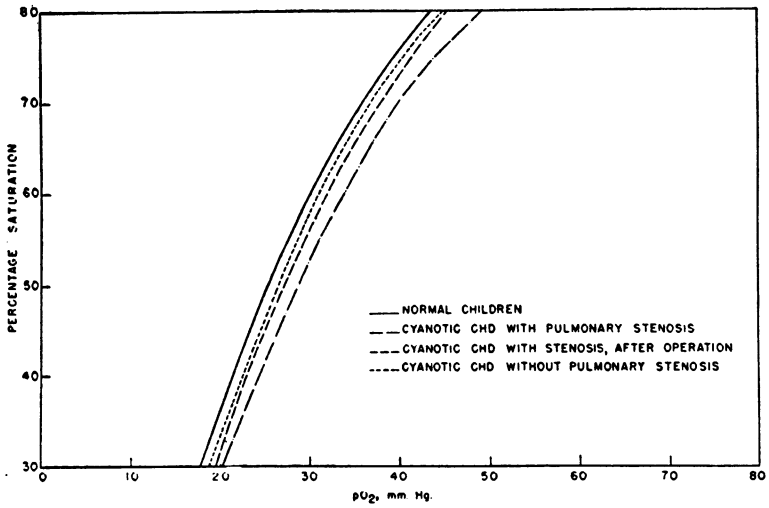

FIG. 1. A COMPARISON OF THE OXYGEN DISSOCIATION CURVE OF THE BLOOD OF NORMAL CHILDREN WITH THOSE OF CHILDREN WITH CYANOTIC CONGENITAL HEART DISEASE

Each curve represents the mean of the group.

the right of the normal by an amount which increases from an average of 2.6 mm. Hg at 30 per cent saturation to 4.4 mm. at 80 per cent saturation. These differences are significantly greater (Table I) than those at corresponding levels in the group with cyanosis but without stenosis. They also appear to decrease in value after pulmonary blood flow is increased artificially by operation, for differences in pO_2 between the groups before and after the operation, increasing from 0.8 mm. Hg at 30 per cent saturation to 2.8 mm. at 80 per cent saturation, are probably significant. Only four individuals were studied both before and after the operation. Their results suggest that the shift toward the normal is a slow process. Two cases who were studied eight days and one

TABLE I

Mean differences between the pO_2 of the groups specified, at various points on the oxygen dissociation curves; measures of the significance of these differences in terms of the probability that the differences are due to chance sampling

Saturation		Groups compared		
		Cyanotic C.H.D. without stenosis *vs.* normal children	Cyanotic C.H.D. with stenosis *vs.* without stenosis	Cyanotic C.H.D. with stenosis before *vs.* after Blalock operation
per cent		*mm. Hg*	*mm. Hg*	*mm. Hg*
30	Mean Δ pO_2±S.E.	+1.07±0.41	+1.49±0.49	+0.76±0.40
	P	0.02	<0.01	0.10
40	Mean Δ pO_2±S.E.	+1.38±0.36	+1.69±0.53	+1.50±0.54
	P	0.001	<0.01	0.02
50	Mean Δ pO_2±S.E.	+1.31±0.42	+2.15±0.56	+1.52±0.36
	P	<0.01	<0.01	0.001
60	Mean Δ pO_2±S.E.	+1.06±0.48	+2.90±0.68	+1.79±0.45
	P	0.05	<0.001	<0.01
70	Mean Δ pO_2±S.E.	+1.24±0.52	+3.05±0.79	+1.76±0.71
	P	0.05	<0.01	<0.05
80	Mean Δ pO_2±S.E.	+1.11±0.79	+3.33±0.93	+2.80±0.53
	P	0.2	<0.01	<0.001

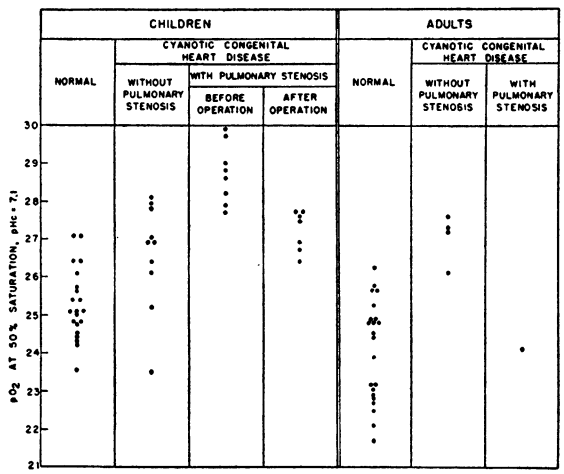

FIG. 2. FREQUENCY DISTRIBUTIONS OF OXYGEN TENSION AT 50 PER CENT SATURATION, $pH_c = 7.1$, IN NORMAL BLOOD AND IN THE BLOOD OF PATIENTS WITH CYANOTIC CONGENITAL HEART DISEASE

and a half months post-operatively showed no change in pO_2 at 50 per cent saturation, whereas the other two showed a decrease in pO_2 of 3.3 and 1.4 mm. Hg at eight and ten months post-operatively.

In 20 of the patients studied it was possible to secure arterial blood samples. Only three of these patients had pulmonary stenosis. In Figure 3 arterial oxygen saturations, oxyhemoglobin capacities, CO_2 combining powers of the plasma, and arterial pH_s, derived by analysis of these samples, are plotted against the corresponding displacements of the oxygen dissociation curves, as measured by the deviations of pO_2 at 50 per cent saturation from the normal average. There is no evidence of relationship between any of these characteristics of the arterial blood and the relative displacement of the dissociation curve. Since the displacement

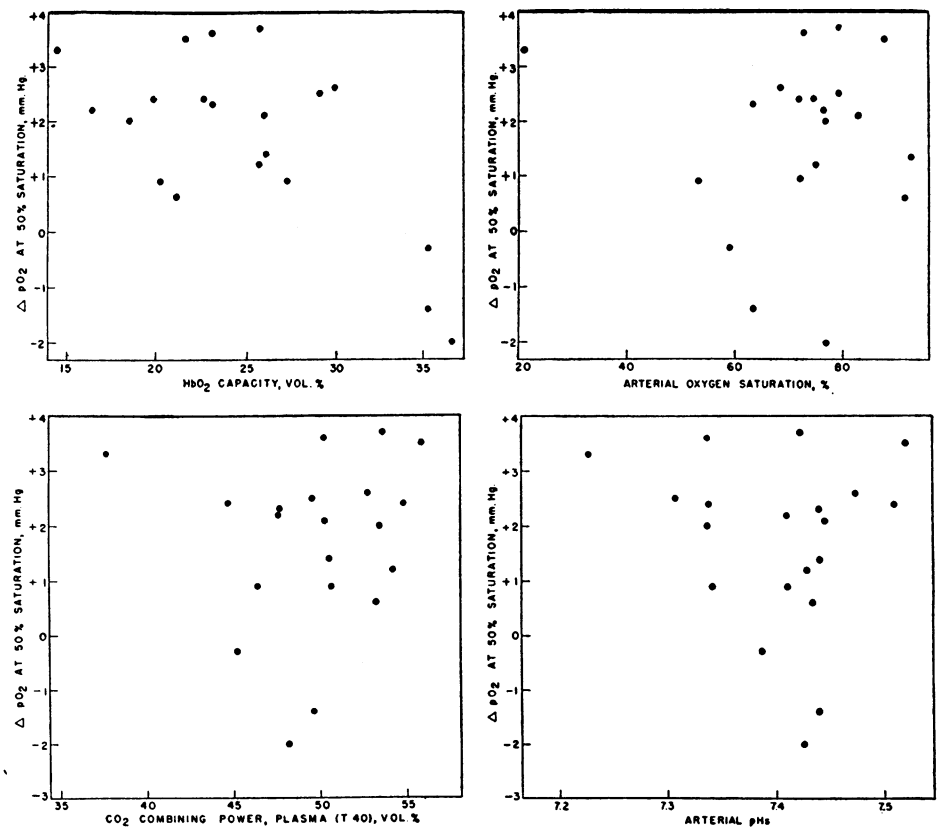

FIG. 3. SCATTERGRAMS SHOWING THE LACK OF RELATIONSHIP BETWEEN THE DISPLACEMENT OF THE DISSOCIATION CURVE AND FOUR CHARACTERISTICS OF THE BLOOD IN CYANOTIC CONGENITAL HEART DISEASE

of the dissociation curve of the blood may be looked upon as a compensatory mechanism to maintain the oxygen tension of the tissues at a more nearly normal level, it is surprising to see that the deviations from the normal curve in cyanotic congenital heart disease are apparently unrelated to the degree of arterial unsaturation. Similar displacements occur, whether the arterial saturation is as low as 21 per cent or as high as 88 per cent. It is of interest that the three individuals whose bloods do not show displacement of the dissociation curve to the right are those with marked polycythemia, with oxyhemoglobin capacities greater than 35 volumes per cent.

The displacement of the dissociation curve in cyanotic congenital heart disease does not appear to be related to the presence of other forms of hemoglobin such as methemoglobin. In a number of cases an attempt was made to evaluate quantitatively by spectrophotometric analysis the amount of methemoglobin present in the blood of these patients. In every case tested the amount of methemoglobin present was so small that it lay within the limits of error of the method.

DISCUSSION

The results of this study furnish evidence that the oxygen dissociation curve of the blood, as determined by the *in vitro* tonometer method, tends to be displaced to the right in individuals with cyanotic congenital heart disease. Such a displacement may be looked upon as a compensatory mechanism to reduce tissue hypoxia since, by promoting the dissociation of oxyhemoglobin as the blood passes through the capillaries, the mean capillary oxygen pressure for a given degree of arterial and venous unsaturation is increased and diffusion of oxygen through the capillary walls to the tissues is facilitated. While the increase in oxygen tension for a given percentage saturation is comparatively small, it is of the same order of magnitude as the average displacement measured in the blood of residents at high altitudes.

In addition to increasing the mean capillary oxygen pressure, the displacement of the oxygen dissociation curve to the right serves to increase the reserve capacity for oxygen transport by lowering the venous saturation for a given pO_2 level. This concept was suggested by Keys, Hall and Barron (1) as one of the adaptive processes at high altitudes. In the case of congenital heart disease the increase in oxygen transport capacity would be less for a given displacement of the curve than in residents at high altitudes because the lowering of the venous saturation level in response to stress would also lower the arterial oxygen level by admixture through the congenital defects.

The finding that the displacement of the curve tends to be greater if pulmonary stenosis is present and is decreased if pulmonary flow is increased as a result of operation suggests a relation between the displacement of the curve and relative pulmonary blood flow. It is quite possible that this relation is not direct but depends upon some other change, as, for example, the increase in either pulmonary arterial or systemic arterial oxygen saturation which occurs after the operation. The lack of correlation between the displacement of the curve and systemic arterial saturation is evidence against decreased arterial saturation as the sole stimulus for the decreased affinity of hemoglobin for oxygen. A more quantitative measure of the relation of the displacement of the curve to relative blood flow could be made if data from right heart catheterization were available. It would be instructive to know whether equivalent arterial unsaturations of pulmonary origin would have a comparable effect on the displacement of the curve.

It seems improbable that arterial unsaturation, low mean capillary pressure or tissue hypoxia can affect directly the affinity of hemoglobin for oxygen. It is more probable that the equilibrium is influenced by some change in the chemical environment of the hemoglobin in the red cell, for it is well known that the affinity of hemoglobin for oxygen is reduced by the presence of electrolytes. Decreased alkali reserve in the blood and plasma was observed by Dill, Talbott and Consolazio (9) as a result of residence at high altitudes. Similar observations in the case of cyanotic congenital heart disease were made by both Bing (10) and Talbott (11) and their collaborators. Their findings are supported by our data (Figure 3). Sidwell and his associates (12) found by spectroscopic methods that, of all the common anions of the blood, the bicarbonate ion was most effective in decreasing the affinity of hemoglobin

for oxygen. The decrease in CO_2 combining power which characterizes the blood or plasma of patients with cyanotic congenital heart disease or of residents at high altitudes is therefore a factor tending to cause a displacement of the curve to the left. It is possible that the displacement of the curve to the right was reduced, and in a few cases prevented (Figure 3), by the reduced CO_2 combining power of the blood.

The effect of the pH_c during equilibration was eliminated by applying a correction factor. The factor used represents the mean for the blood of members of the International High Altitude Expedition at sea level (1). Since all of the tonometers contained CO_2 at a tension of approximately 40 mm. Hg, the pH_c varied with the CO_2 combining power and the degree of oxygenation of each blood sample. Since the CO_2 combining power of the blood of members of the group with pulmonary stenosis tended to be lower than those of the other groups studied, the pH_c of equilibrated samples from that group was usually less, and the correction to a pH_c of 7.1 correspondingly higher. Technical errors would affect all groups alike, but an error due to variation of the individual pH factor from the mean value reported by Keys, Hall and Barron (1) would affect the values for the group with pulmonary stenosis to a greater extent because of the greater magnitude of the correction required for that group. Doubts arising from consideration of this factor might have been avoided if it had been technically practical to adjust the CO_2 tension of the gas phase of the tonometer to the CO_2 combining power of the blood for each individual.

Those patients with cyanotic congenital heart disease whose blood pH is lower than normal have the benefit of further displacement of the curve to the right through the Bohr effect. According to our data (Figure 3) only a few patients possess that advantage. Of the 20 cases with cyanotic congenital heart disease whose arterial pH_s was calculated, six had values below 7.35, while three had values above 7.45. The majority of pH_s values lay between 7.40 and 7.45.

The question of the possible existence of two different adult forms of hemoglobin with different affinities for oxygen has been discussed in the preceding report. Available evidence for two adult forms of hemoglobin is inconclusive. The most convincing evidence depends upon differences in the rate of denaturation of the hemoglobin with alkali at a given pH. It would be interesting to test this possibility for that form of hemoglobin which shows marked decrease in affinity for oxygen which is found in the blood of patients with cyanotic congenital heart disease with pulmonary stenosis.

Our finding that the position of the oxygen dissociation curve lies farther to the right in childhood than in later life may be interpreted as an adjustment of the organism to facilitate oxygen supply to the tissues at a time when growth is proceeding and metabolic activity, even at rest, is high. It is possible that the further displacement of the curve to the right in cyanotic congenital heart disease is an extension of the same process and occurs in response to oxygen need in the tissues. The linking of changes in the affinity of hemoglobin for oxygen with growth suggests that the environmental factors in the red cell which affect the hemoglobin-oxygen equilibrium may include hormones as well as electrolytes and pH.

SUMMARY

The oxygen dissociation curve of the blood in cyanotic congenital heart disease tends to be displaced to the right of its position in normal healthy individuals of approximately the same age, but the shape of the curve is not essentially different from the normal. The degree of displacement is small, within a few mm. Hg. It tends to be greater in cyanotic individuals with pulmonary stenosis than in those without stenosis and decreases after the effects of stenosis are ameliorated by increasing pulmonary blood flow through the creation of an anastomosis between pulmonary artery and aorta.

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