Myocardial Infarction in a 14-Year-Old Boy with Normal Coronary Arteriograms

Studies of Blood Oxygen Release Rates*

Irwin J. Schatz, M.D., F.C.C.P.;** Hiroshi Mizukami, Ph.D.; James Gallagher, M.D.; and Frank S. Greenslit, M.D.

A 14-year-old boy sustained a transmural myocardial infarction, with subsequent angina. Coronary angiograms were considered normal, and no risk factors were apparent. Studies immediately after an episode of angina revealed markedly slowed blood oxygen release rates as determined by measuring oxygen dissociation rate constants with a stopped-flow apparatus. These results were significantly different from those found on two separate occasions when the patient was asymptomatic, and from a group of apparently healthy control individuals.

The specific cause and effect relationship that exists between obstructive coronary artery disease and myocardial infarction is an accepted clinical-pathologic fact.1-3 Nevertheless, occasional reports appear of patients with varying degrees of myocardial necrosis who have apparently normal coronary arteries at arteriography or at necropsy.4,7 Infarction in these cases is usually subendocardial and patchy, and its etiology is obscure. We describe the case of a 14-year-old boy with an acute transmural myocardial infarction, subsequent angina, and normal coronary arteriograms. In searching for pathogenetic factors other than obstructive coronary artery disease due to atherosclerosis, serial investigations were performed, with a newly developed method, of the rate of release of oxygen by the blood. These studies were made when the patient was asymptomatic, and immediately after an episode of spontaneous angina.

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Convalescence was uneventful. On December 15, 1970, however, a grade 2/6 apical holosystolic murmur was first heard, unaccompanied by any diastolic murmurs. Physical examination and chest roentgenograms revealed no significant change in heart size, or evidence of pulmonary congestion. He was discharged on December 30, 1970, to be followed as an outpatient.

Second Admission

The patient was admitted as an emergency on January 29, 1971, to Harper Hospital, Detroit, because of severe lower subternal pain with some radiation to the neck; these symptoms had been present for several hours. The interim history was unremarkable; in particular, the patient denied using any amphetamines since his release from the hospital. Results of examination had not changed appreciably. The heart was not clinically enlarged and the characteristics of the grade 2/6 apical holosystolic murmur were the same.

Serial electrocardiograms and serum enzymes did not confirm any myocardial damage. The following laboratory tests were performed and the results were negative or normal: hemoglobin, hematocrit, leukocyte count with differential, erythrocyte sedimentation rate, tests for lupus erythematous cells, antinuclear factor, venereal disease research laboratory test, serum protein electrophoresis, serum cholesterol, serum triglycerides, lipoprotein electrophoresis, throat culture, and chest roentgenograms.

Catheterization of the right and left sides of the heart was performed. Pressures in all chambers and in the pulmonary vessels were normal. The left ventriculogram revealed poor contraction near the apex. Contrast media regurgitated into the left atrium, consistent with a mild degree of mitral regurgitation. Selective cine coronary arteriograms demonstrated normal origin, distribution, and caliber of the coronary arteries (Fig 2A, B C).

The patient was discharged on March 2, 1971 to be followed as an outpatient.

Third Admission

The patient was readmitted to Harper Hospital on April 27, 1971, because of a recurrence of subternal chest pain. He indicated that since his discharge he had been having infrequent episodes of subternal chest pain with radiation to the neck and jaw, and occasionally in his left arm, when he would try to walk rapidly, or sometimes with excitement. These symptoms would last two or three minutes and would be relieved promptly by rest.

The results of physical examination were unchanged from those of the previous admission. Relevant clinical and laboratory investigations again failed to confirm the presence of any recent myocardial necrosis. He was discharged on May 8, 1971.

SPECIAL INVESTIGATIONS

Red Cell Oxygen Kinetics

Determination of the oxygen dissociation rate constants was performed with a stopped-flow apparatus. This procedure is a modification of previously described methods and similar to what has been used by Salhany and co-workers. In spite of the fact that spectrophotometric measurement of a turbid solution requires a sensitive instrument to pick up a small intensity of light, when the change of absorbance is sufficiently large compared with the change of quality of light-scattering (induced by the structural change of the particle during reaction), compensation for the change of absorbance by light scattering is virtually unnecessary. This argument can be substantiated by observing the change of absorbance at the isosbestic point of oxy- and deoxy-rcb.

Human blood (4.5 ml) was collected by venipuncture in a
temperature (25°C±2°) for 30 minutes. One hundred milliliters of the buffered saline solution at pH 7.6 was flushed with nitrogen for 20 minutes and 0.1 G sodium dithionite as added under nitrogen pressure.

An Amino-Morrow stopped-flow apparatus with 4 mm light-path was mounted on a Beckman DU spectrophotometer. The wavelength was set at 610 nm unless indicated otherwise. The phototube was, however, replaced with an R 212 Hamamatsu photomultiplier and was connected to an Amino-Microphotometer. The signal from the photomultiplier was observed with a Tektronix 564 storage oscilloscope. Between the mixing cell of the stopped-flow apparatus and the photomultiplier, a silver-coated glass tubing of 3 mm ID was placed as a light-guide tube. Most of the scattered light from the back of the mixing cell was thus guided by the light guide tube to the photomultiplier.

The deoxygenation reaction was treated as pseudo-first-order kinetics:

\[
\frac{dk}{dt} = -k_d (\text{rbc-O}_2)
\]

Hence: \( \log Y = -2.3kt \)

where \( t \) is the time of reaction and \( Y \) is the fraction of oxygenated rbc. The dissociation constant, \( k_d \) can then be determined from the slope of the plot \( \log Y \) vs time. For each sample, three photographic traces on the oscilloscope were obtained.

The effects of light scattering were examined by measuring the absorbance change at absorption peaks \( \gamma (P) \) and troughs \( (T) \) of oxy- and deoxy- states, at isosbestic points \( (1) \), and at relatively longer wavelengths where the absorption is small. These wavelengths include: 640, 620, 590, 588, 586(1), 577(P), 569(1), 560(T), 555(1), and 542(P) nm. At each of these wavelengths, spectral bandwidths were adjusted to less than 2 nm. To demonstrate experimental reproducibility, three successive traces were recorded on the same photograph using a wavelength of 610 nm.

Oscilloscope traces for deoxygenation reactions at various wavelengths are shown in Figure 3 A, B, C, D. The ordinate represents the “relative percent transmittance” scale and the abscissa is measured in 100 msec for each large division. In all experiments, spectral bandwidths were less than 2 nm, but the electronic sensitivity was changed for each trace in order.

Table 1—Deoxygenation Kinetic Constants of RBC Determined at Various Wave Lengths

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10 ml vacutainer containing 0.5 ml of 0.1 M sodium oxalate with 0.2 mg/M sorbic acid. Buffered saline was prepared with two parts of 0.25 M Bis-tris at pH 7.4 and 8 parts of 0.85 percent NaCl, and was used to dilute the blood sample. After a series of experiments, a dilution of 15 X was found to be most appropriate. After diluting the fresh blood with the buffered saline, the sample was equilibrated to air at room temperature (25°C±2°) for 30 minutes. One hundred milliliters of the buffered saline solution at pH 7.6 was flushed with nitrogen for 20 minutes and 0.1 G sodium dithionite as added under nitrogen pressure.

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to demonstrate a sufficient change of absorbance. It can be seen that the directions of change of absorbance at both sides of the wavelengths of the isosbestic points are opposing. The absorbance changes at the wave lengths where changes are sufficiently large are again computed as previously for the purpose of obtaining the dissociation constants; the results are shown in Table 1. General agreement between the isosbestic points reported for hemoglobin and the wavelengths where no absorbance change is observed in this work, and the fact that all the wavelengths studied provide the same kinetic constants, suggest that suspensions of erythrocytes obey basic laws of spectrophotometry under these experimental conditions. Possible spectrophotometric error produced by change in the degree of light scattering during the reaction, therefore, is minimal compared to the large absorbance change during the deoxygenation reaction. Experimental reproducibility is demonstrated in Figure 4 in which three successive oscilloscope traces are superimposed.

For each sample at least three experiments were performed and the average dissociation constant, $k_d$ was calculated. The BORR is an empirical parameter intended to represent the overall efficiency of oxygen release from whole blood. It is obtained by multiplying the constant for the rate of oxygen release with the hematocrit.

This erythrocyte enzyme (2,3-diphosphoglycerate-2,3-DPG) was measured according to the method of Keitt.\textsuperscript{11}

Blood samples were collected from 14 apparently healthy individuals between ages 18 and 42. Immediately after collection, an aliquot of each sample was fixed in perchloric acid for determination of 2,3-DPG; kinetic experiments were performed within six hours.

**RESULTS**

**Red Cell Oxygen Kinetics**

Deoxygenation rate constants ($k_d$), blood oxygen delivery rates (BORR) and intracellular 2,3-DPG are summarized in Table 2. In controls, the average rate constant is $4.11 \pm 0.2$ SD (sec$^{-1}$); that of BORR is $196.5 \pm 20.0$ SD (Hct/sec), and that of 2,3-DPG is $4.45 \pm 0.56$ SD (mM/1L rbc).

On February 24, 1971, while the patient was asymptomatic, $k_d$ was 4.03, BORR was 176.2 and 2,3-DPG was 4.02. They were near the lower limits of the normal range. Hematocrit, however, was lower than normal. On May 4, 1971, during an episode of spontaneous angina, $k$ was decreased by 20 percent.

![Figure 4. Three successive oscilloscopic tracings are superimposed, demonstrating experimental reproducibility.](https://journal.publications.chestnet.org/pdffile/.../data/journals/chest/20939/)
Table 2

<table>
<thead>
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<th>Hematocrit (%)</th>
<th>kB* (sec^-1)</th>
<th>BORR** (mM/L RBC)</th>
</tr>
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<tr>
<td>Controls (N = 14)</td>
<td>47.7 ± 2.67</td>
<td>198.5 ± 20.5</td>
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<tr>
<td>Patient 2/23/71 (Asymptomatic)</td>
<td>43.7</td>
<td>4.03</td>
</tr>
<tr>
<td>5/4/71 (Immediately after angina)</td>
<td>47.7</td>
<td>3.22</td>
</tr>
<tr>
<td>9/14/71 (Asymptomatic)</td>
<td>49.0</td>
<td>4.58</td>
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*Deoxygenation rate (kinetic) constant.
**Blood oxygen release rate expressed as a product of the deoxygenation rate constant and hematocrit in percent.
1,2,3-diphosphoglycerate.

of the previous value. In spite of an increased hematocrit, BORR was further decreased. A 5.4 percent reduction of 2,3-DPG, however, was considered to be within the range of experimental error. On September 4, 1971, again when the patient was asymptomatic, k was above normal and the hematocrit was within the normal range. Consequently, BORR became normal in spite of 33 percent increase in 2,3-DPG.

DISCUSSION

General Considerations

Clinically detectable myocardial infarction almost always occurs in the presence of significant obstructive coronary arterial disease. Autopsy and coronary angiographic studies of the hearts of patients who have suffered myocardial infarction have revealed a minimum of 50 percent narrowing of at least one, and usually several major coronary arteries.1,2,3,13-14 Nevertheless, occasional reports of patients with unequivocal evidence of infarction and normal coronary arteriograms have appeared.4-6 In addition, necropsy studies of groups of children,7 and of women with infarction,8 both of which had normal coronary arteries, have been reported. It is possible that in some of these cases oxygen delivery to the myocardium was critically impaired because of the presence of serious systemic conditions such as anemia, pulmonary embolism, or connective tissue disorders. In addition, conceivably disease of the smaller coronary arteries was overlooked, or angiograms were misinterpreted, as James has suggested may occur.16 In spite of these possibilities, however, there are patients in whom such explanations seem unlikely, who provide indisputable evidence for myocardial infarction, and in whom coronary angiograms are normal. We believe that such has been the situation in our patient. Because of this, an attempt was made to detect other mechanisms which possibly might be implicated in the pathogenesis of his myocardial infarction. This search consisted of serial investigations into the status of the tissue oxygen delivery system.

A clinical factor which deserves attention in this case is consideration of the chronic oral use of amphetamines. Clearly, any conclusions with respect to their etiologic role here is conjectural, but from a careful review of the relevant medical literature, it would seem to be unimportant. To our knowledge, no cases of myocardial infarction subsequent to the use of amphetamines have been reported. In the studies of fatal17 and nonfatal18,19 amphetamine overdosage, no cardiac manifestations were said to have been observed. Zalis and co-workers20 gave lethal intravenous doses of amphetamines to unanesthetized dogs and found patchy myocardial necrosis, similar to the changes which occur with experimental hyperthermia. Wenzel21 citing Kawamura,22 states that metamphetamines administered daily for long periods to mice or rabbits resulted in myocardial degeneration. It is known that amphetamines may cause a transient rise in systemic blood pressure; however, since our patient showed no clinical signs of amphetamine effect on any of our examinations, it seems unlikely that the past use of these agents played any part in the genesis of his myocardial infarction, or subsequent chronic intermittent myocardial ischemia.

Red Cell Oxygen Kinetics

Mizukami and Eliot23 described changes in hemoglobin-oxygen dissociation curves in patients with angina who had normal coronary angiograms. Subsequently, Shappell and co-workers24 showed reduced affinity of hemoglobin for oxygen in a group of patients with angina induced by atrial pacing, with no associated changes in certain red blood cell enzymes. The significance25 of these observations is unclear, for it cannot be determined if such curve shifts are due to an altered rate of release of oxygen, an altered degree of binding of oxygen, or both. It is known, however, that numerous factors affect hemoglobin-oxygen equilibria,26 including levels of erythrocyte 2,3-DPG, adenosine triphosphate, and erythrocyte and blood pH. For example, increased levels of erythrocyte 2,3-DPG occur when individuals are exposed to environments with reduced PO2. Presumably, this is a compensatory physiologic adjustment by which the elevated 2,3-DPG levels cause an increased rate of oxygen release from the blood and a rightward shift of the hemoglobin-
oxygen dissociation curve. Furthermore, it has been suggested that blood gases do not come to complete equilibrium with the tissues during passage through capillaries. Using a monolayer method, our observations support this concept, for even when an erythrocyte is exposed to a completely oxygen free environment, at least 0.5 seconds is required to release 50 percent of the hemoglobin-bound oxygen.

Clearly, in those clinical situations in which arterial perfusion is limited because of occlusive disease, the length of time each erythrocyte remains in the capillary, and the rate of release of erythrocyte oxygen become critical factors. For these reasons, the status of blood tissue oxygen transport might be better assessed by measuring the actual rate of release of oxygen from blood than by constructing a hemoglobin oxygen dissociation curve. Accordingly, we modified previously described methods to use in this case.

At this point it is important to review the correlation between \( k_4 \) and 2,3-DPG. Under constant extracellular pH, Salhany and co-workers have shown that if the change of 2,3-DPG is large, a statistically significant correlation exists between these two parameters. However, our search for a linear correlation among the normal controls studied in this investigation revealed an associated probability of only 0.24, which is of no statistical significance. This lack of correlation between these two parameters under normal conditions may be explained in two ways: (1) experimental errors are too large to distinguish small changes observed in these parameters or, (2) factors other than 2,3-DPG play an important role in determining \( k_4 \) or both. Assuming experimental error of ±5 percent for \( k_4 \) and ±8 percent for 2,3-DPG, poor correlation between the two parameters excludes the first possibility. Results obtained from clinical samples seem to suggest that the second hypothesis is valid. On one occasion 20 percent loss of \( k_4 \) was accompanied by a decrease of only 5 percent of 2,3-DPG. However, when 2,3-DPG was increased (5.05), \( k_4 \) was also increased. Consequently, we assume that 2,3-DPG is only one of many intracellular determinants of \( k_4 \).

Data from this patient, as well as from a 37-year-old woman with angina and normal coronary angiograms reflect a significantly reduced rate of release of oxygen from blood, removed immediately after angina, compared to results from these same patients when they were asymptomatic and from 14 apparently healthy controls (Table 2). In an earlier report by Eliot and associates and in a recent review, measurements of deoxygenation kinetics of hemoglobin in solution, both from normal individuals and from four patients with ischemic heart disease are given, using a slightly different methodology. Similar differences between these two groups are observed. Furthermore, results from preliminary study of the effects of oral acetazolamide on a group of angina patients indicated increased rates of release of oxygen. Presumably, the induction of chronic acidosis may have been responsible; a parallel improvement in symptoms was noted in six of the ten patients studied.

Cause and effect relationships between reduced BORR and myocardial ischemia are uncertain; clearly, they may not be explained solely in terms of changes in levels of erythrocyte 2,3-DPG. It may be just as tenable to presume that reduced rates of oxygen release are the result of, rather than the cause for, ischemia in these patients. Perhaps compensatory physiologic adjustments which normally exist under certain circumstances have been altered. Obviously, conclusions with respect to these data must await further investigations. Nevertheless, the possibility that reduced rates of release of oxygen were an important contributing cause of myocardial infarction and chronic intermittent ischemia or both in this patient must be kept in mind.

REFERENCES

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Changes in cardiac output measured by using a thermodilution technique were obtained in three of the six dogs. The changes in cardiac output were inversely proportional to the degree of hypoxemia produced by reducing the inspired oxygen from 0.3 to 0.15.

Intravenous infusion of hydrochloric acid (HCl) produced a significant and rapid decrease in Pao2, the arterial oxygen tension, to half of its initial value in 16 of the 240 experiments (approximately 6.7% of the total). The results were similar to those obtained in preliminary studies in adult dogs with severe hypoxic episodes. In these studies, intravenous infusion of HCl was shown to be a useful tool for producing hypoxemia, which can be used to determine thresholds for violence, sudden death, and other hypoxic events.

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