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Research Article

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Respiratory alkalosis was a frequent occurrence in these patients and 2,3-diphosphoglycerate was positively associated with blood pH as well as with the time-averaged proportion of deoxyhemoglobin in arterial and venous blood.

Hemoglobin-oxygen affinity measured at standard conditions and the mixed venous oxygen saturation were equally good indicators of reduced arterial oxygen flow rate in patients without shock. However, Svo_2 is more easily measured and is a more useful indicator of reduced oxygen flow rate, since its relationship to oxygen flow appears to be independent of affinity […]

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ABSTRACT The interrelationships of arterial oxygen flow rate index, oxygen binding by hemoglobin, and oxygen consumption have been examined in patients with acute myocardial infarction. Proportional extraction of oxygen increased in close association with decreasing oxygen flow rate, and hence, whole body oxygen consumption was constant over nearly a threefold variation in arterial oxygen flow rate. A reduction in hemoglobin-oxygen affinity at in vivo conditions of pH, P_{CO_2} and temperature also occurred in proportion to the reduction in arterial oxygen flow rate. Therefore, the increased proportional removal of oxygen from arterial blood at low oxygen flow rates, required to maintain oxygen consumption, may have been facilitated by the reduced affinity of hemoglobin for oxygen at in vivo conditions. However, the decrease in affinity did not appear to explain more than 30–40% of the increased extraction.

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INTRODUCTION

Decreased hemoglobin concentration, oxygen saturation of hemoglobin, or blood flow can result in a decrease in systemic arterial oxygen flow, an increase in red cell 2,3-diphosphoglycerate (2,3-DPG)[1] and a decrease in hemoglobin's affinity for oxygen at standard conditions of measurement in vitro (1, 2). The first two causes of reduced oxygen flow, anemia (1–4) and hypoxia (1, 2, 4–6) have been studied extensively. Few studies have been made of red cell adaptive changes during low blood flow states. Woodson, Torrance, Shappell, and Lenfant (7) and Metcalfe, Dhindsa, Edwards, and Mourdjinis (8), studying patients with chronic cardiac decompensation, have shown that reduced cardiac output is associated with elevated red cell 2,3-DPG (7) and decreased hemoglobin-oxygen affinity (7, 8). Kostuk, Suwa, Bernstein, and Sobel observed decreased affinity after acute myocardial infarction (9). However, P_{50} did not correlate with cardiac index (CI) or with red cell 2,3-DPG, leaving the pathogenesis of the affinity change in doubt.

Our studies were undertaken to examine in further detail (*a*) the effect of acute myocardial infarction on oxygen binding by hemoglobin at in vivo conditions; (*b*) the relationship of changes in blood flow and arterial oxygen content to changes in affinity; (*c*) the role of altered pH, oxygen saturation, and red cell 2,3-DPG content in the modulation of the affinity changes; (*d*) the role of changes in hemoglobin-oxygen affinity in the maintenance of whole body oxygen utilization; and (*e*) the usefulness of changes in red cell 2,3-DPG

[1] *Abbreviations used in this paper:* BE, basic excess; CI, cardiac index; 2,3-DPG, 2,3-diphosphoglycerate; HFI, hemoglobin flow index; MIRU, Myocardial Infarction Research Unit; OFI, oxygen flow index; ta, time-averaged.

content and oxygen binding by hemoglobin as indexes of severity of myocardial functional impairment and of clinical status.

METHODS

Study population. 62 consecutive patients (44 men and 18 women, aged 30–66) with acute myocardial infarction were studied in the Myocardial Infarction Research Unit (MIRU) of the Strong Memorial Hospital. History, electrocardiographic changes, and elevated levels of serum glutamic-oxaloacetic transaminase, lactic dehydrogenase, and creatine phosphokinase confirmed the diagnosis of acute myocardial infarction in 61 of the 62 patients. 33 subjects had anterior or anterolateral wall infarction and 26 had diaphragmatic infarction. One patient had unstable angina without infarction. In two patients, although infarction was definite from history and changes in serum enzymes, the site of the infarct could not be determined electrocardiographically.

Of the total 62 patients studied, 13 consecutive patients were studied in detail, prospectively. Data from the 49 additional patients were obtained retrospectively from measurements made on all patients admitted to the MIRU. All patients were classified as to the severity of clinical disease as described by Interiano, Hyde, Hodges, and Yu (10). At entrance to the MIRU, 19 patients were in class I (no evidence of congestive failure); 24 in class II (rales and third heart sound); 12 in class III (pulmonary edema); and 5 in class IV (cardiogenic shock). These clinical classifications were made without knowledge of the results of the oxyhemoglobin affinity studies, and were independently reviewed and confirmed.

Hemodynamic studies. A Swan-Ganz balloon catheter was passed to the pulmonary artery and an 18-gauge long-dwell catheter was placed in the brachial artery in each patient. Pulmonary artery, pulmonary capillary wedge, and systemic artery pressures were monitored through either Statham p37 or Micron Instruments MP-15 pressure transducers (Statham Instruments, Inc., Oxnard, Calif.; Micron Instruments, Inc., Los Angeles, Calif.) and recorded on a Brush direct writer. (Brush Instruments Div., Cleveland, Ohio). Cardiac output was determined by either indicator dilution or thermal dilution technique. Indicator dilution curves were inscribed after 2 ml of indocyanine green dye was injected into the pulmonary artery and blood was withdrawn from the brachial artery with a Harvard constant withdrawal pump (Harvard Apparatus Co., Inc., Millis, Mass.). A Gilford densitometer was used to measure dye concentration (Gilford Instrument Laboratories, Inc., Oberlin, Ohio). When output was measured by thermal dilution, injections of 10 ml of iced saline were made into the right atrium and temperature monitored by a catheter-tipped thermister positioned in the pulmonary artery. All outputs were measured in duplicate. In all cases, extrapolation of curves and integration of areas beneath curves were performed by a Xerox Sigma 3 computer (Xerox Corp., El Segundo, Calif.).

Blood gas studies. Blood samples from all patients were collected either from a right atrial or from a pulmonary artery catheter in the presence of heparin. Samples were obtained during the first 4 days after admission to the MIRU.

In the 13 patients studied prospectively, an Instrumentation Laboratory (Instrumentation Laboratory, Inc., Lexington, Mass.) gas-mixing module (model 2081), oxygen monitor (model 2083), and tonometer (model 137) were used to adjust oxygen tension (P_{O_2}) to between 15 and 60 torr while carbon dioxide tension (P_{CO_2}) was maintained at 40±0.2 torr. The oxygen saturation of blood (S_{O_2}) was measured with a model 182 cooximeter. pH, P_{O_2}, and P_{CO_2} were determined with a model 113 pH-gas analyzer. Each determination was made in duplicate. The P_{O_2} at which 50% of hemoglobin was saturated with oxygen at 37°C, pH = 7.4, P_{CO_2} = 40 torr (P_{50} std) was derived from a least-squares analysis of the experimental points. Base excess (BE) was calculated from the blood pH and P_{CO_2}, as suggested by Severinghaus (11).

In the 49 patients studied retrospectively, pH, P_{O_2} and P_{CO_2} were measured with an Instrumentation Laboratory model 113 blood gas analyzer and S_{O_2} was determined either by the manometric method of Van Slyke and Neill (12) or with an American Optical Corp. (Southbridge, Mass.) macroreflection oximeter. The P_{O_2} of the pulmonary artery samples was between 25 and 50 torr. The P_{50} std at 37°C, pH = 7.40, P_{CO_2} = 40 torr was determined from the P_{O_2} and S_{O_2} of the pulmonary artery blood by an extrapolation to P_{50} made on the assumption that the observed P_{O_2} and S_{O_2} were on a sigmoid curve that paralleled the standard oxyhemoglobin dissociation curve.

Calculation of Hb/HbO_2 time-averaged (ta) ratio, hemoglobin flow index, oxygen content, oxygen flow index, oxygen consumption and P_{50} in vivo. The ratio of the proportion of deoxyhemoglobin (Hb) to oxyhemoglobin (HbO_2) was calculated in systemic and pulmonary arterial blood. Based on the estimate that 40% of the blood volume is distributed on the arterial side of the circulation and 60% on the venous side, the following formula was used to derive an estimate of the time-averaged ratio:

$$Hb/HbO_2\ (ta) = 0.4(Hb_a/HbO_{2a}) + 0.6(Hb_{\bar{v}}/HbO_{2\bar{v}}).$$

Hemoglobin flow index (HFI) was calculated by the formula:

$$HFI\ (g/min\ per\ m^2) = Hb\ (g/liter) \times CI\ (liter/min\ per\ m^2).$$

Oxygen content of blood was calculated by the formula:

$$C_{O_2}\ (ml/liter) = Hb\ (g/liter) \times 1.39\ (ml/g) \times S_{O_2}\ (proportional\ saturation).$$

Oxygen flow index (OFI) was calculated by the formula:

$$OFI\ (ml/min\ per\ m^2) = C_{O_2}\ (ml/liter) \times CI\ (liter/min\ per\ m^2)$$

Oxygen consumption was calculated from the formula:

$$\dot{V}_{O_2}\ (ml/min\ per\ m^2) = OFI_a - OFI_{\bar{v}}$$

P_{50} std was converted to an estimate of the P_{50} present in vivo in arterial blood by the formula:

$$\log P_{50}\ i.v. = \log P_{50}\ std + 0.48(7.40 - pH) + 0.0013\ (BE) + 0.024(T\text{-}37°C).$$

pH and BE were those measured in arterial blood.

Chemical determinations. Blood hemoglobin was measured in duplicate by the cyanmethemoglobin method and hematocrit was measured in triplicate in an International Equipment Company (Needham Heights, Mass.) microhematocrit centrifuge at approximately 10,000 *g* for 5 min. Red cell 2,3-DPG was measured by the method of Rose and Liebowitz (13).

Statistical methods. Means, variances, linear regressions, simple, multiple, and partial correlation coefficients, confidence and tolerance intervals, and significance tests were performed with formulae entered into a Wang 600 programmable calculator (Wang Laboratories, Inc., Tewksbury, Mass.) The equations for statistical tests were obtained from three sources (14–16).

RESULTS

Correlation of components of arterial oxygen flow with oxygen-hemoglobin affinity. The determinants of systemic arterial OFI (OFI_a) are presented in Fig. 1. They include those elements that determine Ca_{O_2} (i.e. oxygen capacity and saturation of arterial blood), as well as the rate of systemic blood flow, i.e. CI. Each component of OFI_a has been examined for its separate influence on oxygen binding by hemoglobin in the 13 subjects studied prospectively. The data gathered on each patient at each point of study are presented in Table I.

P_{50} std was moderately, although significantly correlated with each of the three components of oxygen flow index; Hb, Sa_{O_2}, and CI (Table II). OFI_a, i.e. the product of Hb, Sa_{O_2} and CI, representing the summation of oxygen availability as blood approaches tissue capillaries, was more strongly correlated with P_{50} std than was its components. However, the association of Ca_{O_2}, the product of Hb and Sa_{O_2}, with P_{50} std was as strong as that of OFI_a with P_{50} (Fig. 2). In view of this, we considered the possibility that CI was correlated with P_{50} std as a result of a dependence of CI on Ca_{O_2}. However, the correlation of CI with Ca_{O_2} was weak and not significant (Table II). Moreover, P_{50} std correlated with Ca_{O_2} ($r = -0.68$, $P < 0.001$) and with CI ($r = -0.47$, $P < 0.05$), when the effect of the alternate variable was held constant with partial correlation statistics. Hence, Ca_{O_2} or CI could influence P_{50} std independent of its contribution to OFI_a. Therefore, we computed the combined influence of these two variables on P_{50} std with multiple regression analysis. The multiple correlation of P_{50} std with both Ca_{O_2} and CI was stronger ($r = 0.76$) than that of P_{50} std with OFI_a ($r = -0.71$), although the difference did not reach statistical significance.

Since any change in P_{50} that respresents a response to low flow might be delayed, we also studied the relationship between P_{50} std and the determinants of arterial oxygen flow measured on the preceding hospital day. The correlations were virtually identical to those relating P_{50} to flow state and oxygen content measured on the same day, because CI and Ca_{O_2} were relatively similar within each patient over the period of study, and the studies were performed in nearly all cases relatively long after the onset of symptoms (> 24 h) (Table I).

Mechanism of altered affinity in response to changing arterial oxygen flow. Although Kostuk and coworkers failed to find a correlation between P_{50} after myocardial infarction and red cell 2,3-DPG level (9), a basis for the affinity changes in our subjects was sought in the well-established dependence of P_{50} std on red cell 2,3-DPG. We found P_{50} std to be highly correlated with red cell 2,3-DPG ($r = 0.87$, $P < 0.001$) (Fig. 3A).

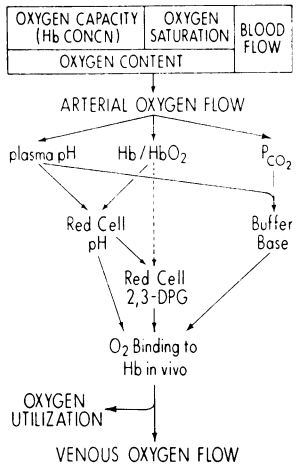

FIGURE 1 The major components of arterial oxygen flow (Hb, S_{O_2} and CI) are shown. The possible role of pH and Hb/HbO_2 ratio in mediating the effects of reduced oxygen flow on red cell 2,3-DPG is depicted. Increased blood pH and decreased P_{CO_2} appear to be frequent sequelae of decreased arterial oxygen flow. The major factors contributing to the affinity of hemoglobin for oxygen in vivo, i.e. red cell pH, 2,3-DPG, and the pH-independent direct effect of CO_2 are shown. Red cell pH is closely dependent on blood (plasma) pH. Buffer base derived from the pH and P_{CO_2} can be used to represent the pH-independent effect of P_{CO_2}·Hb/HbO_2 ratio can influence the intracellular pH and may increase total cellular 2,3-DPG by its effects on the level of free 2,3-DPG content. The difference between arterial and venous oxygen flow represents oxygen consumption.

Relationship of red cell 2,3-DPG and P_{50} std to blood pH and Hb/HbO_2 (ta). Intraerythrocytic pH is an important determinant of red cell glycolytic rate (17) and also of the steady-state level of 2,3-DPG (18). Two important mechanisms may initiate an alteration in red cell pH: one is a change in plasma pH, since red cell pH is directly dependent on plasma pH (19), and a second is an increase in the ratio of deoxygenated to oxygenated hemoglobin (20). The latter effect occurs because Hb binds protons more avidly than HbO_2. The effect of such a change in intracellular pH is dual. An instantaneous result on oxygen binding by hemoglobin is mediated by the Bohr effect (21). A later effect of red cell pH appearing after 36–48 h is an alteration in red cell 2,3-DPG content (22). Reduction in Hb/HbO_2 ratio also has a pH-independent delayed effect that may further influence red cell 2,3-DPG content. Deoxygenated hemoglobin has a higher affinity for 2,3-DPG than HbO_2. By increasing the Hb/HbO_2 ratio, free 2,3-DPG is decreased and acceleration of 2,3-DPG synthesis occurs (20). Since Hb/HbO_2 ratio will be markedly different in arterial and venous circulations, a weighted average of the two ratios was

TABLE I

Component Variables for Calculation of Oxygen Flow, Oxygen Consumption

Subject and class	Date of study	Time from onset of symptoms	Hb	Pa_{O_2}	Sa_{O_2}	Ca_{O_2}	$P\bar{v}_{O_2}$	$S\bar{v}_{O_2}$	$C\bar{v}_{O_2}$	CI	HFI	OFI_a	$OFI_{\bar{v}}$
		h	*g/liter*	*torr*	%	*ml/liter*	*torr*	%	*ml/liter*	*liter/min per m²*	*g/liter per m²*	*ml/min per m²*	*ml/min per m²*
L. C. II	7/27/72	45	138	70	95.0	182	27.0	46.0	88	3.05	421	555	268
A. L. I	9/6/72	51	148	65	94.0	193	34.5	68.0	140	3.13	463	604	438
J. N. I	9/13/72	23	149	62	93.0	193	31.0	63.5	132	2.39	356	461	315
	9/14/72	45	137	67	93.0	177	36.0	71.0	135	2.53	347	448	342
	9/15/72	69	130	65	93.0	168	28.0	54.5	98	2.39	311	402	234
L. H. II	9/19/72	46	150	66	95.0	198	—	—	93	3.92	588	776	365
	9/20/72	66	143	65	95.0	189	37.0	77.0	153	4.29	613	811	656
B. L. I	9/25/72	40	137	51	89.0	169	35.5	68.9	131	4.02	551	679	527
	9/26/72	63	136	59	94.0	178	33.5	69.5	131	3.09	420	550	405
W. D. I	10/30/72	94	145	67	94.0	189	35.0	74.0	149	3.82	554	722	569
D. J. I	10/30/72	97	149	65	95.0	197	29.0	62.6	130	3.64	542	717	473
J. B. I	11/16/72	70	141	67	96.0	188	32.0	63.7	125	2.84	400	534	355
J. O. I	12/11/72	61	130	92	96.5	174	35.0	71.5	129	3.49	454	607	450
	12/12/72	85	117	63	93.8	153	33.5	66.7	108	3.39	397	519	366
D. M. III	12/26/72	40	137	39	84.8	161	18.0	29.6	56	2.76	378	444	155
	12/27/72	60	124	45	88.0	152	22.0	40.7	70	3.02	374	459	211
	12/28/72	83	121	—	—	150	—	—	—	2.86	346	429	—
H. M. III	12/28/72	60	131	36	78.0	142	20.0	30.0	55	2.85	373	405	157
C. G. IV	2/7/73	6	156	147	83.0	180	30.0	55.0	119	2.54	396	457	302
	2/8/73	25	128	55	91.0	162	26.0	44.7	80	2.24	287	363	179
	2/9/73	51	107	101	98.0	146	25.0	46.8	70	1.97	211	288	138
A. T. II	2/5/73	62	131	171	99.4	181	31.0	63.3	115	3.37	441	610	388
	2/6/73	84	112	56	92.1	143	29.0	57.6	90	4.01	449	573	361
n		23	23	22	22	23	21	21	22	23	23	23	22
Mean		57.7	135	71.5	92.3	172	29.9	58.3	109	3.11	420	540	348
SD		22.8	12.6	31.9	5.04	18.1	5.38	13.9	29.8	0.634	99.0	137	139
SE		4.76	2.64	6.81	1.08	3.78	1.17	3.03	6.36	0.132	20.6	28.5	29.6

used to evaluate its relationship to oxygen flow (see Methods). The dependence of red cell 2,3-DPG on arterial pH, Hb/HbO_2 (ta), or both was examined. There was a moderately strong and significant positive correlation of red cell 2,3-DPG content with arterial pH ($r = 0.46$) and with Hb/HbO_2 (ta) ($r = 0.55$). The multiple correlation of 2,3-DPG with both arterial pH and Hb/HbO_2 (ta) was stronger and highly significant: $r = 0.68$, $P < 0.001$ (Table IV).

Alkalosis was a constant feature in these patients. Mean arterial pH 7.493±0.039 (SD) was significantly higher than normal (7.400±0.055). The pH range of 7.42–7.57 in the 13 subjects indicates that the entire study population was shifted into the alkalotic range. P_{CO_2} was low and base excess slightly elevated in arterial blood (Table I).

Relationship of Ca_{O_2} and CI to blood pH and Hb/HbO_2 (ta). We next considered the possibility that Ca_{O_2} and CI exerted their influence on red cell, 2,3-DPG in one of the following ways. Firstly, changes in Ca_{O_2} and CI might have influenced 2,3-DPG by influencing arterial pH or Hb/HbO_2 (ta). Alternatively, they may have influenced 2,3-DPG independently of an effect on pH or the ratio.

Ca_{O_2} was correlated significantly, although only moderately, with both arterial pH ($r = -0.43$) and Hb/HbO_2 (ta) ($r = -0.49$). The multiple correlation of Ca_{O_2} with both pH and Hb/HbO_2 (ta) was stronger ($r = 0.60$, $P < 0.01$) (Table IV). CI was not correlated with arterial pH ($r = 0.03$) and correlated weakly and not significantly with Hb/HbO_2 (ta) ($r = -0.38$).

Red cell 2,3-DPG was found to be correlated independently with Ca_{O_2} ($r = -0.48$) and CI ($r = -0.34$) when the effects of pH and Hb/HbO_2 (ta) were held constant with partial correlation statistics. The latter analysis is compatible with the possibility that factors independent of pH and Hb/HbO_2 (ta) may contribute to the relationship of Ca_{O_2} and CI with 2,3-DPG, although the intercorrelations of variables and the imperfect statistical techniques make it necessary to draw guarded inferences.

Oxygen binding to hemoglobin at in vivo conditions. To estimate the net change in P_{50} in vivo, P_{50} std was adjusted based on the presumptive additional effects of P_{CO_2}, pH, and temperature (See Methods). P_{50} in vivo was correlated with red cell 2,3-DPG ($r = 0.59$), although this association was significantly less than that of P_{50} std with 2,3-DPG ($r = 0.87$) (Fig. 3B). P_{50}

$\dot{V}_{O_2}$	Proportional extraction	pH_a	pH_v	Hb/HbO_{2a}	Hb/HbO_{2v}	Hb/HbO_2	$Paco_2$	B.E.$_a$	Body temperature	Red cell 2,3-DPG	P_{50} std	P_{50} i.v
ml/min per m²						ta	*torr*		*°C*	*μmol/g Hb*	*torr*	*torr*
287	0.52	7.42	7.39	0.0526	1.174	0.725	36	−1.0	38.2	18.4	27.5	28.7
166	0.27	7.47	7.45	0.0638	0.471	0.308	37	+3.0	37.2	15.7	27.3	25.8
146	0.32	7.44	7.41	0.0753	0.575	0.375	40	+3.0	37.6	14.1	25.0	24.9
106	0.24	7.49	7.46	0.0753	0.408	0.275	37	+5.0	38.2	15.0	26.0	25.5
168	0.42	7.50	7.46	0.0753	0.835	0.531	37	+5.0	37.9	16.0	27.3	26.1
—	—	7.48	7.43	0.0526	1.237	0.763	38	+5.0	38.0	13.1	24.5	24.1
155	0.19	7.50	7.47	0.0526	0.299	0.200	38	+6.0	37.0	13.6	24.5	22.3
152	0.22	7.46	7.45	0.1240	0.451	0.320	35	+2.0	38.3	14.2	26.0	26.3
145	0.26	7.55	7.54	0.0638	0.439	0.289	28	+3.0	38.0	15.1	26.3	23.8
153	0.21	7.46	7.45	0.0638	0.351	0.236	32	0.0	37.3	13.6	23.5	22.4
244	0.34	7.48	7.45	0.0526	0.597	0.379	34	+2.0	38.0	14.1	23.8	23.2
179	0.34	7.53	7.52	0.0417	0.570	0.359	34	+6.0	38.1	19.6	27.3	25.6
157	0.26	7.50	7.46	0.0363	0.399	0.254	36	+5.0	38.7	15.2	24.0	24.0
153	0.29	7.49	7.46	0.0661	0.499	0.326	32	+1.5	38.0	17.4	26.5	25.5
289	0.65	7.50	7.49	0.1790	2.378	1.498	33	+2.5	37.4	18.8	29.0	26.7
248	0.54	7.57	7.51	0.1360	1.457	0.929	30	+6.0	37.2	19.8	30.0	25.6
—	—	7.52	—	0.1240	—	—	—	—	38.0	19.6	28.0	—
248	0.61	7.52	7.49	0.2820	2.333	1.513	30	+2.0	38.0	21.7	29.5	27.5
155	0.34	7.44	—	0.2050	—	—	34	0.0	37.9	16.1	28.0	28.2
184	0.51	7.44	7.41	0.0989	1.237	0.782	40	+3.0	38.4	16.7	27.4	28.6
150	0.52	7.54	7.48	0.0204	1.137	0.690	31	+4.0	38.2	19.2	28.5	26.4
222	0.36	7.53	7.49	0.0060	0.580	0.350	39	+9.0	37.3	17.8	27.5	24.9
212	0.37	7.50	7.47	0.0858	0.736	0.476	35	+4.0	37.3	17.7	28.0	25.8
21	21	23	21	23	21	21	22	22	23	23	23	22
187	0.371	7.492	7.461	0.0825	0.865	0.551	34.8	+3.5	37.8	16.6	26.8	25.5
50.8	0.136	0.0385	0.0365	0.0634	0.601	0.379	3.36	—	0.454	2.42	1.84	1.79
11.1	0.0298	0.00803	0.00794	0.0132	0.131	0.0827	0.72	—	0.0946	0.504	0.384	0.382

in vivo was also significantly correlated with CI ($r = -0.59$) and Ca_{O_2} ($r = 0.46$). Thus when the effects of pH, BE, and temperature were considered, in addition to that of red cell 2,3-DPG, P_{50} was more strongly associated with CI than Ca_{O_2}. When P_{50} in vivo was correlated with CI, with the effect of temperature control, the correlation remained significant, although it was slightly reduced ($r = 0.53$). P_{50} in vivo was also correlated with OFI_a ($r = -0.68$, $P < 0.001$) (Fig. 4), and with CI + Ca_{O_2} (multiple correlation) ($r = 0.67$, $P < 0.001$) (Table IV).

Relationship of oxygen consumption to OFI_a and P_{50}. Oxygen consumption after myocardial infarction was independent of Ca_{O_2} ($r = -0.22$), CI ($r = 0.06$), or OFI_a ($r = 0.04$) over a wide range of OFI_a from 288 to 811 ml/min per m² (Fig. 5). The maintenance of $\dot{V}_{O_2}$ was explained by a marked proportional increase in oxygen extraction as arterial oxygen flow rate fell. Indeed, the correlation of extraction with OFI_a was highly significant (Fig. 6). Extraction increased 7.0% for every 100 ml/min per m² decrement in OFI_a. In addition, as can be seen in the Table insert in Fig. 5, a stepwise increase in P_{50} in vivo also occurred when the subjects were divided into three groups of equal numbers by decreasing OFI_a. Indeed, proportional extraction was strongly associated with P_{50} in vivo ($r = 0.64$, $P < 0.01$) (Fig. 7). Hence, decreasing hemoglobin-oxygen affinity could account for about 40% (0.64^2) of the increment in proportional extraction, although the association does not establish causality.

We further quantified the possible contribution of reduced affinity to oxygen delivery by comparing the oxygen consumption that would have resulted if the position of the oxygen-hemoglobin dissociation curve present in subject L. H., with the highest OFI_a, was present in subject C. G., with the lowest OFI_a, and Pa_{O_2}, $P\bar{v}_{O_2}$, and CI were unchanged. As shown in Table V, $\dot{V}_{O_2}$ would have been severely reduced if proportional extraction had not increased to 0.52. If the position of the oxygen-dissociated curve in vivo in subject C. G. was the same as L. H., $\dot{V}_{O_2}$ would have been 120 ml/min per m² and proportional extraction 0.42. A very similar result occurred if the P_{50} in vivo of subject C. G. was positioned at his in vivo conditions of pH, temperature, and P_{CO_2} and a normal red cell 2,3-DPG content. Two important inferences can be

TABLE II

Association of Variables (Correlation Coefficients)

	1 Hb	2 $S\bar{v}O_2$	3 CaO_2	4 CI	5 HFI	6 OFI_a	7 pH_a	8 Hb/HbO_2 (ta)	9 2,3-DPG	10 P_{50} std	11 P_{50} in vivo
A Hb		−0.12	+0.86	+0.18	+0.53	+0.50	−0.50	−0.18	−0.57	−0.47	−0.21
B $S\bar{v}O_2$			+0.43	+0.19	+0.15	+0.34	+0.08	−0.76	−0.37	−0.50	−0.49
C CaO_2				+0.27	+0.58	+0.64	−0.41	−0.51	−0.71	−0.70	−0.47
D CI					+0.92	+0.91	−0.03	−0.34	−0.43	−0.51	−0.59
E HFI						+0.98	−0.21	−0.35	−0.61	−0.64	−0.62
F OFI_a							−0.18	−0.47	−0.65	−0.71	−0.69
G pH_a								+0.15	+0.46	+0.37	−0.29
H Hb/HbO_2 (ta)									+0.65	+0.67	+0.54
I 2,3-DPG										+0.87	+0.59
J P_{50} std											+0.73

$0.41 \leq r \leq 0.52$, $P < 0.05$; $0.53 \leq r \leq 0.63$, $P < 0.01$; $r \geq 0.64$, $P < 0.001$.

The regression equations for each pair of variables in this table are given in Table III. The letter-number coordinates can be used to find the appropriate regression equation. For example, the regression of CI (Y) on Hb (X) can be found listed in Table III as coordinate 4, A.

developed from this comparison. First, about 30% of the increase in proportional extraction [(0.52 − 0.42) ÷ (0.52 − 0.19) = 0.10 ÷ 0.33] that occurred with decreased OFI_a could be ascribed to a reduction in the binding of oxygen by hemoglobin; second, most of the increase in oxygen extraction at low oxygen flow appears to occur for other reasons.

P_{50} std vs. $S\bar{v}O_2$ as index of oxygen availability. To examine the usefulness of P_{50} std or red cell 2,3-DPG as an index of systemic arterial oxygen delivery to

TABLE III

Linear Regression Equations for Variables Examined in 13 Subjects Studied Prospectively

Table II coordinates	Regression	Table II coordinates	Regression
2, A.	$S\bar{v}O_2 = 98.6 - 0.0468$ Hb	6, D.	$OFI_a = 195$ CI $- 69.2$
3, A.	$CaO_2 = 7.39 + 1.23$ Hb	7, D.	$pH_a = 7.50 - 0.00199$ CI
4, A.	CI $= 1.93 + 0.00876$ Hb	8, D.	Hb/HbO_2 ta $= 1.19 - 0.201$ CI
5, A.	HFI $= 4.18$ Hb $- 142$	9, D.	2,3-DPG $= 21.8 - 1.66$ CI
6, A.	$OFI_a = 5.35$ Hb $- 180$	10, D.	P_{50} std $= 31.4 - 1.48$ CI
7, A.	$pH_a = 7.70 - 0.00153$ Hb	11, D.	P_{50} in vivo $= 30.7 - 1.65$ CI
8, A.	Hb/HbO_2 ta $= 1.30 - 0.00560$ Hb	6, E.	$OFI_a = 1.35$ HFI $- 29.2$
9, A.	2,3-DPG $= 31.3 - 0.109$ Hb	7, E.	pH $= 7.53 - 0.0000809$ HFI
10, A.	P_{50} std $= 36.1 - 0.0691$ Hb	8, E.	Hb/HbO_2 ta $= 1.11 - 0.00310$ HFI
11, A.	P_{50} in vivo $= 29.7 - 0.0304$ Hb	9, E.	2,3-DPG $= 22.9 - 0.0148$ HFI
3, B.	$CaO_2 = 33.9 + 1.51\ S\bar{v}O_2$	10, E.	P_{50} std $= 31.8 - 0.0119$ HFI
4, B.	CI $= 0.917 + 0.0239\ S\bar{v}O_2$	11, E.	P_{50} in vivo $= 30.3 - 0.0111$ HFI
5, B.	HFI $= 152 + 2.94\ S\bar{v}O_2$	7, F.	$pH_a = 7.52 - 0.0000513\ OFI_a$
6, B.	$OFI_a = 9.23\ S\bar{v}O_2 - 307$	8, F.	Hb/HbO_2 ta $= 1.25 - 0.00128\ OFI_a$
7, B.	$pH_a = 7.44 + 0.000582\ S\bar{v}O_2$	9, F.	2,3-DPG $= 22.8 - 0.0115\ OFI_a$
8, B.	Hb/HbO_2 ta $= 6.21 - 0.0610\ S\bar{v}O_2$	F, 10.	$OFI_a = 1943 - 52.4\ P_{50}$ std
9, B.	2, 3-DPG $= 32.6 - 0.174\ S\bar{v}O_2$	11, F.	P_{50} in vivo $= 30.4 - 0.00899\ OFI_a$
10, B.	P_{50} std $= 44.0 - 0.187\ S\bar{v}O_2$	8, G.	Hb/HbO_2 ta $= 1.46\ pH_a - 10.4$
11, B.	$S\bar{v}O_2 = 127 - 1.37\ P_{50}$ in vivo	9, G.	2,3-DPG $= 29.0\ pH_a - 200$
4, C.	CI $= 1.49 + 0.00945\ CaO_2$	10, G.	P_{50} std $= 17.9\ pH_a - 107$
5, C.	HFI $= 3.15\ CaO_2 - 122$	11, G.	P_{50} in vivo $= 124 - 13.2\ pH_a$
6, C.	$OFI_a = 4.81\ C_{aO_2} - 289$	9, H.	2,3-DPG $= 14.2 + 4.17\ Hb/HbO_2$ ta
7, C.	$pH_a = 7.65 - 0.000881\ C_{aO_2}$	10, H.	P_{50} std $= 24.8 + 3.32\ Hb/HbO_2$ ta
8, C.	Hb/HbO_2 ta $= 2.40 - 0.0107\ C_{aO_2}$	11, H.	P_{50} in vivo $= 24.3 + 2.31\ Hb/HbO_2$ ta
9, C.	2,3-DPG $= 33.0 - 0.0951\ CaO_2$	10, I.	P_{50} std $= 15.8 + 0.659$ 2,3-DPG
10, C.	P_{50} std $= 39.0 - 0.0710\ CaO_2$	11, I.	P_{50} in vivo $= 18.2 + 0.445$ 2,3-DPG
11, C.	P_{50} in vivo $= 33.7 - 0.0470\ CaO_2$	11, J.	P_{50} in vivo $= 6.98 + 0.696\ P_{50}$ std
5, D.	HFI $= 143$ CI $- 26.5$		

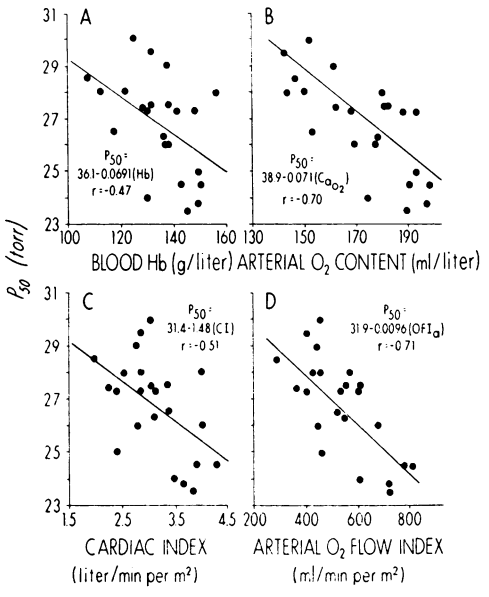

FIGURE 2 The regressions of P_{50} std on A. Hb, B. Ca_{O_2}, C. CI, and D. OFI_a are shown.

tissue capillaries, we compared their relationship to OFI_a with that of the relationship of $S\bar{v}_{O_2}$ to OFI_a. $S\bar{v}_{O_2}$ is a commonly used index of tissue oxygen uptake (23, 24). The correlations of P_{50} std ($r = -0.71$, $P < 0.001$) or red cell 2,3-DPG ($r = -0.65$, $P < 0.001$) with OFI_a were very similar to that of the association of $S\bar{v}_{O_2}$ with OFI_a ($r = 0.67$, $P < 0.001$). The correlation of P_{50} std with components of OFI_a, i.e., CI ($r = -0.51$) and Ca_{O_2} ($r = -0.70$) resembled that of $S\bar{v}_{O_2}$ with CI ($r = 0.51$) and Ca_{O_2} ($r = 0.66$). The regression of OFI_a on P_{50} and $S\bar{v}_{O_2}$ is shown in Fig. 8.

The correlation coefficients indicated that variations in OFI_a explained on the average 50% of the variance

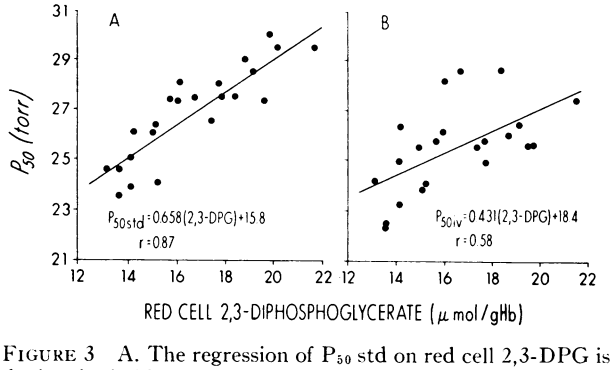

FIGURE 3 A. The regression of P_{50} std on red cell 2,3-DPG is depicted. A highly significant association was present. P_{50} std increased 1.0 torr for each increment of 2,3-DPG of 1.5 μmol/g Hb. B. The regression of P_{50} in vivo on red cell 2,3-DPG is shown. The increment in P_{50} in vivo is significantly less than that of P_{50} std with increased 2,3-DPG concentration. P_{50} in vivo increased 0.64 torr for each increment of 2,3-DPG of 1.5 μmol/g Hb.

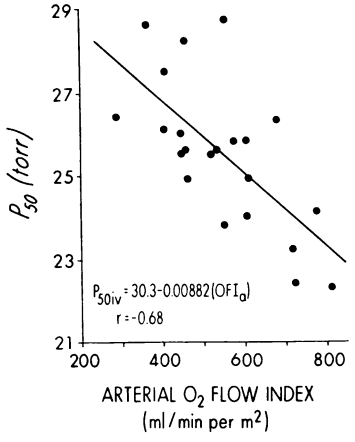

FIGURE 4 The regression of P_{50} in vivo on OFI_a is shown. The increment in P_{50} in vivo is 0.88 torr per 100 ml/min per m² reduction in OFI_a.

in P_{50} (i.e., r^2) and similarly it explained 45% of the variance in $S\bar{v}_{O_2}$. $P\bar{v}_{O_2}$ was highly correlated with $S\bar{v}_{O_2}$ ($r = +0.98$) over this range of $P\bar{v}_{O_2}$, which is in the central, nearly linear, portion of the oxygen-hemoglobin dissociation. Hence, the results were similar with either $P\bar{v}_{O_2}$ or $S\bar{v}_{O_2}$ for analysis.

The multiple correlation of $S\bar{v}_{O_2}$ with Ca_{O_2}, CI, and P_{50} in vivo was very strong ($r = 0.77$, $P < 0.001$). (Table IV). This suggests that on the average about 60% of the variance (0.77^2) in $S\bar{v}_{O_2}$ could be explained by changes in OFI_a plus changes in affinity.

Relationship of P_{50} to clinical status. Reduction in Ca_{O_2} and CI should be correlated with a severity of

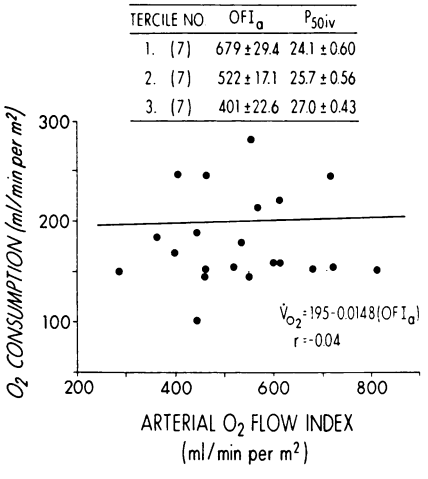

FIGURE 5 Oxygen consumption is shown in relationship to OFI_a. The slope of the regression of oxygen consumption on OFI_a is zero. The inserted table shows the mean±SD of the P_{50} in vivo for three ranges of OFI_a: normal, moderately reduced, and markedly reduced. A stepwise increase in P_{50} in vivo is seen. The mean differences in P_{50} are highly significant when tested by analysis of variance ($P < 0.01$).

TABLE IV

Multiple Correlation Coefficients and Linear Multiple Regression Equations

Multiple regression equation	Correlation coefficient	*P*
2,3-DPG = 23.3 pH_a + 3.82 Hb/HbO_2 ta − 160	$r = 0.74$	0.001
P_{50} std = 40.5 − 0.0615 Ca_{O_2} − 1.00 CI	$r = 0.77$	0.001
P_{50} in vivo = 35.8 − 0.0339 Ca_{O_2} − 1.41 CI	$r = 0.68$	0.001
Ca_{O_2} = 1,324 − 152 pH_a − 22.5 Hb/HbO_2 ta	$r = 0.60$	0.01
$S\bar{v}_{O_2}$ = 70.5 + 0.312 Ca_{O_2} − 3.10 P_{50} in vivo + 4.39 CI	$r = 0.79$	0.001

myocardial infarction, as judged by clinical criteria. Indeed, this was corroborated in this series of 13 subjects, since the plasma creatine phosphokinase activity was inversely correlated with CI and Ca_{O_2}, measured on the day after the serum enzyme measurement (data not shown).

We examined the possibility that P_{50} std might also reflect the severity of the infarction as judged by clinical criteria. Oxygen flow, binding, and utilization as well as blood pH and Hb/HbO_2 (ta) were calculated in the 49 patients in the MIRU who were studied retrospectively (Table VI). Mean arterial pH was elevated in each class of patients. However, the proportion of subjects with arterial pH below 7.36 increased with increasing severity of infarction (class I + II = 1/31 or 3%, class III + IV = 4/18 or 22%). Hb/HbO_2 (ta) increased and $S\bar{v}_{O_2}$ decreased significantly with severity of clinical state. Although $S\bar{v}_{O_2}$ was correlated with Ca_{O_2} ($r = 0.35$, $P < 0.02$) and CI ($r = 0.51$, $P < 0.001$), it was most strongly associated with OFI_a ($r = 0.60$, $P < 0.001$).

P_{50} std of 17 normal subjects measured in our laboratory was 26.6±0.75 (SD) torr. Mean initial P_{50} std was similar to normal in class I patients, whereas it was significantly elevated in class II patients and highly significantly elevated in class III patients. In class IV subjects, P_{50} std was not increased significantly. P_{50} std was significantly ($P < 0.05$) but weakly correlated with CI ($r = -0.23$), Ca_{O_2} ($r = -0.31$) and OFI_a ($r = -0.36$) in the 49 subjects studied on admission to MIRU. These correlations were stronger if class IV subjects were omitted. Moreover, the correlations are a function of time-dependent changes in red cell 2,3-DPG that may not have occurred at the time of the initial study.

P_{50} in vivo was significantly elevated in subjects in class II and III. Despite a stepwise and marked decrease in OFI_a as severity of infarction increased,

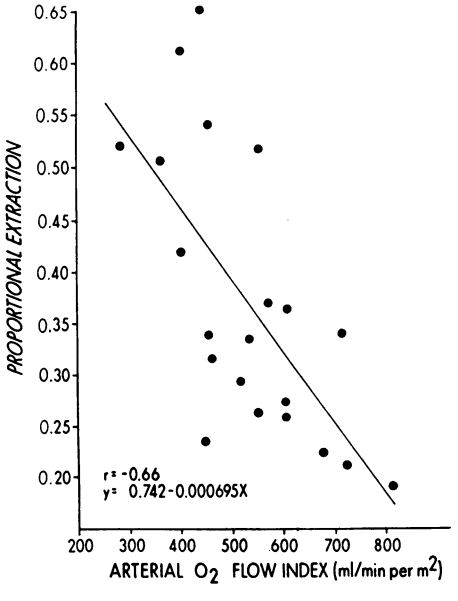

FIGURE 6 The relationship of proportional extraction of oxygen from arterial blood to oxygen flow rate index is shown.

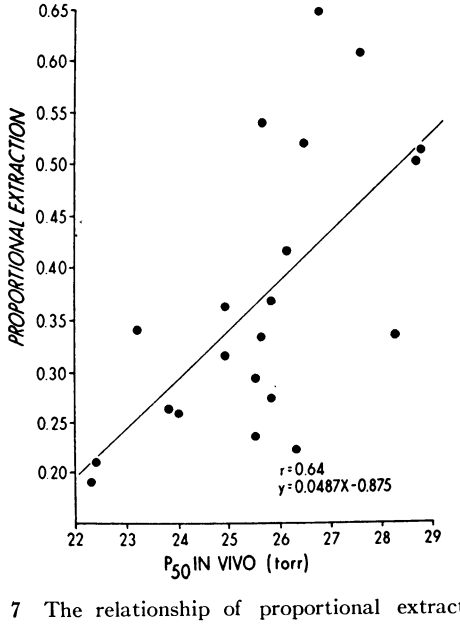

FIGURE 7 The relationship of proportional extraction of oxygen to P_{50} in vivo is shown.

TABLE V

The Influence of P_{50} in vivo on Proportional Extraction of Oxygen

	Subject L. H. observed	Subject C. G.			
		Observed	Expected*	Expected‡	Expected§
OFI_a, *ml O_2/min per m^2*	811	288	288	288	288
$\dot{V}_{O_2}$, *ml O_2/min per m^2*	155	150	55	120	126
PE	0.19	0.52	0.19	0.42	0.44

PE = proportional extraction of oxygen = $\dot{V}_{O_2}/OFI_a$.

* The $\dot{V}_{O_2}$ expected if proportional extraction did not increase with decreasing OFI_a.

† The $\dot{V}_{O_2}$ expected if the P_{50} in vivo in subject C. G. was the same as in subject L. H.

§ The $\dot{V}_{O_2}$ expected if C. G.'s red cell 2,3-DPG was 14.0 (normal mean) rather than 19.2 μmol/g Hb (observed value) and P_{50} in vivo was reduced based on the relationship of P_{50} to 2,3-DPG (Fig. 3B).

mean oxygen consumption ($\dot{V}_{O_2}$) increased slightly in class II and III subjects as compared to class I subjects. Like P_{50} in vivo, $\dot{V}_{O_2}$ did not increase in class IV patients; rather, the latter two variables were not different from class I subjects.

The possible quantitative role of oxygen-hemoglobin affinity in maintaining tissue oxygen consumption was examined (Fig. 9). Mean OFI_a decreased linearly from clinical class I to class IV (Fig. 9A), but mean P_{50} in vivo, $\dot{V}_{O_2}$, and proportional extraction of oxygen were correlated with mean OFI_a only in classes I through III. This relationship was broken when class IV subjects were examined (Fig. 9). The lines in Fig. 9 do not represent the regression for the 49 individual observations. They are the best fit lines connecting the means of subjects in classes I through III. If $\dot{V}_{O_2}$ for class II, III, and IV subjects was recalculated at the P_{50} in vivo of class I subject, $\dot{V}_{O_2}$ and proportional extraction would have been reduced as shown by the open squares in Figs. 9C and D. Even so, proportional extraction increased, and $\dot{V}_{O_2}$ would have been 89% (class II), 75% (class III), and 94% (class IV) of the observed values in the absence of an increase in P_{50} in vivo. We conjecture, from these data, that class IV subjects, already extracting oxygen maximally, are compromised further by an inability to decrease oxygen binding to hemoglobin and to thereby satisfy the

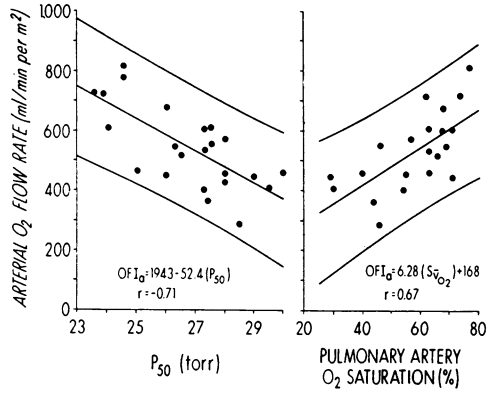

FIGURE 8 The relationship of OFI_a to either P_{50} std or $S\bar{v}_{O_2}$ is shown.

TABLE VI

Oxygen Flow, Binding and Utilization during Initial 24 h after Myocardial Infarction in 49 Subjects

	Class			
	I $n = 14$	II $n = 17$	III $n = 13$	IV $n = 5$
pH_a	7.429±0.013	7.471±0.014	7.432±0.023	7.428±0.043
Hb/HbO_2 (ta)	0.29±0.022	0.40±0.042	0.62±0.12	0.73±0.17
P_{50} std, *torr*	26.9±0.75	28.7±0.91	31.2±0.98	27.1±1.3
P_{50} i.v., *torr*	26.0±0.81	28.0±1.0	31.4±1.1	26.8±1.3
$S\bar{v}_{O_2}$, %	70.6±1.4	63.9±2.7	55.5±4.1	48.6±5.8
OFI_a *ml/min per m^2*	587±35	520±40	434±31	325±64
$\dot{V}_{O_2}$, *ml/min per m^2*	139±8.3	149±12	179±16	148±15

Mean±SE.

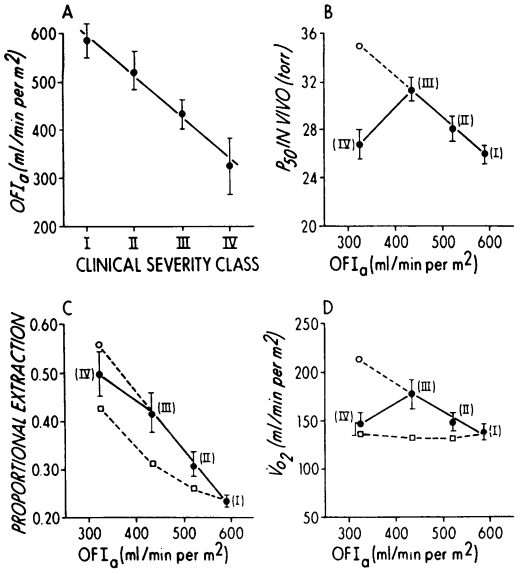

FIGURE 9 A. The arterial oxygen flow rate index (mean±SE) as a function of clinical class. B. The P_{50} in vivo (mean±SE) of each class of patients plotted against the mean OFI_a for each class. The open circle indicates the P_{50} in vivo expected in class IV subjects bas edon a linear extrapolation of the regression line. C. The proportional extraction of oxygen (mean±SE) for each class of subjects plotted against their mean OFI_a. The open circle represents the expected extraction based on the extrapolation of the linear regression. The open squares indicate the mean extraction if $\dot{V}_{O_2}$ in class II, III, and IV subjects was calculated based on the P_{50} in vivo observed in class I subjects. D. Oxygen consumption (mean± SE) for each class of subjects plotted against the mean OFI_a for each class. The open circle indicates the $\dot{V}_{O_2}$ expected in class IV subjects based on the linear extrapolation of the regression line. The open squares indicate the expected mean $\dot{V}_{O_2}$ if P_{50} in vivo of class II, III, and IV subjects was that of class I subjects.

oxygen consumption projected for this group of subjects.

DISCUSSION

We have studied the variables that determine arterial oxygen flow, individually and in combination, to determine the magnitude of their changes and the effect of such changes on oxygen binding by hemoglobin, and oxygen utilization, in patients with myocardial infarction. The association of P_{50} std with hemoglobin concentration, CI, and hemoglobin flow rate in subjects with myocardial infarction studied at least 24 h after onset of symptoms confirmed results reported previously by Woodson and coworkers in subjects with chronic heart failure (9). In fact, the quantitative relationships of P_{50} std with blood hemoglobin, CI, and HFI were virtually identical in our study to those found by Woodson et al.

The dependence of P_{50} std upon hemoglobin concentration in the present study was less than that observed in anemic subjects in our own (25) and other laboratories (26, 27). This is likely due to the fact the blood pH and Hb/HbO_2 ratio were dependent on other variables, as well as hemoglobin concentrations in these subjects. P_{50} std (i.e., red cell 2,3–DPG content) was most strongly associated with Ca_{O_2} and OFI_a and the dependence of P_{50} on OFI_a was significantly greater than on HFI, indicating the additional importance of oxygen saturation of hemoglobin. HFI explained, on the average, 35% of the variation in P_{50}, whereas OFI explained 50% of the variation in P_{50}.

In contrast to the reported results of Kostuk and colleagues (9), the changes observed in P_{50} std in our patients were nearly entirely dependent on changes in red cell 2,3-DPG content. The precise cause of the alterations in red cell 2,3-DPG with reduced arterial oxygen flow has been partially elucidated. Alkalosis in arterial blood was a constant feature in our subjects and correlated with OFI_a and 2,3-DPG. Descriptive studies in man (28, 29) and animals (30) have indicated that an initial respiratory alkalosis in response to altitude hypoxia precedes a later elevation in red cell 2,3-DPG. A strong association of blood pH and red cell 2,3-DPG has also been shown in analytical studies of patients with changes in acid-base balance (25, 31–36). In addition, experimental studies in man have provided evidence of the causal dependence of red cell 2,3-DPG content on blood pH (22, 25, 32). The possible role of elevated pH in modulating rates of enzyme activity leading to the heightened cellular 2,3-DPG levels have been discussed in detail previously (2, 30, 37). Hence, blood pH could have been a causal intermediary between reduced OFI_a and elevated 2,3-DPG. The association of pH with red cell 2,3-DPG in these studies was lower than correlations previously reported by others in various clinical disorders. The effect of pH on red cell 2,3-DPG is time-dependent and hence, the correlation of a single pH value with 2,3-DPG is at best an approximation, especially during an acutely changing clinical disorder. From the considerable evidence relating red cell 2,3-DPG to blood pH, we infer that the elevated blood pH in our subjects contributed to the elevated red cell 2,3-DPG.

When plasma alkalosis is the central stimulus to increased 2,3-DPG elevation, little if any net reduction in oxygen binding by hemoglobin occurs in vivo, since the two opposing effects on red cell pH cancel each other (22, 25). In our studies, although a significant regression of P_{50} in vivo on red cell 2,3-DPG was present, mean P_{50} in vivo for all the study subjects (25.5 torr) was slightly below normal for our laboratory (26.6 torr), despite an increase in mean 2,3-DPG of about 3 μmol/g Hb, due to alkalosis. The significant

regression of P_{50} in vivo on red cell 2,3-DPG was related to the reduced P_{50} in vivo in alkalotic subjects with as yet normal 2,3-DPG concentrations. Hence, temporal factors may have accounted for the residual regression, the surmise being that in time 2,3-DPG accumulation in alkalotic subjects would restore P_{50} in vivo to an approximately normal value (25). Also, the residual regression of P_{50} in vivo may be explicable by the role of the Hb/HbO_2 ratio as a mediator of red cell 2,3-DPG content after myocardial infarction. It has been suggested that the proportion of deoxyhemoglobin in the red cell is an important determinant of red cell 2,3-DPG content (20, 38).

In the present studies Hb/HbO_2 (ta) ratio was significantly correlated with OFI_a and 2,3-DPG. Time-averaging allowed us to approximate the Hb/HbO_2 ratio during transit through venous as well as arterial circulation, since the effect of the ratio on red cell pH and the proportion of 2,3-DPG bound to Hb would be most consequential in venous blood. Although the importance of the proportion of deoxyhemoglobin as a determinant of red cell 2,3-DPG has been noted (20, 38), the mechanism of the effect of the Hb/HbO_2 has not been defined with certainty. Since deoxyhemoglobin is a weaker acid than oxyhemoglobin, the concentration of hydrogen ions in the cell is reduced by desaturation of hemoglobin. Red cell pH increases about 0.025 units as oxygen saturation of hemoglobin falls from 100 to 50% (39). If Hb/HbO_2 ratio operates to increase 2,3-DPG by an elevation of red cell pH, this effect is not considered in the P_{50} in vivo equation, which makes a pH correction based on the effects of plasma pH changes only. This additional correction would reduce the regression of P_{50} in vivo on 2,3-DPG and reduce even further the contribution of decreased affinity to maintenance of oxygen consumption. An additional effect of deoxygenation relates to the role of 2,3-DPG as a modulator of enzyme reactions in the Embden-Meyerhof and Rapoport-Luebering pathways (2, 37). The acceleration of enzymes in these pathways as a result of binding of free 2,3-DPG to deoxygenated hemoglobin has been suggested as an additional contribution to an elevated red cell 2,3-DPG content. Such an effect could decrease affinity without the cost of intracellular alkalosis, although the role of such an effect is speculative.

A proportional increase in the extraction of oxygen resulted in a similar oxygen consumption in the 13 subjects studied prospectively, despite a nearly three-fold variation in OFI_a. The mechanism for the increased extraction could not be fully explained. About one-third of the increase in oxygen removal with decreased OFI_a may have been related to the decrease in hemoglobin-oxygen affinity. This partial effect of affinity change was also evident in the larger group of subjects studied retrospectively, in whom about one-quarter to one-half of the increase in proportional extraction could be explained by affinity changes. However, $\dot{V}_{O_2}$ was maintained at "normal" levels, due to a heightened extraction from a reduced arterial oxygen flow even in the absence of an affinity change. The possible clinical importance of the maintenance of $\dot{V}_{O_2}$ with decreased affinity, as seen in class III subjects, as contrasted to a lower $\dot{V}_{O_2}$ and failure to decrease affinity in class IV subjects, cannot be assessed from our data.

The failure to find an increased mean P_{50} std (i.e. red cell 2,3-DPG) in the clinical class IV subjects could be related to three factors: first, the small number of observations in that group; second, the presence of nonalkalemic subjects; and third, the time required for red cell 2,3-DPG accumulation after alkalosis or arterial blood desaturation (22). Three of the five subjects in class IV were first studied within 26 h of onset of symptoms. We anticipated the analyses of these data would be complicated by important temporal considerations. Even so, it was of interest to examine the usefulness of P_{50} std as an index of severity of infarction by correlating it with class early in the clinical evaluation.

P_{50} std or red cell 2,3-DPG proved to be as good an index of reduced blood flow or oxygen flow rate as $S\bar{v}_{O_2}$ in the 13 subjects studied prospectively. However, these subjects were for the most part in class I or class II (10 of 13), all were alkalotic, and the studies were done, in almost all cases, more than 24 h after onset of symptoms. $S\bar{v}_{O_2}$ appears to be the better of the two variables as an index of reduced OFI_a, since its correlation with OFI_a was not influenced by temporal considerations and did not appear to be affected by the presence or absence of affinity changes (see Table IV). Neither is a highly accurate predictive index of oxygen flow in an individual subject, since the 95% tolerance limits for OFI_a for a given $S\bar{v}_{O_2}$ or P_{50} std are too broad to be used precisely. Nevertheless, serial measurements of $S\bar{v}_{O_2}$ may be of value, as has been previously suggested (26, 27).

It has been suggested that red cell 2,3-DPG or its counterpart P_{50}, measured at pH 7.40 and P_{CO_2} of 40 torr are biochemical indicators of tissue oxygenation (27). The implication is that red cell 2,3-DPG increases as oxygen supply is compromised. This is not necessarily true if alkalosis or marked desaturation is not an accompanying event and if time-dependent changes have not occurred. Alkalosis appears to be a frequent response to reduced arterial oxygen flow rate, whether the latter occurs due to anemia, hypoxia, or low flow. However, in the presence of acidosis, even if Hb/HbO_2 is increased, changes in red cell 2,3-DPG are blunted. This may explain the failure of 2,3-DPG to increase

in certain subjects with hypoxic chronic pulmonary disease (40) and anemic subjects with severe azotemia (25), each of whom are limited in their ability to develop alkalosis in response to reduced OFI_a

The initial hours of myocardial infarction in many subjects appear to be marked by respiratory alkalosis and therefore increased binding of oxygen by hemoglobin. This may impair oxygen delivery before adaptive red cell changes and contribute to the high rate of early complications. Acidosis, on the other hand, impairs the ability of the red cell to generate 2,3-DPG and may compromise a critical aspect of the later adaptation to falling arterial oxygen flow. Further examination of the role of acid-base changes after myocardial infarction should be made to determine what constitutes an optimal metabolic response and whether therapeutic modification of a deleterious response can be made.

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