Coronary Haemodynamic Studies in Chronic Severe Anaemia

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The response of central haemodynamics to chronic severe anaemia in man has been the subject of several studies (Sharpey-Schafer, 1944; Brannon *et al.*, 1945; Leight *et al.*, 1954; Bishop, Donald, and Wade, 1955; Whitaker, 1956; Roy *et al.*, 1963), but its effect on the coronary circulation has received little attention (Bing *et al.*, 1949; Kobelt *et al.*, 1957; Regan *et al.*, 1963). In this communication we report our observations on the coronary haemodynamics in chronic severe anaemia and the haemodynamic response to the correction of the anaemia.

SUBJECTS AND METHODS

Coronary haemodynamic studies performed on 14 patients with anaemia of at least 4 months' duration, and a haemoglobin value of 6.5 g./100 ml. or less (range 1.6 to 6.5 g., average 4.4 g.) form the basis of this report. Anaemia was due to ankylostomiasis in 10 patients, nutritional deficiency in 3 patients, and chronic pyelonephritis with uraemia in 1 patient. The average age of the patients was 24 years (range 14 to 40 years). No patient was in congestive heart failure at the time of study: 8 of them had slight to moderate cardiomegaly; and in 7, non-specific "T" wave changes were seen in the electrocardiogram, which reverted to normal after correction of the anaemia. Patients were kept in the hospital for 8 to 12 weeks until their haemoglobin values became 10.0 g./100 ml. or more. All patients were carefully examined and investigated to rule out evidence of associated cardiovascular disease.

To determine if the haemoglobin level *per se* affects the coronary circulation, patients were arbitrarily divided into two groups: *group A* consisted of 6 patients with a haemoglobin of less than 4.0 g. (average 2.9 g.), and *group B*, between 4.0 to 6.5 g. (average 5.5 g.), consisted of 8 patients (Table I). Eight of the subjects were restudied (2 from group A and 6 from group B) after correction of their anaemia. Control

data were obtained by studying 7 apparently healthy subjects. They were among 28 young people referred to the Cardiac Clinic with vague cardiac complaints but who on careful screening were found to be healthy. The details of coronary blood flow studies were explained to the 28 subjects, their guardians, and their relatives. Only 7 of them (including a woman) volunteered for the study. They were factory apprentices (Cases 1 and 2), school teachers (Cases 3 and 4), and

TABLE I
CLINICAL DETAILS OF NORMAL SUBJECTS AND ANAEMIC PATIENTS STUDIED

Case No.	Age (yr.)	Sex	Body surface area (m. ²)	Hb (g./100 ml.)	Duration of symptoms (mth.)
Normals (7)					
1	20	M	1.54	14.1	—
2	18	M	1.74	13.9	—
3	28	F	1.36	12.9	—
4	40	M	1.63	13.0	—
5	30	M	1.50	15.2	—
6	25	M	1.68	15.6	—
7	28	M	1.72	15.2	—
Average	27		1.59	14.3	
Anaemia Group A (6)					
8	22	M	1.56	1.6	36
9	25	M	1.40	2.4	16
10*	25	M	1.32	3.0	10
11*	28	M	1.20	3.5	4
12	35	M	1.52	3.5	8
13	19	M	1.40	3.7	6
Average	27		1.40	2.9	13.3
Anaemia Group B (8)					
14*	22	F	1.46	4.7	11
15	40	M	1.22	4.8	60
16	20	M	1.58	5.0	21
17	14	M	1.28	5.1	8
18	22	M	1.48	6.0	12
19†	22	M	1.44	6.1	6
20	28	M	1.54	6.1	9
21	19	F	1.43	6.4	8
Average	22		1.43	5.5	16.9

* Patients with megaloblastic anaemia.

† Patient with uraemia and normocytic anaemia.

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sedentary workers (Cases 5, 6, and 7). No financial inducement was offered to the volunteers.

Studies were carried out in a fasting state without sedation. Right heart catheterization was performed by the usual technique, using Goodale-Lubin catheters. A peripheral artery was cannulated with a Stille's needle for arterial blood samples and pressures. Cardiac output was estimated by the Fick's method. Oxygen content of the blood was estimated by the method of Van Slyke and O'Neill (1924). Intracardiac and intravascular pressures were obtained through Statham P23 AA strain gauge manometers, and recorded on a multichannel single gun photographic recorder. Mean pressures were obtained by electronic integration. The baseline for all pressure measurements was taken as half the chest thickness at the second costal cartilage with the patient supine (Roy, Gadbois, and Dow, 1957).

For the determination of coronary flow, the catheter was placed in the coronary sinus in a deep enough position to enable sampling of unmixed coronary sinus blood. The nitrous oxide desaturation method of Goodale and Hackel (1953) was employed, wherein a partition coefficient of 1.0 for nitrous oxide and myocardium was assumed for the measurement of coronary blood flow. Other parameters were obtained by using the following formulae (Goodale and Hackel, 1953; Gorlin, 1960; Gorlin *et al.*, 1964):

severe anaemia (average 159 ml., range 109–222 ml./100 g. LV/min.) when compared to normal subjects (average 80 ml., range 69–90 ml./100 g. LV/min.). The increase was greater in group A than in group B patients (average values 189 ml. versus 133 ml./100 g. LV/min.). High coronary blood flow in anaemic patients was inversely related to the haemoglobin level (Fig. 1) and directly related to the high cardiac index (Fig. 2). The coronary blood flow when expressed as a fraction of the cardiac output was similar in groups A and B and in normal subjects (1.7%, 1.7%, and 1.6%, respectively). Coronary vascular resistance was lower than normal in patients with severe anaemia, the decrease being greater in group A than in group B. An inverse correlation was evident between the coronary blood flow and coronary vascular resistance (Fig. 3).

Oxygen Data (Table II). As compared to normal subjects, the oxygen content of the coronary sinus blood was lower in patients with anaemia, the reduction being greater in group A. The peripheral arterial blood was normally saturated. The coronary sinus blood oxygen content and the

Coronary diastolic vascular resistance (units)	=	$\frac{\text{Peripheral arterial diastolic mean pressure (mm. Hg)} - \text{coronary sinus mean pressure (mm. Hg)} \times \text{diastolic filling period (sec./min.)}}{\text{Coronary blood flow (ml. 100 g. LV/min.)} \times 0.75}$ 0.75 = fraction of total coronary flow in diastole
Myocardial oxygen consumption ml./100 g. LV/min.	=	$\text{Coronary blood flow (ml./100 g. LV/min.)} \times \text{coronary arteriovenous oxygen difference (vol. \%)}$
Myocardial oxygen extraction coefficient	=	$\frac{\text{Arterial O}_2 \text{ content (vol. \%)} - \text{coronary sinus O}_2 \text{ content (vol. \%)}}{\text{Arterial O}_2 \text{ content (vol. \%)}}$
Oxygen utilization coefficient	=	$\frac{\text{O}_2 \text{ cost per sec. contraction (ml.)}}{\text{Left ventricular work (kg.m./min.)}}$
Where		
Oxygen cost per second of contraction	=	$\frac{\text{Myocardial O}_2 \text{ consumption ml./100 g. LV/min.}}{\text{Systolic sec./min.}}$
Left ventricular work index (kg.m./min./m. ²)	=	$\frac{(\text{Left ventricular systolic mean pressure (mm.)} - \text{left ventricular filling pressure}) \times \text{cardiac index (l./min./m.}^2) \times 1.36}{100}$
Mechanical efficiency index	=	$\frac{\text{Left ventricular work index (kg.m./min./m.}^2)}{\text{Myocardial O}_2 \text{ consumption (ml./100 g. LV/min.)} \times 2.06}$ where 2.06 = energy equivalent of 1 ml. O ₂ in kg.m.

Identical techniques were employed for restudy of the 8 patients, after correlation of their anaemia when their average Hb value was 13.0 g. (range 10.1 to 14.1 g.). The interval between the initial and restudy ranged from 34 to 94 days (average 55 days).

RESULTS

Coronary Blood Flow and Coronary Vascular Resistance (Table II). The coronary blood flow was significantly raised in patients with chronic

oxygen extracted by the myocardium were inversely related to the increased coronary blood flow (Fig. 4 and 5), the higher coronary blood flows being recorded in patients with lower coronary sinus blood oxygen content and in whom less oxygen was extracted by the myocardium.

The oxygen extraction coefficient was normal in group B patients, and slightly increased in group A. But the myocardial oxygen utilization coefficient deviated considerably from normal. It was

FIG. 1.—Distribution of coronary blood flow in 14 patients with chronic severe anaemia, as determined by nitrous oxide desaturation technique. The open circles are 6 cases in Group A with haemoglobins below 4 g./100 ml., and closed circles are 8 cases in Group B whose haemoglobin level was between 4.0 to 6.5 g./100 ml.

FIG. 2.—Satisfactory correlation between coronary blood flow (CBF) and cardiac output expressed per square metre of body surface area.

0.024 and 0.045, respectively, for group A and B patients as compared to 0.103 for normal subjects. In general the reduction was proportionate to the degree of anaemia, patients with the severest grades

of anaemia showing the greatest deviation of oxygen usage (Fig. 6).

Myocardial oxygen consumption of 5.42 and 6.52 ml./100 g. LV/min. in group A and B patients,

FIG. 3.—Inverse relation between coronary blood flow and coronary vascular diastolic resistance.

FIG. 4.—Coronary blood flow (CBF) correlated to oxygen content of the coronary sinus blood.

TABLE I
CORONARY HAEMODYNAMIC PARAMETERS IN

Case No.	Heart rate (beats/min.)	Cardiac index (l./min./m. ²)	Stroke index (ml./beat/m. ²)	Periph. artery		Coron. sinus		Coron. blood flow (ml./100 g. LV/min.)
				O ₂ content (vol. %)	O ₂ satn (%)	O ₂ content (vol. %)	O ₂ satn (%)	
1	72	3.4	47	12.12	96	6.90	36	Normal
2	84	3.9	46	17.00	92	5.95	32	89
3	68	3.1	46	17.00	98	3.50	20	90
4	92	3.1	34	16.92	97	5.36	31	87
5	64	3.0	47	19.82	97	7.89	39	74
6	74	3.0	41	20.16	96	7.92	38	75
7	70	2.8	40	20.01	98	6.67	33	68
Average	75	3.1	43	18.43	95	6.31	33	80
SD	—	± 0.37	± 4.9	—	—	—	± 6.38	± 8.67
SEM	—	0.14	1.85	—	—	—	2.41	3.28
8	96	11.0	115	2.10	98	0.36	17	Anaemi
9	75	8.2	109	2.92	92	0.66	21	222
10*	98	5.6	57	3.78	94	1.08	27	198
11*	96	7.4	75	4.53	96	0.91	29	160
12	75	7.8	104	4.40	93	0.90	19	193
13	100	10.0	100	4.47	90	0.73	15	208
Average	90	8.3	93	2.10	94	0.36	21	189
SD	± 11.76	± 1.73	± 22.5	—	—	—	± 5.59	± 27.5
SEM	5.26	0.86	9.8	—	—	—	2.28	11.23
p value	< 0.07	< 0.01	< 0.01	—	—	—	< 0.05	< 0.01
14*	104	5.5	53	6.10	97	2.00	32	Anaemi
15	78	6.6	83	6.12	95	3.05	47	155
16	75	4.3	57	6.60	98	1.38	19	139
17	98	6.7	68	6.39	94	1.85	27	136
18	80	5.8	72	7.23	90	1.86	23	177
19†	98	5.0	51	8.02	98	2.52	31	121
20	75	4.9	65	7.90	91	2.16	26	109
21	75	5.5	73	7.93	92	1.40	16	140
Average	85	5.5	65	7.04	95	2.03	28	138
SD	± 12.36	± 8.3	± 11.0	—	—	—	± 9.57	± 21.4
SEM	4.38	0.29	3.90	—	—	—	3.38	7.55
p value	—	< 0.01	< 0.01	—	—	—	—	< 0.01

* Patients with megaloblastic anaemia.

† Patient with uraemia and normocytic anaemia.

respectively, was considerably less than the value obtained for normal subjects (9.62 ml./100 g. LV/min.). The 7 patients with ischaemic "T" wave changes in the electrocardiogram had lower myocardial oxygen consumption (average, 5.39 ml./100 g. LV/min.) as compared to those with a normal electrocardiogram (average 6.71 ml./100 g. LV/min.). A direct correlation was evident between depressed myocardial oxygen consumption and haemoglobin level in anaemic patients (Fig. 7). Coronary blood flow, on the other hand, was more or less inversely related to the oxygen consumed by the myocardium (Fig. 8). This was more marked in group A than in group B.

Ventricular Work and Mechanical Efficiency of Left Ventricle. Left ventricular work index in all patients with anaemia was greater than normal (4.52 kg. m./min.), the work index for group A (11.48 kg. m./min.) being more than for group B

(6.99 kg. m./min.) patients. Since the arterial systolic mean pressures of these patients and the normal subjects were the same, this increase in the work index was due to increased cardiac output. Because of increased left ventricular work index, and a reduction of myocardial oxygen consumption, the mechanical efficiency index of anaemic patients was high (79% as compared to the normal average of 23%). Like ventricular work, the mechanical efficiency was higher with severer grades of anaemia (group A—110%, group B—55%).

Changes in Coronary Circulation after Correction of Anaemia (Table III). Coronary blood flow re-estimated in 8 subjects when their haemoglobin values increased to 10.1 to 14.1 g./100 ml. was invariably lower than pretreatment values (Fig. 9). However, the flow was still slightly higher (average 87 ml., range 76–94 ml./100 g. LV/min.) than that of normal subjects (average 80 ml., range 68–90

I

NORMAL SUBJECTS AND ANAEMIC PATIENTS

	Myocardial O ₂ cons. (ml./100 g. LV/min.)	Coron. vasc. diast. resist. (units)	O ₂ EC	O ₂ UC (ml. O ₂ /syst. sec./kg.m.)	LV work index (kg.m./min./m. ²)	ME index (LV) (0/0)
7)	10.04 9.94 11.74 8.55 8.94 8.32 10.13	44 44 50 61 44 67 50	0.62 0.65 0.79 0.68 0.60 0.61 0.66	0.108 0.112 0.133 0.085 0.098 0.078 0.107	4.90 5.25 4.05 4.38 4.12 4.81 4.11	24 26 17 25 22 29 20
	9.67 ± 1.22 0.46	51 ± 9.17 3.46	0.66 ± 0.065 0.025	0.103 ± 0.015 0.007	4.52 ± 0.61 0.23	23.0 ± 4.0 1.51
Group A (6)	3.84 4.46 4.32 6.99 7.28 5.65	13 14 19 21 14 33	0.83 0.77 0.71 0.80 0.79 0.84	0.013 0.017 0.026 0.031 0.045 0.014	13.76 13.05 6.78 9.06 8.59 17.68	173 142 75 63 57 152
	5.42 ± 1.48 0.61 < 0.01	19 ± 7.56 3.08 < 0.01	0.78 ± 0.047 0.019 0.01	0.024 ± 0.012 0.005 < 0.01	11.48 ± 4.05 1.66 < 0.01	110 ± 51.96 21.22 < 0.01
Group B (8)	6.35 4.27 5.73 6.23 6.50 7.08 8.03 7.97	20 39 24 22 28 45 23 36	0.67 0.50 0.64 0.55 0.74 0.68 0.73 0.82	0.038 0.031 0.076 0.041 0.040 0.035 0.056 0.044	6.58 9.87 4.15 5.92 7.89 8.36 6.53 6.66	50 112 35 46 59 57 40 41
	6.52 ± 1.22 0.43 < 0.01	30 ± 9.22 3.26 < 0.01	0.67 ± 0.11 0.04	0.045 ± 0.014 0.005 < 0.01	6.99 ± 1.69 0.60 < 0.05	55 ± 24.17 8.65 < 0.05

O₂ EC, oxygen extraction coefficient of left ventricle.
O₂ UC, oxygen utilization coefficient of left ventricle.
ME index, myocardial efficiency index of left ventricle.

ml./100 g. LV/min.). The reduction of coronary blood flow after correction of anaemia ranged from 17.5 to 57 per cent (average 42%). Similarly, average cardiac index value decreased from 5.8 to 3.6 l./min./m.² Coronary vascular resistance increased *pari passu* with decrease of coronary blood flow and returned to almost normal levels. The average post-treatment value was 48 units (range 40–66 units) as compared to 51 (range 44–67) for the normal subjects. Coronary sinus blood oxygen content and oxygen saturation returned to within the normal range after the correction of anaemia.

Myocardial oxygen consumption also returned towards normal level in these 8 patients. It was well within the normal range in 5 patients, but in 3 others the myocardial oxygen consumption was still lower than normal (7.28 ml., 8.09 ml., and 8.06 ml.). This was not related to haemoglobin levels at the time of restudy, since these three

patients had haemoglobin values of 13.3, 14.0, and 10.1 g., respectively. Left ventricular work index decreased considerably (average reduction of 30.5% after correction of anaemia). The post-correction myocardial efficiency index averaged 26 per cent as compared to 63 per cent before treatment (a reduction of 58.7%), and approached the normal myocardial efficiency index of 23 per cent.

DISCUSSION

From the data presented, it appears that long-standing severe degree of anaemia is associated with increased coronary blood flow, as estimated by the nitrous oxide desaturation technique. Similar observations have been made in a smaller number of patients by Bing *et al.* (1949), Kobelt *et al.* (1957), and Regan *et al.* (1963). However, coronary blood flow at high flow rates when estimated by nitrous oxide technique is to be interpreted cautiously,

TABLE
PRE- AND POST-TREATMENT STUDIES OF

Case No.	Hb (g./100 ml.)	Heart rate (beats/min.)	Cardiac index (l./min./m. ²)	Stroke index (ml./beat/m. ²)	Periph. artery		Coron. sinus	
					O ₂ content (vol. %)	O ₂ satn (%)	O ₂ content (vol. %)	O ₂ satn (%)
9	B 2.4	75	8.2	109	2.92	98	0.66	21
	A 14.0	70	3.9	56	18.79	99	7.87	41
10	B 3.0	98	5.6	57	3.78	94	1.08	27
	A 13.3	75	3.3	44	17.45	98	8.00	45
14	B 4.7	104	5.5	53	6.10	97	2.00	32
	A 12.2	75	4.1	55	15.78	97	3.58	22
16	B 5.0	75	4.3	57	6.60	98	1.38	19
	A 14.1	75	3.0	40	18.25	96	5.80	31
17	B 5.1	98	6.7	68	6.39	94	1.85	27
	A 14.0	76	4.7	62	17.86	95	7.22	38
18	B 6.0	80	5.8	72	7.23	90	1.86	23
	A 13.4	72	3.3	46	16.94	94	5.77	32
19	B 6.1	98	5.0	51	8.02	98	2.52	31
	A 10.1	78	3.8	49	12.87	95	3.92	29
20	B 6.1	75	4.9	65	7.90	96	2.16	26
	A 13.2	70	2.9	41	16.84	95	4.55	26
Average	B 4.5	88	5.8	87	6.12	96	1.69	26
p value	A 13.0	74	3.6	49	16.82	96	5.84	33

B—Before treatment.
A—After treatment.

because of the possible lesser reliability of complete desaturation of the gas under such circumstances. But as 8 of the patients were restudied and acted as their own control, and as normal data were obtained from 7 healthy normal volunteers, the present results appear reliable. The increase in coronary blood flow could generally be related to the haemo-

globin levels, severer grades of anaemia having larger flows. It should, however, be noted that patients with almost similar haemoglobin values had different (though always increased) coronary blood flow. Thus, Cases 11, 12, and 13, with haemoglobin values of 3.5, 3.5, and 3.7 g./100 ml., had coronary blood flows of 193, 208, and 151

FIG. 5.—Coronary blood flow values plotted against amount of oxygen extracted by the left ventricular myocardium expressed in volume per cent. The oxygen extracted by the myocardium has been taken as the difference in the oxygen content values between the peripheral arterial and the coronary sinus blood.

FIG. 6.—The oxygen utilization coefficient (expressed as a ratio of oxygen cost per second of contraction to the left ventricular work) is related to the haemoglobin level of the patient.

II

CORONARY CIRCULATION IN CHRONIC SEVERE ANAEMIA

Coron. blood flow (ml./100 g. LV/min.)	Myocard. O ₂ cons. (ml./100 g. LV/min.)	Coron. vasc. diast. resist. (units)	O ₂ EC	O ₂ UC (ml. O ₂ /syst. sec./ kg.m. ²)	LV work index (kg.m./min./m. ²)	ME index (%)
198	4.46	14	0.77	0.017	13.05	142
94	10.26	43	0.58	0.128	5.36	25
160	4.32	19	0.71	0.026	6.78	75
77	7.28	40	0.53	0.075	4.44	30
155	6.35	20	0.67	0.038	6.58	50
99	12.07	41	0.71	0.138	5.24	17
136	5.73	24	0.64	0.076	4.15	35
84	10.44	59	0.68	0.109	4.49	21
177	6.23	22	0.55	0.041	5.92	46
76	8.09	42	0.60	0.124	4.35	26
121	6.50	28	0.74	0.040	7.89	59
80	8.80	45	0.66	0.097	4.80	26
109	7.08	45	0.68	0.035	8.36	57
90	8.06	66	0.69	0.061	7.87	47
140	8.03	23	0.77	0.056	6.53	40
94	11.55	44	0.73	0.123	4.69	20
150	6.09	24	0.69	0.041	7.41	63
87	9.57	48	0.65	0.108	5.15	26
<0.01	<0.01	<0.01		<0.01	<0.04	<0.02

ml./100 g. LV/min., respectively. Hence, it was possible to qualitate, but not to quantitate, the coronary flow from the haemoglobin level. The inverse correlation between coronary blood flow and decreased levels of haemoglobin has also been reported by Guz, Kurland, and Freedberg (1960) and Regan *et al.* (1963) in experimental animals.

Though the coronary blood flow was much greater than normal in absolute quantity, this increase was proportional to the increase in the cardiac output. Hence, coronary blood flow when expressed as a

fraction of the cardiac output was almost the same in anaemic patients as in normal subjects. A similar relation between hepatic blood flow and cardiac output was seen in chronic severe anaemia (Roy, Bhatia, and Joseph, 1966). This was in contrast to the marked reduction in effective renal blood flow, and renal blood flow to cardiac output ratio in chronic severe anaemia (Roy *et al.*, 1966). These preferential flows probably indicate selective alterations of the vascular resistance in different organs. However, in discussing the coronary circulation

FIG. 7.—A satisfactory relation is seen between left ventricular myocardial oxygen consumption ($\dot{MVO}_2$) and haemoglobin level.

FIG. 8.—Coronary blood flow is plotted against the myocardial oxygen consumption. Generally, the higher the flow, the less the oxygen consumption.

FIG. 9.—Relation of coronary blood flow to haemoglobin level in 8 subjects before and after the treatment of anaemia. The area between the broken lines is the range of normal values.

the apparent constancy of coronary blood flow to cardiac output ratio has to be viewed guardedly, as the coronary blood flow for the entire left ventricle is not known because the nitrous oxide method only estimates flow per unit weight of left ventricle. Left ventricular hypertrophy is known to occur in chronic severe anaemia (Porter, 1937; Norman and McBroom, 1958; Paplanus, Zbar, and Hays, 1958), and it is quite possible that the total coronary blood flow might be much larger. If this is so, the extra increment in flow when related to the cardiac output will result in a new ratio in favour of the coronary flow. Without the knowledge of the left ventricular weights, this assumption remains a speculation.

The coronary blood flow in anaemic subjects with inversion of "T" wave in the electrocardiogram was on an average lower than in the group without these electrocardiographic changes. None of these patients gave a history of angina pectoris. The exact reason for this difference is not clear. The relatively young age of these patients makes it unlikely that significant coronary artery disease was responsible for less than the expected increase of coronary blood flow. Nor could the difference be related to the degree, type, or duration of anaemia. Since no metabolic or enzyme studies were carried out, the role of these factors as determinants of increased coronary blood flow cannot be elucidated. One of the determinants of increased

coronary blood flow in anaemia was the marked reduction in the coronary vascular resistance. Its exact mechanism is not clear. Regan *et al.* (1963) felt that reduced red cell mass and attendant changes in viscosity of the blood were important regulatory mechanisms of coronary blood flow in anaemia. Others have suggested the importance of the local effect of hypoxia and the action of locally or peripherally generated vasodilator substances (Hilton and Eichholtz, 1925; Guz *et al.*, 1960; Berne, Blackmon, and Gardner, 1957; Hellemis *et al.*, 1957). The diminished resistance was an important determinant factor for a large increase in the coronary blood flow, with normal perfusion pressure head. In an effort to maintain normal oxygen delivery to the myocardium, increased coronary blood flow was the major compensatory mechanism in chronic severe anaemia. However, in very severe grades of anaemia, besides an increase in the coronary blood flow, an additional mechanism appeared to be an increase in the extraction of the oxygen by the myocardium, as evidenced by the increased oxygen extraction coefficient. This is in contrast to observations by Regan *et al.* (1963) who did not find any changes in oxygen extraction coefficient in anaemia. Gorlin *et al.* (1964) observed coronary venous oxygen saturation to decrease with exercise in patients with angina pectoris due to coronary artery disease. This decrease which occurred in association with some increase of coronary blood flow and slight decrease of coronary vascular resistance was interpreted by them as an indication of an anatomically inadequate coronary circulation. Though coronary artery disease cannot be entirely excluded in our patients, it would be unlikely because of their youth. A conspicuous increase in the coronary blood flow, with greater than normal unsaturation of coronary sinus blood in severely anaemic subjects, may indicate that the vasodilating capacity of the coronary vascular bed has been exceeded, and increased oxygen extraction may be regarded as an additional mechanism for the supply of extra oxygen to the myocardium.

On the other hand, diminished myocardial oxygen consumption in the anaemic subjects needs some scrutiny. The left ventricular work index in these patients was very high and it would be expected that the oxygen consumption would be proportionately increased. The increased work load in anaemia is probably a volume load, and may be partly responsible for this observation, since it is known that volume loads cause a proportionately smaller increase of myocardial oxygen consumption than work load against increased resistance (Sarnoff *et al.*, 1958). Nevertheless, left ventricular

muscular hypertrophy has been observed in chronic severe anaemia (Porter, 1937; Norman and Mc-Broom, 1958; Paplanus *et al.*, 1958). On the other hand, myocardial function may not closely correlate with oxygen usage, as has been observed in other situations. Perfusion of the canine heart with lactate solution reduces oxygen consumption without change of myocardial function, as measured by the product of heart rate and arterial pressure (Feinberg, Katz, and Boyd, 1962). Lipaemia in experimental animals and man is also known to reduce myocardial oxygen consumption without altering left ventricular function (Kuo *et al.*, 1960; Regan *et al.*, 1961). Also, during conspicuous arterial hypoxaemia myocardial efficiency of the left ventricle rises without a decline in left ventricular function (Hellems *et al.*, 1957; Katz, 1959). Regan *et al.* (1963) suggested that altered oxidative metabolism in the cardiac tissue of subjects with iron-deficiency anaemia because of diminished enzyme activity might be responsible for lower oxygen usage by the myocardium. Diminished enzyme activity has been found in studies of iron deficiency (Beutler, 1959). This, however, does not explain the reduced oxygen usage by the myocardium in patients with non-iron deficiency anaemia. In addition, the greater oxygen extraction from coronary sinus blood seen in severely anaemic group A patients indicates an actively working oxidative enzyme system. The problem in anaemic patients thus appears to be in the maintenance of adequate coronary blood flow rather than in diminished oxygen extraction from the available blood. It can be calculated that even if 100 per cent oxygen was extracted from the coronary sinus blood, severely anaemic patients would require severalfold increase of coronary blood flow, which may not be possible even with maximal dilatation of a normal coronary bed. It is possible that in such a situation anaerobic pathways of energy provision for the myocardium might become operative as an alternative or additional mechanism. That, under some circumstances, such mechanisms do operate is seen in subjects with coronary artery disease where anaerobic energy is developed during the stress of effort (Guz *et al.*, 1960). Since biochemical data were not included in the present study, the anaerobic energy cannot be proved. Very high left ventricular mechanical efficiency calculated in the study may be partly fallacious, because if left ventricular mass increases in chronic severe anaemia, then total myocardial oxygen consumption would be higher and the efficiency would thus not be so high. A real increase in efficiency might be present because of possible anaerobic myocardial metabolism. Left ventricular work of patients with chronic

severe anaemia was high. This increase was mainly due to an increase in the cardiac output, since the arterial systolic mean pressure was normal. The cardiac index was determined in the present study by Fick's method, and some error in determination of arteriovenous oxygen difference at these low levels of haemoglobin cannot be ruled out. However, in previous studies from this laboratory a satisfactory correlation of cardiac output by both Fick's and indicator dilution method in normal subjects and patients with anaemia has been seen (Roy, Virmani, and Bhatia, 1961; Roy *et al.*, 1963).

Changes in coronary circulation in chronic anaemia are temporary and completely reversible. This was evident from the results of restudy of patients after correction of their anaemia. Coronary blood flow decreased and returned to normal or near normal levels. Myocardial oxygen extraction, oxygen usage, left ventricular work, and left ventricular mechanical efficiency also approached normal values. Similar reversibility of changes in the central haemodynamics in treated patients of chronic severe anaemia has been previously reported (Roy *et al.*, 1963).

SUMMARY

Data on the coronary haemodynamic studies performed in 14 patients with chronic severe anaemia are given. Increased coronary blood flow appears to be the major compensatory mechanism to maintain normal oxygen delivery to the myocardium. The diminished vascular resistance and blood viscosity (severity of anaemia) can be related to the increased coronary blood flow. An additional mechanism for increasing the oxygen supply to the myocardium appears to be an increase in the extraction of oxygen by the myocardium as evidenced by increased oxygen extraction coefficient. The possibility of utilization of anaerobic energy for the increased mechanical efficiency of the left ventricle is postulated.

Restudy data after correction of the anaemia show that the changes observed in coronary haemodynamic parameters during anaemia are completely reversible.

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