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THE IDIOPATHIC HIGH CARDIAC OUTPUT STATE *

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The high cardiac output state has occasioned much interest in recent years, particularly when associated with clinical heart failure. The etiology of a high cardiac output is often clinically obvious or easily ascertained by pertinent laboratory tests. Most persistent elevations of cardiac output can be attributed to arteriovenous fistulae, to arterial anoxemia or anemia, or to metabolic or hormonal alterations in vasomotor tone and blood flow distribution. Isolated elevations of blood flow unexplained by these mechanisms can usually be related to the occurrence of anxiety at the time of study (1).

Although a discrete alteration in the "set" of the regulatory mechanism for cardiac output has yet to be described, disturbances of the mechanism for the regulation of heart rate (2) and blood pressure (3) are well known. On the other hand, almost every cardiovascular laboratory has seen an occasional patient in whom cardiac output is persistently and inexplicably increased. It is the purpose of this report to present a group of individuals who show in association a persistently elevated cardiac output, cardiac murmur and cardiac hypertrophy. No specific etiology for these changes could be demonstrated by known clinical or laboratory methods. The patients came to our attention initially either because of the presence of unexplained cardiac murmurs detected on routine physical examination¹ or because of abnormal electrocardiograms.

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¹ The authors are deeply indebted to Dr. J. C. Wells of the Harvard University Department of Hygiene who re-

MATERIALS AND METHODS

Eight patients were studied. A complete history was obtained and physical examination performed. A 12-lead electrocardiogram, urinalysis and chest X-ray and fluoroscopy were obtained; and the hematocrit and blood urea nitrogen determined. Cardiac catheterization was carried out in all with measurement of pulmonary and systemic pressures. Left to right intracardiac shunts were sought by analysis of oxygen or nitrous oxide samples (4) drawn consecutively from the pulmonary artery, right ventricle, right atrium, venae cavae and innominate vein. Cardiac output was measured during the catheterization by the direct Fick method. Repeat outputs were obtained on at least one and usually two or more subsequent occasions, utilizing both continuous sampling and external surface counting direct writing isotope (¹²⁵I albumin) dilution techniques (5).

A total of 30 measurements of cardiac output was made in eight individuals during the resting state. Values were recorded during a four minute exercise period in six patients and 10 minutes after *recovery* from effort, at which time pulse rate was at or below pre-exercise levels. Outputs were estimated one to two hours following sedation in five patients. In addition, in five patients cardiac outputs were determined only after nighttime sedation had been followed by a four to five hour period of rest (or sleep) in a darkened room free of auditory and visual stimuli. The brachial arterial pressure curve was recorded on at least two occasions with measurements of phasic and mean pressures and the duration of systolic ejection. Arterial pH, pCO₂ and O₂ saturations were determined (6); blood lactates and pyruvates were analyzed² (7, 8); thyroid function was studied by means of basal metabolic rate, 24 hour ¹²⁵I uptake and measurement of protein-bound iodine. Blood catechol amines² were measured by the Aronow and Howard modification of the method of Weil-Malherbe and Bone (9, 10) at rest and on exercise. Calculations of cardiac work and peripheral vascular resistance were carried out as described elsewhere (4).

ferred two of the patients and aided in their follow-up. Dr. Lewis Dexter graciously permitted us to report data on two patients studied in his laboratory.

² The authors are grateful to Drs. Dale Friend and Albert Renold of the Harvard Medical School through whose laboratory assistance we were able to obtain catechol amine levels and lactate-pyruvate studies.

TABLE I
Clinical, ECG and X-ray findings in patients with idiopathic high output state

	G. S.	R. L.	L. P.	R. A.	R. R.	B. H.	T. M.	A. N.	Total
Clinical examination									
Related symptoms	0	0	0	0	0	+	0	+	2/8
Systolic murmur:									
Duration	1 yr.	19 yrs.	6 wks.	15 yrs.	2 yrs.	42 yrs.	24 yrs.	10 yrs.	
Location and radiation	LSB* to base	3 LIS† to rt. P-C‡	LSB to apex + base	base	LSB to apex	apex to P-C	3 LIS to base + P-C	LSB to base + apex	
Characteristics	short mid-systolic	blowing pan-systolic	blowing early systolic	blowing pan-systolic	short mid-systolic	blowing pan-systolic	short high-pitched systolic	rough pan-systolic	
Grade	II	III	II	III	II	IV	IV	III	
Overactivity:									
Carotid artery	+	N	+	+	+	+	+	+	7/8
Left ventricle	N	+	+	+	N	+	+	+	6/8
Right ventricle	N	N	N	N	N	+	N	+	2/8
Systolic hypertension	+	+			+			+	4/8
ECG									
Right ventricular hypertrophy						+			1/8
Incomplete right bundle branch block		+					+	+	3/8
Left ventricular hypertrophy	+		+	+	+		+	+	6/8
X-ray									
Cardiac enlargement						+		+	2/8
Right ventricular prominence						+	+	+	3/8
Left ventricular prominence					+		+	+	3/8
Pulmonary artery prominence					+	+	+	+	4/8
Pulmonary vascular prominence	+				+	+	+	+	5/8

* LSB = left sternal border.

† LIS = third left intercostal space.

‡ P-C = precordium.

Subjects

All were males between the ages of 17 and 48 with an average age of 27 years. One patient had associated mild mitral stenosis, atrial fibrillation and disabling pulmonary symptoms. Of the remaining seven patients, only one (A. N.) had symptoms referable to the heart. He had moderate exertional dyspnea and fatigue and was the patient with the greatest cardiac enlargement; he also showed electrocardiographic evidence of combined ventricular involvement. All eight patients could be characterized as "anxious" but, nevertheless, effective individuals. One was a trained athlete, and three were engaged actively in sports. Patients T. M., R. L. and B. H. have had known heart murmurs since childhood.

The patients as a group were well-developed, well-nourished individuals with normal eating

habits and average diets and, excluding the patient with mitral stenosis, revealed the following physical findings. A precordial systolic murmur varying from Grade II to IV³ was heard in all patients; the murmurs varied in locale somewhat but were loudest along the left sternal border with frequent radiation to the base or apex; the quality and configuration of systolic murmur varied from patient to patient (Table I). Position and respiration had no consistent effect, while effort increased the intensity of the murmur. A right ventricular (left sternal border) heave was noted in two, a forceful apical thrust (left ventricular overactivity) in six, and hyperactivity of the carotid arteries in seven. Blood pressure was noted to be labile from examination to examination, and four of the individuals showed a moderate systolic hypertension. No bruits were noted over any of

³ Graded on a scale I to VI.

TABLE II
Special laboratory tests in patients with high cardiac output

Patient	Hemato- crit	Total blood volume	Protein- bound iodine	Systemic arterial			Plasma catechol amines		Lactate	Pyruvate	Cold pressor test
				pH	p CO ₂	O ₂ sat.	Epi- nephrine	Norepi- nephrine			
		L./M. ³	μg./ 100 ml.		mm. Hg	%	μ/L.	μ/L.	mg./ 100 ml.	mg./ 100 ml.	
G. S.	48	2.5	4.0	7.37	34	94	5.7	1.2	8.6	0.48	+
R. L.	47	3.8	4.8	7.42		97	0.3	1.5	10.6	0.5	+
L. P.	50	2.7		7.36	40	96					
R. A.	45	3.3	5.4	7.40	34	96	0.9	3.2	8.2	0.23	+
R. R.	38	3.2	3.0	7.43	32	95	0	1.1	7.6	0.46	neg.
B. H.	45		24%*			92					
T. M.	50	2.7	5.0	7.39	42	97	1.0	2.2	12.3	0.39	+
A. N.	43	4.3	6.0	7.39	35	97	1.5	6.7	15.9	0.47	+
Average	46	3.2	4.6	7.39	36	95	1.2	2.4	10.5	0.42	5/6

* Twenty-four hour I¹³¹ uptake.

the limbs or visceral organs, and there was no evidence of skin or mucous membrane angiomas. Electrocardiographic examination (Table I) revealed right ventricular hypertrophy⁴ in one; in-

⁴ Right ventricular hypertrophy was indicated by right axis deviation, R/s quotient greater than one in V₁, and associated T wave changes. Incomplete right bundle branch block was evidenced by a polyphasic ventricular complex (type r s R', RsR', and so forth) with a duration of less than 0.12 second in right precordial leads. Left ventricular hypertrophy was inferred from increased voltage (QRS greater than 26 mm. in V₆ or V₅ or S_{V₁}, plus R_{V_{5 or 6}} greater than 35 mm.) and delayed intrinsicoid deflection in left precordial leads (11). Three of the cases with left ventricular hypertrophy showed the slightly elevated, upwardly concave ST segments and peaked T waves in the left precordium that have been described as "diastolic overloading" (12).

complete right bundle branch block⁴ in three and left ventricular hypertrophy⁴ in six. In Patient T. M. hypertrophy had been known to be present for 13 years. It is perhaps of greatest importance that in no patient was the electrocardiogram entirely within normal limits. X-ray examination (Table I) revealed a normal size heart in six of the eight patients. The patient with mitral stenosis (B. H.) showed enlargement in the typical mitral configuration. The eighth case (A. N.) revealed generalized cardiomegaly with enlargement of both right and left ventricles and marked pulmonary arterial plethora. Prominence of the right ventricle, as indicated by shouldering in the left anterior oblique view and contiguity of half of the cardiac silhouette with the anterior chest

TABLE III
Hemodynamic data at rest during cardiac catheterization in patients with high cardiac output

Patient	Age	Body surface area	Oxygen con- sump- tion	Arterio- venous oxygen differ- ence	Cardiac index	Heart rate	Stroke index	Brachial artery		Systemic vascular resist- ance	Left ventric- ular work index	
								Pressure	Systolic ejection period			
		M. ²	cc./ min./ M. ²	vol. per cent	L./ min./ M. ²	min.	cc./ beat/ M. ²	S/D*	Mean	sec./ beat	dynes- sec.- cm. ⁻⁴	Kg. M./ min./ M. ²
G. S.	18	1.85	197	3.4	5.8	65	89	147/94	109	0.36	816	9.9
R. L.	22	1.78	205	3.0	6.8	95	72	150/75	95	0.24	625	10.8
L. P.	17	1.73	162	2.7	6.0	81	74	122/74	94	0.28	735	8.3
R. A.	35	1.80	158	2.6	6.1	77	79	105/65	85	0.33	675	7.7
R. R.	18	2.05	210	2.7	7.8	76	103	148/75	100	0.28	432	13.3
B. H.	48	1.67	171	2.7	6.3	105†	60	152/82	110	0.26	869	11.0
T. M.	27	1.73	125	2.2	5.7	76	75	124/55	78	0.28	650	8.0
A. N.	27	1.88	189	2.9	6.5	77	84	143/81	103	0.32	600	11.3
Average	27	1.81	177	2.8	6.4	81	80	136/75	95	0.29	657	10.0

* S/D = systolic/diastolic.

† Auricular fibrillation.

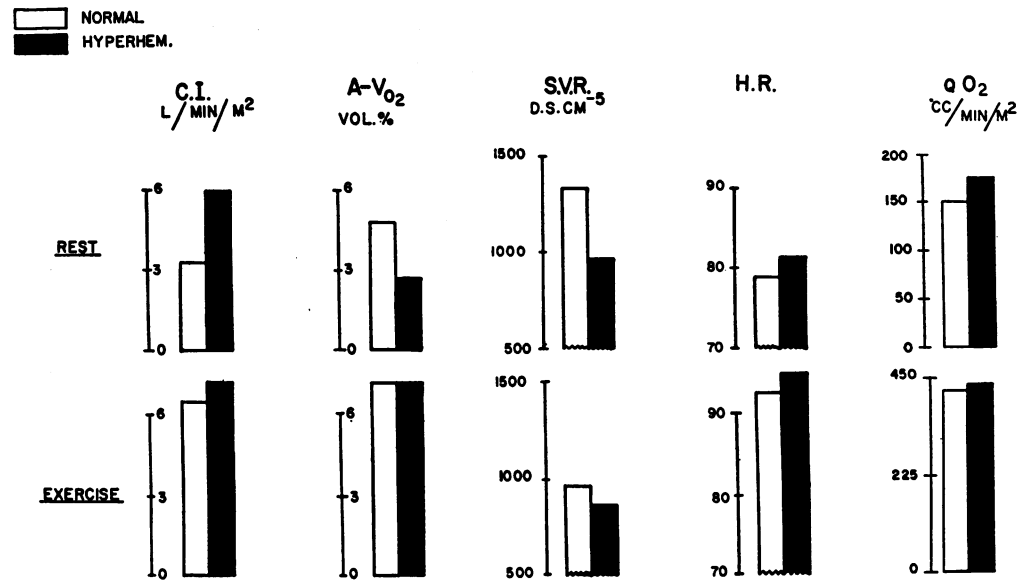


FIG. 1. COMPARISON OF AVERAGE HEMODYNAMIC VALUES AT REST AND DURING EFFORT BETWEEN NORMALS AND PATIENTS WITH HIGH CARDIAC OUTPUT

CI = cardiac index; A-V O_2 = arteriovenous oxygen difference; SVR = systemic vascular resistance (dynes-sec.-cm.⁻⁵); HR = heart rate; qO_2 = oxygen consumption.

wall, was seen in three patients. Prominence of the left ventricle, as indicated by increased convexity of the left border in the posteroanterior view and posterior enlargement in the left anterior oblique view, was seen in three individuals. The main pulmonary artery was increased in four and the vasculature was prominent in five. X-ray abnormalities had been present in Patient T. M. for the past 15 years.

Clinical laboratory tests

Hematocrit reading (Table II), blood urea nitrogen and urinalysis in all patients were normal. Bone films taken in one individual, whose head appeared to be slightly enlarged, revealed no evidence of Paget's or other bone disease. A cold pressor test was positive in five out of six patients tested (Table II).

Hemodynamic observations (Table III, Figure 1)

The cardiac output was measured 30 times in the resting state (Figure 2) by at least two different methods, one of which was always the Fick method (Table III). Output determinations were repeated on subsequent days. Regardless

of the technique used, whether measured before or after exercise, with or without sedation, cardiac outputs averaged twice as high as our laboratory normal value estimated under similar conditions. The values ranged from 4.7 to 8.7 L. per minute per M^2 with an average of 6.0 (S.D. \pm 1.1 L.) (Figure 2), while our normals ranged from 2.5 to 4.7 L. per minute per M^2 with an average of 3.5 L. per minute per M^2 (S.D. \pm 0.6 L.).⁵ In T. M. the first elevated cardiac output was measured in 1946 and was still increased when measured again 13 years later. In A. N. and R. R. elevated outputs were recorded in 1957 and in 1959. Observations were made during attempted sleep in five patients. Cardiac output remained unchanged in three but fell from 6.7 to 4.3 L. per minute per M^2 and from 5.3 to 2.6 L. per minute per M^2 in the other two patients (Figure 3). Normally, sleep results in a 40 per cent reduction in cardiac output (13). The arteriovenous difference was narrowed at rest to 60 per cent of normal. The oxygen consumption was 25 cc. (or 15 per cent) higher than our average normal

⁵ The standard error of the difference between the means is 0.27 indicating that the difference is significant and unlikely to have arisen by chance.

value. The heart rate at rest (79 per minute) was normal. The resting stroke volume was twice normal. Pulse pressure at rest was somewhat wider than that of the laboratory normal but was associated, nevertheless, with a normal systolic ejection period for the cardiac rate. Systolic hypertension was noted clinically in four patients and directly recorded in five of the eight patients. Systemic vascular resistance was reduced to approximately 70 per cent of normal, reflecting the peripheral vasodilatation.

Exercise observations (Figure 4)

Six patients were exercised for a four minute period. Oxygen consumption rose an amount equal to or exceeding that of our normal patients, but was met by *increased* oxygen extraction and continued deliverance of the already elevated (but unchanged) cardiac output. The cardiac rate rose normally on effort with a concomitant *fall* in

stroke volume. Blood pressure response on effort was similar to the normal, and systemic vascular resistance, already reduced at rest, changed little. This latter pattern simulated the normal dynamics during effort (Figure 1 and 4) and the overall change from rest dynamics to exercise dynamics simulated that seen in patients with acute transient anxiety subjected to exercise (1).

Special studies—Cardiac catheterization

By means of multiple diagnostic techniques, a left to right shunt at all levels within the heart and great vessels was ruled out in each patient. A high venous oxygen content was observed in both the superior and inferior venae cavae indicating that the vasodilatation was diffuse. Their similarity was additional evidence against a large vessel arteriovenous shunt.

Mild mitral stenosis—calculated mitral valve area = 2.5 cm.² (14)—was detected in one pa-

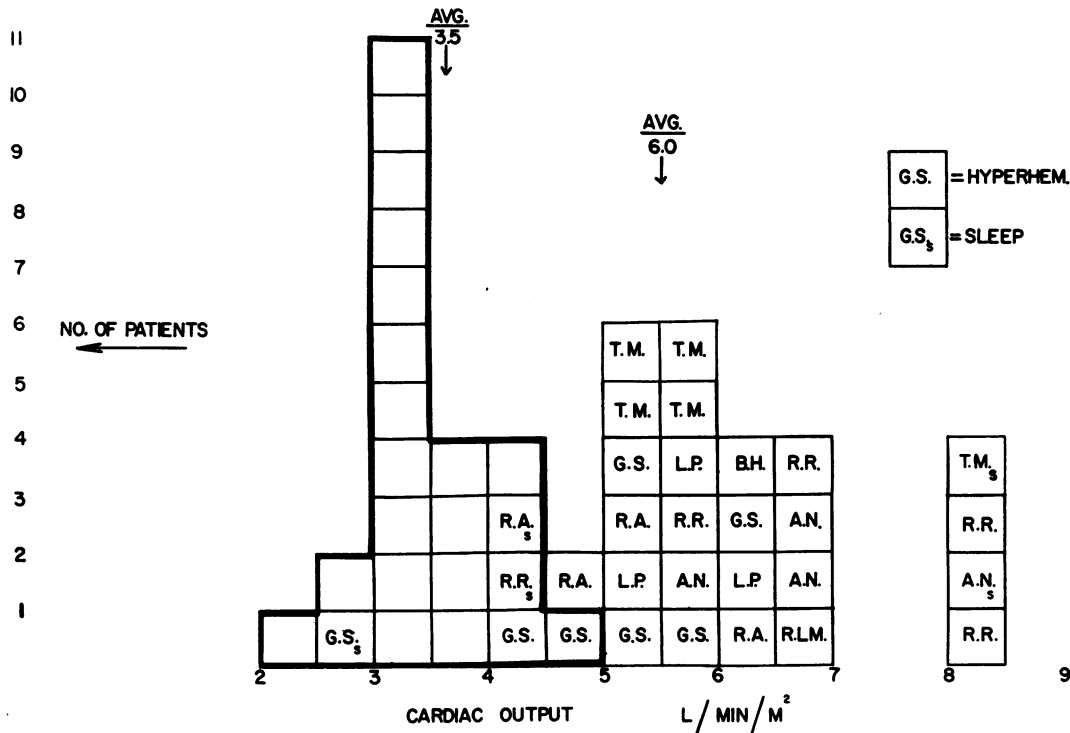


FIG. 2. HEAVILY OUTLINED AREA ENCOMPASSES CARDIAC OUTPUTS DETERMINED AT REST IN 23 NORMAL INDIVIDUALS

The average value was 3.5 L. per minute per M.². Each box containing initials represents a single determination of cardiac output in a patient with high cardiac output. The small "s" is an output estimated during sleep. The average for the group was 6.0 L. per minute per M.².

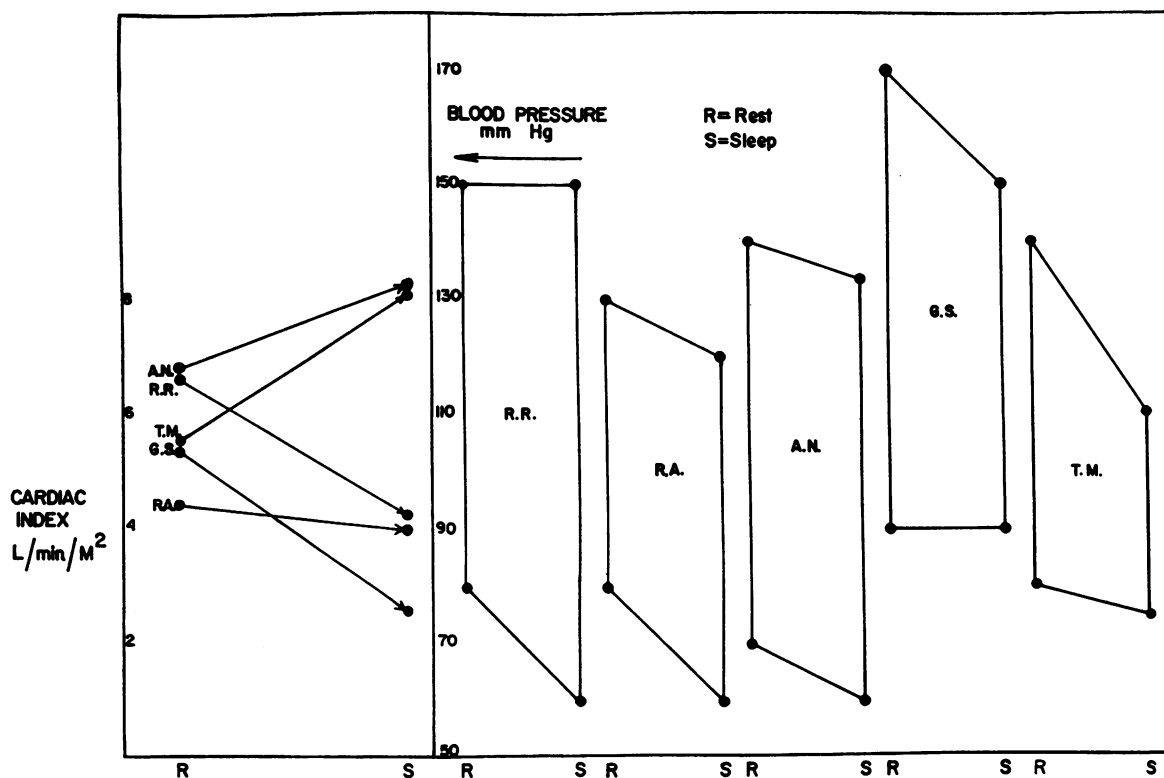


FIG. 3. EFFECT OF SLEEP OR PROLONGED REST IN QUIET DARKENED ROOM ON CARDIAC OUTPUT AND BLOOD PRESSURE

While the blood pressure tended to decrease in all, the cardiac output showed a variable response. In only one patient, however, did output fall to a normal value during sleep. Changes in pulse rate are not shown, as they were normal at rest.

tient (B. H.) and was markedly aggravated by the extremely high rate of blood flow. As a result, pulmonary capillary pressure was elevated to 25 mm. Hg. In Patient A. N. there was evidence for early left ventricular failure as indicated by an increased exercise pulmonary capillary pressure in the absence of mitral stenosis. Pulmonary hemodynamics were normal in the other six patients.

Blood chemical studies (Table II)

Arterial oxygen saturation, $p\text{CO}_2$ and pH were within normal limits; blood lactate and pyruvate and catechol amine levels were normal at rest and on effort. Thyroid studies were normal in all eight patients. Circulating blood volume was within normal limits in six of the seven patients studied. The elevated volume in A. N. may be partly a consequence of associated heart failure.

DISCUSSION

Decreased peripheral resistance is apparently of major etiological significance in most hyperkinetic states as is demonstrated by the opening and closing of an arteriovenous fistula (15-17). On the other hand, to maintain perfusion pressure, the primary resistance fall must be accompanied either by an increased venous return or neurohumoral cardiac stimulation in order for the secondary rise in output to occur (18).

When sympathetic neurohumoral stimulation is the mechanism of the hyperkinetic state, similar coordinated adjustments occur between heart and periphery. As the contractility increases with increased systolic emptying per beat, there is a peripheral vasodilatation particularly in the muscle and splanchnic vascular beds. This could be primary to the sympathetic discharge or secondary to

baro-receptor moderator reflexes as the heart initially discharges at a higher pulse pressure. Because we do not as yet know the precise nature of the syndrome herein presented, it is difficult to ascertain whether the high cardiac output is a primary abnormality or secondary to a decreased peripheral vascular resistance.

In this group of eight young males, intracardiac and great vessel shunts, hyperventilation, acidosis and pheochromocytoma seem to be ruled out by laboratory tests. Evidence against thyrotoxicosis was best obtained from the protein-bound iodine values, rather than from the resting oxygen consumptions which were not measured in the basal state. Mild beriberi is excluded on clinical grounds and by the normal pyruvate values at rest and on effort. Similarly, there was no evidence for arterial unsaturation, anemia, severe pulmonary disease, Paget's disease or hepatic cirrhosis in any of these individuals. Blood vol-

ume was normal in all but one patient, and hypervolemia *per se* has not been shown to induce a *chronic* increase in cardiac output (19, 20). Physical examination and X-ray served to exclude, insofar as one can, the possibility of a large vessel arteriovenous fistula. Also against this possibility was the fact that venous oxygen saturation for both upper and lower venae cavae was similar as well as abnormally high.

The following possibilities must be considered. The first is multiple small vessel aneurysms throughout the body, *i.e.*, a variant of Osler-Weber-Rendu disease. None of these patients had cherry-red spots, telangiectasia or hemangiomas of any sort, nor was there any history of epistaxes or gastrointestinal bleeding. Although unlikely, this possibility cannot be totally disproved. Holmgren and associates (21) have described a syndrome called "vaso-regulatory asthenia." Although all of their cases had high cardiac outputs

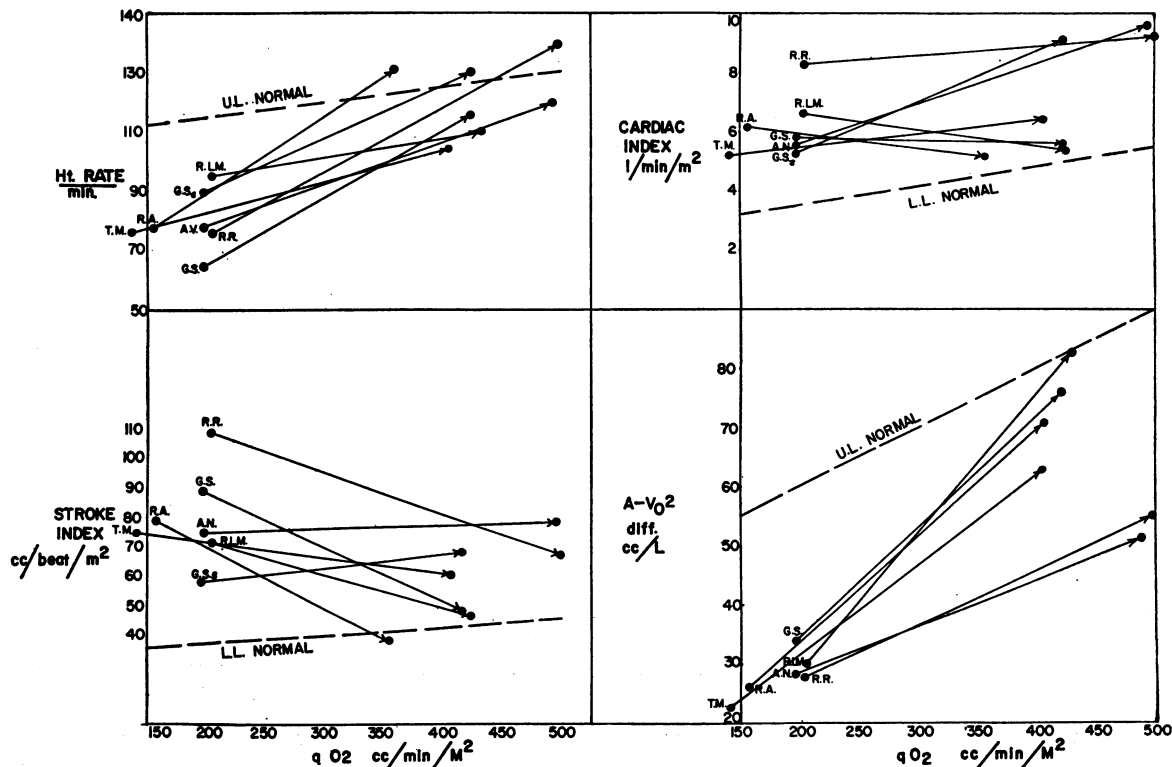


FIG. 4. EFFECT OF EXERCISE ON HEMODYNAMICS

UL = upper limit; LL = lower limit. Note the abnormally high stroke volume at rest which *decreased* to a normal figure for exercise. Cardiac rate was normal at rest and increased in normal fashion on effort. The elevated resting cardiac output generally remained unchanged on effort due to reciprocal changes in rate and stroke output. Oxygen extraction by the tissues, narrow at rest, widened normally on effort.

and narrow arteriovenous oxygen differences, the patients also had marked subjective symptoms of severe fatigue, precordial pain, heart consciousness, breathlessness and dizziness. In comparison, none of our patients had similar symptoms. On the other hand, none of their patients had cardiac murmurs or ventricular hypertrophy, and lungs and heart size were normal on X-ray examination. Whereas the abnormalities reported by Holmgren and co-workers reverted to normal after a period of vigorous physical training, four of our patients were in good physical training at the time of the study. Neurocirculatory asthenia likewise was excluded by lack of symptoms of fatigue, and normal exercise oxygen consumption and lactate levels (2, 22).

Acute *transient* anxiety can produce hemodynamic alterations identical with those seen in our patients (1, 23). Even the fact that heart rates were almost invariably normal and resting oxygen consumptions only slightly elevated would not necessarily rule out the acute anxiety state (1). On the other hand, sedation had no effect on our patients, and sleep caused a diminution in cardiac dynamics in only two cases and relatively minor changes in blood pressure. No conclusions can be drawn from the normal catechol amine levels because the relationship between acute and chronic anxiety states and amine values has not as yet been clearly defined (24, 25). Finally, the multiplicity of studies by simple technics, the persistence of abnormalities over one to 13 year periods, and *other* evidence of *cardiac involvement* militate against these observations reflecting merely an acute *transient* state. On the other hand, a chronic, persistent or frequently recurrent, easily provoked anxiety state could lead to just this situation. It is noteworthy that each of these individuals showed an effect generally characterized as "anxious." They were invariably hard-working and tense, both during laboratory tests and in the performance of their normal daily routines, and had both labile blood pressure and positive cold pressor tests.

It seems probable that a new "set" has been applied to circulatory regulation such that either "resting" output is chronically elevated or the system over-reacts to ordinarily insignificant stimuli. This may be related to an unusual autonomic response to anxiety or to unexplained central and

autonomic nervous dysfunction. Rushmer and Smith (26) have shown that stimulation of a specific site in the dog's midbrain can evoke the complete "exercise response" with elevation of cardiac output and rate. Whether such a center exists in man, and therefore results in high cardiac output through improper regulation, cannot be stated at present.

Whether the persistently elevated output noted during all of our studies remains so at all times outside the laboratory situation, or is intermittent, is unknown. The striking fact remains that, contrary to the usual anxiety state, the hyperactive circulation in these patients occurred in association with other objective evidence of cardiac involvement: cardiac murmurs, cardiac overactivity, electrocardiographic evidence of cardiac hypertrophy and occasional gross enlargement and pulmonary plethora. Other high cardiac output states, patent ductus arteriosus, thyrotoxicosis and arteriovenous fistula (presumably through elevation of cardiac output), eventually lead to left ventricular hypertrophy and ultimately to congestive heart failure. Whether the same is true here is not known. This group may constitute another disease entity characterized by a cardiac output chronically elevated above normal, and this elevation and associated systolic hypertension may lead to or be associated with signs of cardiac damage. Certainly, long duration of the high blood flow state is indicated by T. M. and evidence of ultimate functional impairment is shown in Patient A. N.

Hyman (27), in a report on asymptomatic heart disease in 350 young men, includes 26 patients, all of whom had a point of maximal impulse outside the midclavicular line or below the fifth intercostal space or both. Seven of 11 with electrocardiographic abnormalities had left axis deviation in the limb leads. At the other end of the spectrum, anatomically proved cardiac hypertrophy of unknown etiology in adults has been reported by Levy and Rousselot (28) and others (29-34). Some of these patients at least, particularly from Hyman's series of young men, may represent stages in the natural history of a disease process in which the anatomic abnormality noted is an expression of the same hyperkinetic state found in our patients.

SUMMARY

Eight patients have been studied who had in common the following clinical features: a precordial systolic murmur; hyperkinetic heart and arteries; ventricular hypertrophy by electrocardiogram; and, frequently, pulmonary plethora by X-ray.

Hemodynamic observations revealed peripheral vasodilatation and a persistently elevated cardiac output. This latter finding was confirmed on 30 separate determinations including rest, sedation and sleep in selected patients. Cardiac catheterization and other pertinent studies failed to reveal evidence for the usual causes of the high output state.

The association of a high output state with cardiac murmur, cardiac hyperactivity and hypertrophy suggests the possibility of a distinct clinico-physiologic syndrome.

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