INTERPRETATION OF CHANGES IN "CENTRAL" BLOOD VOLUME AND SLOPE VOLUME DURING EXERCISE IN MAN *

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Under certain circumstances, the volume of a vascular compartment may be estimated by the indicator dilution technic (1, 2). The method usually has been applied to measure the "central" blood volume (CBV). For this, injections of indicator are made into the right side of the heart, with sampling from a peripheral artery. The blood volume thereby measured comprises that of the heart and lungs and that of an ill defined systemic component extending out to a boundary in all vessels temporally equidistant with the sampling site. The latter component accounts for a large proportion of the total CBV under resting conditions, its precise contribution depending upon the sampling site chosen.

Many recent studies (3–8) have shown an increase in the CBV during exercise in man, its extent depending upon the severity of the exercise undertaken and the site of both injection and sampling. However, it has been pointed out by Lammerant (9) and by Gleason, Bacos, Miller and McIntosh (10) that the proportion of the systemic component to the total CBV may change with redistribution of systemic flow.

The present studies were undertaken to determine whether this commonly reported increase in the CBV during exercise could be explained by an increase in the volume of its vague systemic component. If this were so, conclusions could not be drawn about changes in the volume of blood in the lungs and heart.

METHODS

The subjects were 7 healthy men, aged 25 to 35 years, and 1 woman aged 50 years. Studies were performed after a light breakfast. All of the men were thoroughly familiar with the procedure.

The first series of observations was made on 4 subjects lying supine, standing, and then exercising with varying grades of severity on a treadmill inclined at an angle of 12° from the horizontal. The cardiac output was measured by the indicator dilution method. A no. 5 Lehman cardiac catheter was introduced into a brachial vein by percutaneous puncture and advanced until its tip lay at the lower end of the superior vena cava. The catheter was kept filled with cardio-green dye,[1] and successive injections of 7.5 mg of the dye were made by displacement. The duration of each injection (0.5 to 1.0 second) was signaled on the record. The right arm was kept at rest throughout the procedure. Blood was sampled from the right radial artery at a rate of 30 to 50 ml per minute through a Wood cuvet densitometer and was reinfused after each curve. Samples of blood were taken before and after each complete study; known amounts of dye were added to 10-ml aliquots and drawn through the densitometer to obtain calibrations for the dilution curves. At any given concentration of dye, the deflection obtained with the latter blood sample was 0 to 6 per cent less than that with the former because of the persistence of small amounts of background dye in the blood. Allowance for these minor changes in calibration were made in calculating the area subtended by each indicator dilution curve.

The mean transit time of the recorded dilution curve was corrected for delay owing to the sampling system as follows. By means of the apparatus described by Fox, Sutterer and Wood (11), undyed blood followed by a square wave front of dyed blood was drawn through the sampling system at a rate similar to that used in the experiments. The first derivative of the resulting time-concentration curve was identical in contour with that which would have been obtained had the sampling system been tested with a sudden single injection of dye (11, 12). The mean transit time of this curve was calculated; subtraction from that of the recorded curve gave the corrected mean transit time between injection and sampling sites. The CBV was calculated as the product of cardiac output (milliliters per second) and the "true" mean transit time (seconds).

In other studies, the cardiac output and the CBV were measured during leg exercise in the supine position. In two subjects a blood pressure cuff was applied to the right arm; this was inflated to a pressure of 250 mm Hg for 3 minutes while the subject performed leg ex-

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[1] Kindly supplied by Hynson, Westcott and Dunning, Inc., Baltimore, Md.

ercise. The pressure then was suddenly released from the cuff and, while the subject continued to exercise, an indicator dilution curve was obtained from the right radial artery, being completed within 30 seconds of the release of occlusion. It was thus possible to compare the CBV obtained under these circumstances with that obtained while the subject was performing leg exercise of identical severity in the absence of any interference with blood flow to the sampling limb. During this series of observations, blood flow in the forearm was measured by a

TABLE I

Cardiac output, mean transit time and "central" blood volume at rest supine, at rest standing, and during graded exercise on an inclined treadmill *

Subject	BSA	Observation	Condition	Cardiac output	Cardiac index	Mean transit time	"Central" blood volume	
	m^2	no.		L/min	L	sec	ml	ml/m^2
R.M.	2.10	1	Rest, supine	6.90	3.30	18.85	2,160	1,030
			Rest, standing	5.70	2.70	15.90	1,510	720
			1.7 mph	14.30	6.80	12.50	2,980	1,420
			2.5 mph	20.70	9.85	11.20	3,860	1,840
			3.5 mph	25.60	12.20	12.25	5,230	2,490
			Standing after exercise	5.20	2.50	14.05	1,210	580
		2	Rest, supine	6.45	3.10	20.00	2,150	1,020
			Marking time	9.25	4.40	13.50	2,080	990
			3.5 mph	20.00	9.50	14.10	4,700	2,240
		3	Rest, supine	7.35	3.50	17.15	2,100	1,000
			Rest, standing	5.80	2.75	17.50	1,690	800
			Marking time, 1	8.00	3.80	15.15	2,020	960
			Marking time, 2	12.20	5.80	12.30	2,500	1,190
			2.5 mph	15.50	7.40	11.35	2,940	1,400
			3.5 mph	20.00	9.50	11.50	3,830	1,820
			4.5 mph	22.30	10.60	12.45	4,630	2,200
D.W.	1.91	1	Rest supine	7.15	3.75	15.50	1,850	970
			Rest, standing	4.55	2.40	15.75	1,200	630
			1.7 mph	14.20	7.40	8.60	2,040	1,060
			2.5 mph	17.55	9.20	7.15	2,090	1,090
			3.5 mph	20.30	10.60	6.95	2,350	1,230
		2	Rest, supine	6.70	3.50	15.15	1,690	880
			Rest, standing	4.10	2.15	18.35	1,250	650
			1.7 mph	11.30	5.90	9.60	1,810	940
			2.5 mph	16.70	8.75	8.15	2,270	1,190
			3.5 mph	16.60	8.70	8.30	2,300	1,200
		3	Rest, supine	7.50	3.90	14.95	1,870	980
			Rest, standing	3.95	2.05	15.35	1,010	530
			Marking time, 1	6.10	3.20	13.70	1,390	730
			Marking time, 2	7.15	3.75	11.05	1,320	690
			1.7 mph	16.10	8.40	9.20	2,470	1,290
			2.5 mph	17.25	9.05	8.35	2,400	1,260
			3.5 mph	21.60	11.30	6.70	2,410	1,260
Y.W.	1.85	1	Rest, supine	6.55	3.55	19.15	2,090	1,130
			Rest, standing	5.70	3.10	16.10	1,530	830
			1.7 mph	11.10	6.00	13.40	2,480	1,340
			2.5 mph	12.70	6.85	11.20	2,380	1,280
			3.5 mph	18.75	10.15	10.70	3,350	1,810
			4.5 mph	20.20	10.90	9.00	3,030	1,640
			Standing after exercise, 1	5.30	2.85	15.50	1,370	740
			Standing after exercise, 2	4.50	2.45	15.55	1,170	630
		2	Rest, supine	6.05	3.25	23.15	2,340	1,260
			Rest, standing	4.60	2.50	22.50	1,730	930
			Marking time	7.35	3.95	18.50	2,270	1,220
			3.5 mph	19.20	10.35	11.70	3,740	2,020
D.H.	1.73	1	Rest, supine	6.20	3.60	17.05	1,760	1,020
			Rest, standing	4,60	2.65	15.60	1,200	690
			1.7 mph	8.80	5.10	11.90	1,750	1,010
			2.5 mph	12.50	7.20	8.35	1,680	970
			3.5 mph	15.30	8.85	9.45	2,410	1,390
			4.5 mph	14.90	8.60	9.50	2,360	1,360

* Nine observations in four subjects.

modified Whitney mercury-in-rubber strain gage plethysmograph (13, 14) both with the arm at rest and immediately after release of arterial occlusion. In a third subject (J.S.), needles were inserted into both radial arteries, and reactive hyperemia was induced alternately in the two limbs. A fourth subject (W.M.) was kept cold during the early part of the study, and pronounced vasoconstriction was present in the hands and arms. Dilution curves were obtained at rest and during strenuous leg exercise in the supine position. The subject then was warmed by means of blankets and lamps while he continued to exercise at intervals. One hour later, when the hands and arms were warm and he was sweating profusely, dilution curves were obtained during further periods of strenuous exercise, both under normal circumstances and after sudden release of arterial occlusion to the sampling limb.

RESULTS

Observations during upright exercise. Indicator dilution curves from Subject R.M., obtained while resting supine, standing, and then walking up the inclined treadmill at 1.7 and 3.5 miles per hour, are shown in Figure 1. Comprehensive results from all nine studies in the four subjects who performed exercise in the upright position are shown in Table I. In the supine position at rest, the cardiac index averaged 3.54 L, the mean transit time 17.62 seconds, and the CBV 1,034 ml per m² of body surface (Table II). During quiet standing, the cardiac index was reduced to 2.54 L; the mean transit time also was slightly reduced to 17.13 seconds, with a consequent decrease in the CBV to 722 ml per m². During strenuous exercise, the cardiac index was 10.21 L, which was a fourfold increase over the value obtained during quiet standing; the mean transit time was reduced to 9.69 seconds, and the CBV was increased to 1,652 ml per m², an increase by 129 per cent over the value obtained during quiet standing.

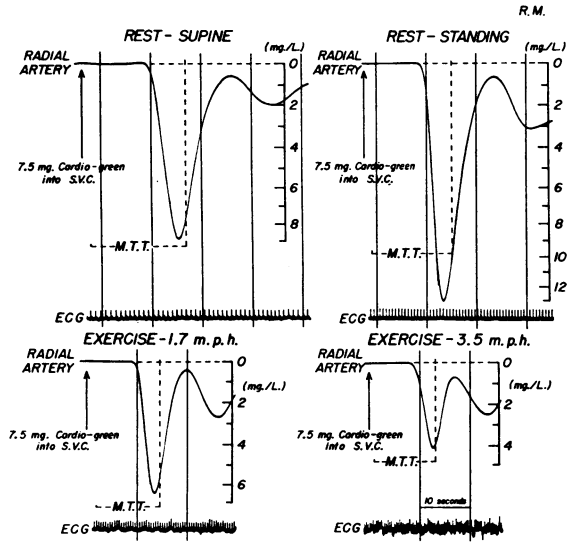

FIG. 1. INDICATOR DILUTION CURVES OBTAINED IN R.M. AT REST AND DURING EXERCISE. The calibrations are on the right. The vertical lines with arrow heads indicate the time of injection. The interrupted horizontal lines show the duration of the mean transit time, corrected for delay in the sampling system.

TABLE II

Mean values and standard deviations for cardiac index, mean transit time and "central" blood volume *

Condition	Type of value	Cardiac index	Mean transit time	"Central" blood volume
		L	*sec*	*ml/m²*
Rest, supine	Mean	3.54	17.62	1,034
	SD	0.20	2.73	185
Rest, standing	Mean	2.54	17.13	722
	SD	0.33	2.33	127
Exercise (3.5 mph on treadmill inclined at 12°)	Mean	10.21	9.69	1,652
	SD	1.15	2.20	457

* Eight observations in four subjects. Studies while standing were not made during the second observation in Subject R.M.

The large values obtained for the standard deviation in the measurements of the mean transit time and the CBV are caused by the fact that Subjects R.M. and Y.W. showed considerably less reduction of the mean transit time during strenuous exercise than did D.W. and D.H. This difference appears to be a real one between individuals, since similar values were obtained in successive observations on the same subject. This is illustrated in Figures 2 and 3, in which results from the three separate studies on R.M. and D.W. are shown. Figure 2 shows the line along which points would lie if the calculated CBV were constant, irrespective of posture or exercise. Points falling to the left of and below the line indicate a decrease in the CBV, and points to the right of and above the line indicate an increase. In R.M., at outputs of 12 L per minute and greater, no further significant reduction of the mean transit time occurred, whereas D.W. showed a continual decrease in the mean transit time up to the maximal exercise undertaken. Figure 3 demonstrates for each of the two subjects a substantial decrease in the CBV with assumption of the erect position. However, the increase in the calculated CBV dur-

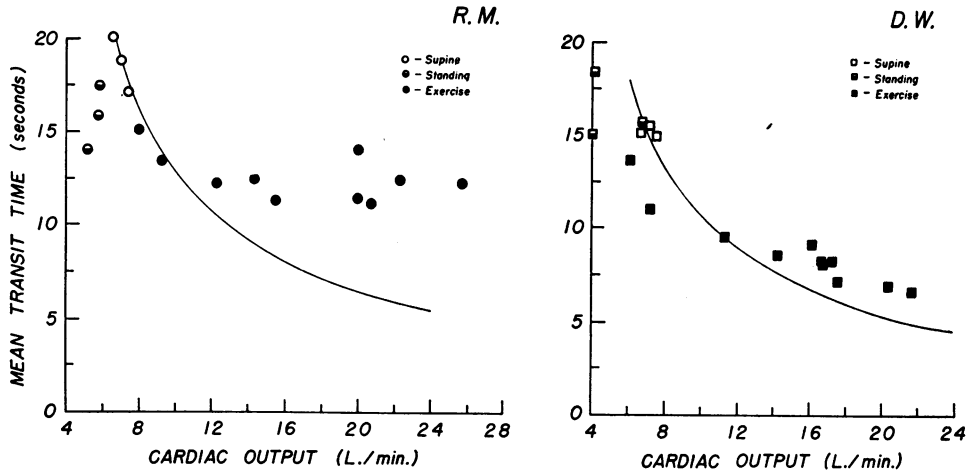

FIG. 2. RELATIONSHIP BETWEEN CARDIAC OUTPUT AND MEAN TRANSIT TIME AT REST AND DURING EXERCISE IN R.M. (LEFT PANEL) AND D.W. (RIGHT PANEL). The continuous lines are those on which the points would lie if the "central" blood volume remained the same during standing and during exercise as that at rest in a supine position. Points to the left of and below the lines correspond to decreases in "central" blood volume, and points to the right of and above the lines correspond to increases.

ing exercise in R.M. was much greater than in D.W.

The CBV was measured in two subjects while they were standing still within 15 minutes of the end of a series of strenuous exercises on the treadmill. Subject Y.W. showed persistent tachycardia, a decrease in arterial blood pressure to 90 mm Hg systolic and 60 diastolic, and facial pallor. The cardiac output in successive determinations was 5.30 and 4.50 L per minute, the stroke volume 41 and 35 ml, and the CBV 1,370 and 1,170 ml, compared with 1,530 ml in the initial determinations with the subject standing prior to exercise. In R.M., the blood pressure was 70/50, the cardiac output 5.2 L per minute, the stroke volume 43 ml and the CBV 1,210 ml, compared with 1,510 ml in the initial observation.

Observations during supine leg exercise. Figure 4 shows indicator dilution curves obtained from the female subject G.J., while she performed mild leg exercise in the supine position. The first curve was obtained without any interference with the circulation in the limb used for sampling. At this time, the blood flow in the forearm was 3 ml

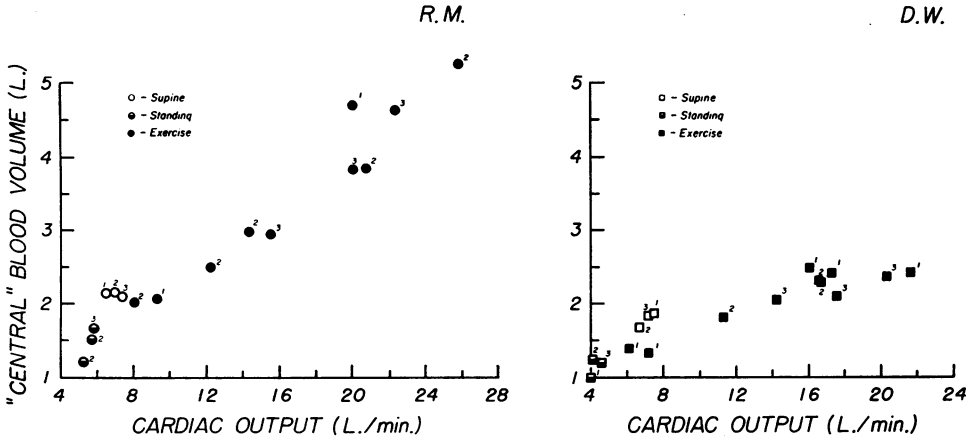

FIG. 3. EFFECT OF CHANGES IN POSTURE AND OF EXERCISE ON "CENTRAL" BLOOD VOLUME IN R.M. (LEFT PANEL) AND D.W. (RIGHT PANEL).

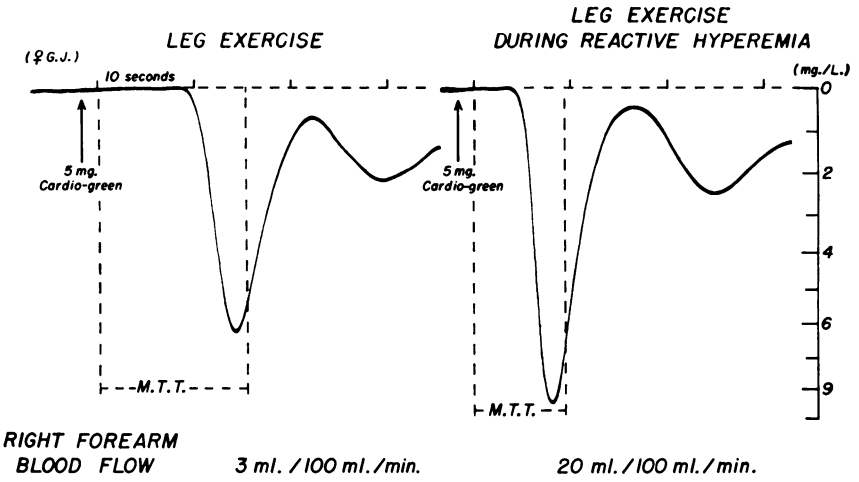

FIG. 4. INDICATOR DILUTION CURVES OBTAINED WHILE G.J. PERFORMED MILD LEG EXERCISE IN THE SUPINE POSITION. The curve in the right panel was inscribed just after release of an arterial occlusion cuff to induce reactive hyperemia in the sampling arm. Note the effect of this maneuver on the contour of the dilution curve, the mean transit time and the forearm blood flow.

per 100 ml of forearm per minute. The second curve was obtained during similar mild leg exercise but immediately after the pressure was released from an arterial occlusion cuff on the sampling limb. At the time of inscription of the dilution curve, the blood flow in the forearm was 20 ml per 100 ml per minute. This resulted in an earlier appearance time, a higher peak concentration, more nearly complete clearing of the dye between the primary circulation and the first recirculation, and a reduction of the mean transit time from 15.3 to 9.2 seconds. The results of this study are summarized in Table III. At rest, the CBV was approximately 1,500 ml; during mild leg exercise, it increased to 2,000 ml, but during similar mild leg exercise, with an increased blood flow to the sampling limb, it was only 1,100 ml, a reduction by about 400 ml from the value obtained at rest.

TABLE III

Effect of reactive hyperemia in sampling arm on measurement of "central" blood volume during supine leg exercise (Subject G.J.)

Condition	Cardiac output	Mean transit time	"Central" blood volume	Forearm blood flow
	l./min	*sec*	*ml*	*ml/100 ml/min*
Rest	4.4	19.9	1,460	3.6
Mild exercise	7.9	15.3	2,000	3.0
Rest	4.8	19.1	1,530	3.4
Mild exercise*	7.5	9.2	1,120	20.0

* Output measured during reactive hyperemia after release of arterial occlusion of the arm used for sampling.

Figure 5 shows indicator dilution curves obtained during strenuous leg exercise in the supine position in J.B. During a period of reactive hyperemia after release of arterial occlusion, the forearm blood flow in the sampling limb was 24 ml per 100 ml per minute, as compared with the control value of 3 ml per 100 ml per minute. The cardiac output corresponding to each of these dilu-

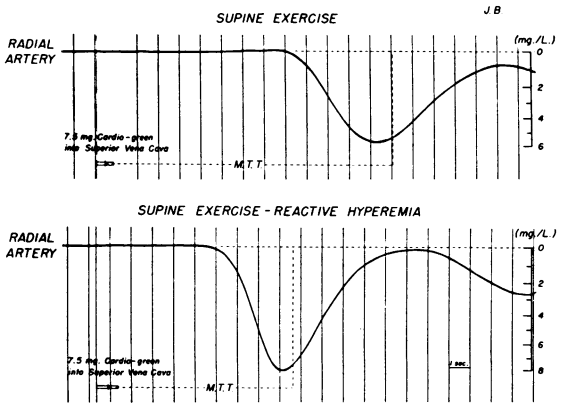

FIG. 5. INDICATOR DILUTION CURVES OBTAINED WHILE J.B. PERFORMED SEVERE LEG EXERCISE IN THE SUPINE POSITION. The curve in the bottom panel was inscribed during a period of reactive hyperemia. Note the reduction of the mean transit time and the increased steepness of the disappearance slope.

TABLE IV

Effect of reactive hyperemia in sampling arm on measurement of "central" blood volume and slope volume during supine leg exercise (Subject J.B.)

Condition	Cardiac output	Mean transit time	"Central" blood volume	Slope volume	Forearm blood flow
	L/min	*sec*	*ml*	*ml*	*ml/100 ml/min*
Rest	7.3	14.2	1,730	280	3.0
Moderate exercise	12.2	14.2	2,890	495	2.8
Moderate exercise*	13.3	8.4	1,860	265	22.6
Severe exercise	15.0	12.5	3,130	590	3.0
Severe exercise*	15.1	7.5	1,890	300	24.0

* Output measured during reactive hyperemia after release of arterial occlusion of the arm used for sampling.

tion curves was approximately 15 L. The pronounced effect of reactive hyperemia in the sampling limb on the contours and time components of the dilution curves is shown in this figure also. The main features are shortening of the appearance time, increased peak concentration, more nearly complete clearance of dye between the primary circulation and the first recirculation, reduction of the mean transit time, and increased steepness of the disappearance slope. The data are summarized in Table IV.

Similar studies were carried out in W.M. (Table V). Initially the subject felt cold; there was severe vasoconstriction of the skin, and the forearm blood flow was 2.2 ml per 100 ml per minute. The calculated CBV was 2,600 ml; during fairly strenuous leg exercise it increased to 3,780 ml. Later, indirect body heating was accomplished by covering the trunk and lower limbs with blankets and using infrared lamps. Identical exercise was performed when the subject was hot and sweating; the forearm blood flow was 7.0 ml per 100 ml per minute and the CBV was 3,080 ml. The exercise was repeated and a dilution curve was obtained just after release of an arterial occlusion cuff, when the blood flow in the forearm was 25.0 ml per 100 ml per minute; the CBV was 2,320 ml, which was less than the value obtained under the original resting conditions.

TABLE V

Effect of body heating and of reactive hyperemia in sampling arm on measurement of "central" blood volume during supine leg exercise (Subject W.M.)

Condition	Cardiac output	Mean transit time	"Central" blood volume	Forearm blood flow
	L/min	*sec*	*ml*	*ml/100 ml/min*
Rest, supine, subject cold	7.20	21.65	2,600	2.2
Exercise, supine, subject cold	16.50	13.75	3,780	2.4
Rest, supine, subject cold	7.20	22.25	2,670	2.4
Exercise, supine, subject hot and sweating	16.45	11.20	3,080	7.0
Exercise, supine, subject hot, reactive hyperemia	16.00	8.70	2,320	25.0

TABLE VI

Effect of reactive hyperemia induced alternately in upper limbs on measurement of "central" blood volume (Subject J.S.)

Condition	Cardiac output	"Central" blood volume		Difference in volume between A and B
		A: SVC* to right radial artery	B: SVC* to left radial artery	
	L/min	*ml*	*ml*	*ml*
Rest	7.6	1,440	1,560	−120
Rest, reactive hyperemia in right arm	8.5	1,060	1,530	−470
Rest	7.5	1,300	1,450	−150
Rest, reactive hyperemia in left arm	7.9	1,350	1,000	+350
Exercise, reactive hyperemia in right arm	12.5	1,280	1,800	−520
Exercise, reactive hyperemia in left arm	14.1	1,850	1,400	+450

* SVC =superior vena cava.

In J.S. the CBV was determined simultaneously at both radial arteries. Under resting conditions the volumes measured to these two sites were similar. Reactive hyperemia was induced in each arm alternately both at rest and during exercise, the other arm serving as a control. The CBV always was decreased in the hyperemic limb as compared with that in the control limb (Table VI). Under these conditions, changes in the CBV were due entirely to alterations in peripheral blood flow.

DISCUSSION

The results of the studies in which the CBV was measured at rest supine, at rest standing, and during graded exercise on an inclined treadmill are comparable with those reported by other workers. With mild exercise, the CBV equaled or exceeded the value in the resting supine position; it continued to increase with further increase in the severity of the exercise (Table II). At a walking

speed of 3.5 miles per hour, when the oxygen consumption ranged from 1,000 to 1,260 ml per m^2 per minute, the CBV averaged 2.29 times, and the cardiac output 4.02 times, the values in the resting standing position. These values are comparable with those reported by Mitchell, Sproule and Chapman (5), who obtained during strenuous exercise an increase in cardiac output of 4.24 times, and in the CBV of 2.13 times, the values at rest. Roncoroni, Aramendia, González and Taquini (6) studied their subjects standing at rest and performing relatively mild exercise in the upright position. They noted an increase in cardiac output from 3.46 to 7.55 L per minute per m^2 and in the CBV from 940 to 1,520 ml per m^2.

In the studies reported here, the extent of the increase in the CBV during exercise in the upright position varied considerably from one subject to another, although it was relatively constant from study to study in the same subject (Table I and Figure 2). In R.M. it reached a value on one occasion of 5,230 ml, which approached the predicted total blood volume of 6.56 L. Indeed, had a peripheral venous site been employed for injections of indicator, the CBV would have exceeded the total blood volume. Kaufmann (3), who made injections into a brachial vein and recorded dye dilution curves from an ear oximeter, obtained values for the CBV equal to those for total blood volume in two subjects performing relatively mild exercise, the cardiac output being 13.7 and 13.5 L per minute, respectively. However, he did not state how the dilution curves were calibrated.

It is clear from these and other studies (7, 8, 15) that a moderate or pronounced increase occurs in the CBV during exercise. What is the interpretation of this increase? It could be caused by an increase in the volume of blood contained in the heart and lungs, or in that volume situated between the aortic valve proximally and the sampling site and all other temporally equidistant sites distally. Lammerant (9) and Gleason and associates (10), among others, have shown how systemic redistribution of blood flow could alter the geometry of this time-limited volume component, thereby leading to the possibility of drawing erroneous conclusions about changes in the CBV.

The problem could be settled by sampling via an arterial catheter from the root of the aorta after central injections. In the dog it is possible to pass a short, wide-lumen catheter via the carotid artery to the aortic arch and to sample at a rate permitting clearance of the dead space in 0.2 second. This has permitted measurement of the volume of blood in the lungs and left side of the heart (16) at rest and during graded exercise on a treadmill. Further experience has confirmed our earlier finding (17) that this volume increases only slightly from rest to strenuous exercise. Figure 6 shows data obtained from 10 intact dogs. Over the range of activity at which the studies were made, the mean increase in cardiac output was about 200 per cent; however, the lung and left heart volume increased by only 7 per cent. In contrast, when blood was sampled from a peripheral artery during similar exercise, a consistent major increase in the blood volume occurred. This also suggested that the increase in the CBV demonstrated in humans should be sought in the systemic rather than in the cardiopulmonary component of the volume. Evidence that this is so was obtained from our studies in which the velocity of blood flow in the arm used for sampling was increased.

In the first of these subjects (G.J.), the CBV was approximately 1,500 ml while she rested in the supine position. During mild leg exercise, it increased to 2,000 ml. During a second episode of comparable exercise, reactive hyperemia was in-

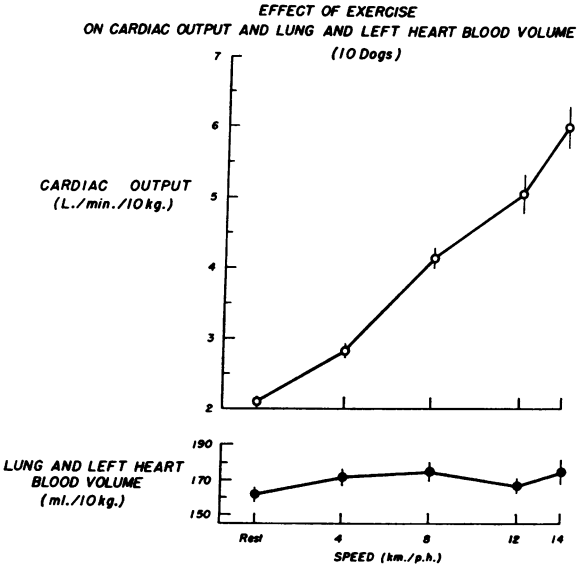

FIG. 6. CARDIAC OUTPUT (TOP PANEL) AND LUNG AND LEFT HEART BLOOD VOLUME (BOTTOM PANEL) IN 10 DOGS STANDING AT REST AND PERFORMING GRADED EXERCISE ON A TREADMILL.

duced in the sampling limb, and the CBV was approximately 1,100 ml, or 400 ml less than the initial value at rest. Since it is unlikely that the deflation of a peripheral blood pressure cuff could have altered the volume of blood in the heart and lungs, this reduction of 900 ml must have been caused by alterations in the systemic arterial component of the volume. During the first episode of leg exercise, the velocity of blood flow to the lower half of the body was increased relative to that to the right arm; during the second period of exercise, the blood flow to the right arm was increased sevenfold, and the time taken for blood to reach the sampling site was reduced by 6 seconds. Hence, the velocity of blood flow down the sampling limb now exceeded that to the lower half of the body. Thus, the former circumstance was characterized by an expansion and the latter by a contraction in the time-equivalent boundaries of the volume.

Similar results were obtained in the other three subjects in whom the effects of induced changes in the velocity of blood flow in the sampling limb were studied. In W.M., body heating increased the forearm blood flow from 2.4 to 7.0 ml per 100 ml per minute, and this resulted in a decrease from 3,780 to 3,080 ml in the CBV during successive periods of comparable leg exercise. In a third episode of exercise, reactive hyperemia also was induced in the sampling limb; the forearm blood flow was now 25.0 ml per 100 ml per minute, and the CBV was reduced further to 2,320 ml, or 300 ml less than the initial value when the subject was at rest.

The remote possibility that the deflation of a blood pressure cuff might reflexly affect the volume of blood in the heart and lungs was ruled out by the observations in J.S. (Table VI). The CBV was measured simultaneously from both radial arteries. The observations were made first with the circulation through each arm undisturbed and were repeated after induction of reactive hyperemia alternately in the two arms. On each occasion, the volume measured to the limb with increased blood flow was reduced and that measured to the opposite limb was unchanged. Thus, the reduction in the former volume was caused by an alteration in its time-equivalent systemic boundaries and not by any change in the cardiopulmonary volume.

Our results confirm and extend the observations of Gleason and associates (10), who sampled simultaneously from the brachial and femoral arteries in resting subjects before and after the release of arterial occlusion cuffs applied to the legs. This maneuver was accompanied by a consistent decrease in the calculated CBV in samples from the femoral artery and by a slight increase in samples from the brachial artery. They concluded that alterations in the CBV cannot be attributed to changes in its intrathoracic component unless it can be shown that any change in blood flow occurs uniformly throughout the arterial system, a most unlikely circumstance.

Braunwald and Kelly (8) noted a slight decrease in the volume between the superior vena cava and the brachial artery when the sampling limb was heated. During leg exercise, the calculated CBV to the warmed limb was greater than under control conditions at rest. However, heating the limb causes only a relatively slight increase in local blood flow compared with that during reactive hyperemia (Table V) and especially with that during strenuous leg exercise (18). Hence, their findings are still fully consistent with the interpretation that the demonstrated increase in the CBV during leg exercise was largely or wholly in the "arterial" component.

The conclusions of many previous studies on patients with heart disease have been based upon the assumption that changes in CBV indicate changes in the volume of blood inside the thorax (19–22). Since an extensive redistribution of systemic venous and arterial blood flow and blood volume occurs in patients with heart disease, such conclusions are invalid. Views that the pulmonary blood volume may act as an important blood reservoir regulating the cardiac output (23–25) are based upon studies to which similar criticism applies. Johnson (23), Lee, Churchill-Davidson, Miles and de Wardener (26), and Etsten and Li (27) noted a decrease in CBV during general anesthesia. However, since the forearm blood flow during anesthesia increases despite a decrease in cardiac output (26), a reduction in the arterial component of the CBV would be expected. This, rather than a change in pulmonary blood volume, could explain these findings. The increase in CBV during infusion of trimethaphan (Arfonad) camphorsulfonate, a ganglion-blocking drug (28),

also could be related to its effects on the peripheral rather than the pulmonary circulation.

Thompson, Berry and McIntosh (7) measured the CBV in patients who were hyperventilating and also while they were performing leg exercise. Each procedure doubled the cardiac output. The CBV increased with leg exercise but not with hyperventilation, and the conclusion was that the response of the cardiac output to these two maneuvers may be brought about by different mechanisms. An alternative explanation is that during hyperventilation, as opposed to leg exercise, the velocity of blood flow to the lower part of the body is unlikely to increase relative to that through the sampling limb, and hence an increase in the systemic arterial component of the volume would not be expected.

In eight observations on four of our subjects, a mean decrease of 30 per cent occurred in the CBV on changing from the supine to the standing position. This is similar to the decrease of 25 per cent noted by Weissler, Leonard and Warren (25). It is indeed probable that the cardiopulmonary component of the volume does diminish but, since qualitative changes in systemic flow occur with the change in posture, it cannot be determined how much of the decrease should be attributed to the lungs and how much to changes in the "arterial" volume. In the absence of more precise data, statements such as "on standing from the supine position about one-quarter of the blood in the lungs goes into the legs" (29) are best avoided.

Thus it is clear that, when either the injection site or the sampling site is peripheral, any maneuver that causes redistribution of systemic blood flow, such as exercise, change of posture or general anesthesia, will be associated with a change in the calculated CBV. Attempts to equate this change quantitatively or even qualitatively with a change in the volume of blood in the lung vessels are, however, fraught with hazard.

Much of the confusion has arisen from attempts to think of the CBV as a conventional three-dimensional volume. Its limits, however, do not conform to any fixed anatomic boundary but are determined by equivalence in a fourth dimension, namely time. The elusive nature of such a volume is attested to by the number of synonyms that have been used, including the intrathoracic volume, the cardiopulmonary volume and the needle-to-needle volume, none of which is satisfactory. From these considerations, it is difficult to justify any further studies on such a nebulous entity as the CBV as it usually has been measured.

McGaff, Jose and Milnor (30), and Dock and co-workers (31) recently attempted to measure the pulmonary blood volume in man by making successive or simultaneous injections into the pulmonary artery, sampling from a common peripheral site, and subtracting the volumes calculated from the corresponding dilution curves. This technic avoids fallacies from changes in the systemic component of the volume. However, the left atrium may be a poor mixing chamber, particularly in patients with rheumatic heart disease. Sampling from the aortic root after injections into the pulmonary artery also avoids fallacies and fulfills the criteria for good mixing at both injection and sampling sites (32). This method has been used in animals (17), but it also has a disadvantage in that the combined blood volume of the lungs and left heart chambers is measured.

Newman, Pearce, and associates (33, 34), developed the concept that the "slope volume," which is calculated from the product of the cardiac output and the rate of declining concentration of indicator in the disappearance phase of the dilution curve, is related to a pulmonary mixing volume. Recently, a more guarded definition of the slope volume has been used (35). It appeared possible that calculation of the slope volume might aid in the interpretation of changes in the pulmonary blood volume occurring during exercise. However, it became clear that the slope volume, like the CBV, was greatly influenced by the systemic redistribution of blood flow. In Subject J.B. (Table IV), the slope volume during strenuous leg exercise was 590 ml. During an identical episode of exercise, reactive hyperemia was induced in the sampling arm. The cardiac output was unchanged, but the disappearance slope was twice as steep; thus, the slope volume was reduced to 300 ml. This, together with similar although less pronounced findings in other subjects, is evidence that the slope volume is affected by linear dispersal of the indicator in peripheral vessels, supporting our recent conclusion from animal studies (36) that the slope volume does not reflect changes in the pulmonary blood volume either quantitatively or qualitatively.

SUMMARY

The "central" blood volume (CBV) was measured in four subjects at rest supine, standing, and during exercise on an inclined treadmill. Injections of indicator were made into the superior vena cava, and dilution curves were obtained from the radial artery. Mean values for the CBV were 1,034 ml per m^2 at rest supine, 722 ml per m^2 while standing, and 1,652 ml per m^2 during walking at 3.5 miles per hour.

In four further subjects, the CBV was increased during the performance of leg exercise in the supine position. Such exercise is associated with an increased flow of blood to the lower limbs. When the rate of blood flow to the arm used for sampling also was increased by sudden release of pressure from an arterial occlusion cuff, a great decrease in the CBV occurred, the values approaching, or even falling below, those obtained under the initial resting conditions. Thus, the increase in the CBV during exercise is partly or wholly caused by an increase in its systemic "arterial" component, in consequence of relative changes in the rates of blood flow to different regions.

Failure to appreciate the significance of such hemodynamic changes, during exercise, change of posture and general anesthesia, has led in the past to unwarranted conclusions about changes in pulmonary blood volume, the reservoir function of the lungs, and the interdependence of pulmonary blood volume and cardiac output. It is difficult to see how any valid information about the pulmonary blood volume can be obtained from measurement of the CBV when a peripheral sampling site is used.

Evidence has been obtained that the "slope volume" is influenced by linear dispersal of indicator in peripheral arteries. Thus, this volume no longer can be held to reflect either quantitatively or qualitatively the volume of any single component of the central circulation, such as the lungs.

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REFERENCES

1. Hamilton, W. F., Moore, J. W., Kinsman, J. M., and Spurling, R. G. Studies on the circulation. IV. Further analysis of the injection method, and of changes in hemodynamics under physiological and pathological conditions. Amer. J. Physiol. 1932, **99**, 534.
2. Meier, P., and Zierler, K. L. On the theory of the indicator-dilution method for measurement of blood flow and volume. J. appl. Physiol. 1954, **6**, 731.
3. Kaufmann, G. Über Kreislaufzeiten und Blutverteilung bei Arbeit. Cardiologia (Basel) 1957, **30**, 102.
4. Mitchell, J. H., Sproule, B. J., and Chapman, C. B. The physiological meaning of the maximal oxygen intake test. J. clin. Invest. 1958, **37**, 538.
5. Mitchell, J. H., Sproule, B. J., and Chapman, C. B. Factors influencing respiration during heavy exercise. J. clin. Invest. 1958, **37**, 1693.
6. Roncoroni, A. J., Aramendia, P., González, R., and Taquini, A. C. "Central" blood volume in exercise in normal subjects. Acta physiol. lat.-amer. 1959, **9**, 55.
7. Thompson, H. K., Berry, J. N., and McIntosh, H. D. Comparison of the cardiac output responses to hyperventilation and exercise (abstract). Clin. Res. 1959, **7**, 136.
8. Braunwald, E., and Kelly, E. R. The effects of exercise on central blood volume in man. J. clin. Invest. 1960, **39**, 413.
9. Lammerant, J. Le Volume Sanguin des Poumons Chez l'Homme. Bruxelles, Éditions Arscia, 1957.
10. Gleason, W. L., Bacos, J. M., Miller, D. E., and McIntosh, H. D. A major pitfall in the interpretation of the central blood volume (abstract). Clin. Res. 1959, **7**, 227.
11. Fox, I. J., Sutterer, W. F., and Wood, E. H. Dynamic response characteristics of systems for continuous recording of concentration changes in a flowing liquid (for example, indicator-dilution curves). J. appl. Physiol. 1957, **11**, 390.
12. Hamilton, W. F., and Remington, J. W. Comparison of time concentration curves in arterial blood of diffusible and non-diffusible substances when injected at constant rate and when injected instantaneously. Amer. J. Physiol. 1947, **148**, 35.
13. Whitney, R. J. The measurement of changes in human limb-volume by means of a mercury-in-rubber strain gauge. J. Physiol. (Lond.) 1949, **109**, 5P.
14. Clarke, R. S. J., and Hellon, R. F. Venous collection in forearm and hand measured by the strain-gauge and volume plethysmograph. Clin. Sci. 1957, **16**, 103.
15. von Nowy, H., Kikodse, K., and Zöllner, N. Über Bestimmungen des Herzminutenvolumens und zentralen Blutvolumens in Ruhe und bei körperlicher Arbeit mit Hilfe der Farbstroffmethode. Z. Kreisl.-Forsch. 1957, **46**, 382.
16. Marshall, R. J., Wang, Y., and Shepherd, J. T. Components of the "central" blood volume in the dog. Circulat. Res. 1960, **8**, 93.
17. Marshall, R. J., Wang, Y., Semler, H. J., and Shepherd, J. T. Flow, pressure, and volume re-

lationships in the pulmonary circulation during exercise in normal dogs and dogs with divided left pulmonary artery. Circulat. Res. In press.

18. Black, J. E. Blood flow requirements of the human calf after walking and running. Clin. Sci. 1959, **18**, 89.
19. Ball, J. D., Kopelman, H., and Witham, A. C. Circulatory changes in mitral stenosis at rest and on exercise. Brit. Heart J. 1952, **14**, 363.
20. Rapaport, E., Kuida, H., Haynes, F. W., and Dexter, L. The pulmonary blood volume in mitral stenosis. J. clin. Invest. 1956, **35**, 1393.
21. Kopelman, H., and Lee, G. de J. Intrathoracic blood volume in mitral stenosis and left ventricular failure. Clin. Sci. 1951, **10**, 383.
22. Doyle, J. T., Lee, R. A., and Kelley, E. B. Observations on the elasticity of the pulmonary vasculature in man. Amer. Heart J. 1952, **44**, 565.
23. Johnson, S. R. The effect of some anaesthetic agents on the circulation in man: With special reference to the significance of pulmonary blood volume for the circulatory regulation. Acta chir. scand. 1950, suppl. **158**, 9.
24. Sjöstrand, T. Volume and distribution of blood and their significance in regulating the circulation. Physiol. Rev. 1953, **33**, 202.
25. Weissler, A. M., Leonard, J. J., and Warren, J. V. The hemodynamic effects of isoproterenol on man: With observations on the role of the central blood volume. J. Lab. clin. Med. 1959, **53**, 921.
26. Lee, G. de J., Churchill-Davidson, H. C., Miles, B. E., and de Wardener, H. E. Circulatory effects of prolonged light anaesthesia in man. Clin. Sci. 1953, **12**, 169.
27. Etsten, B., and Li, T. H. Hemodynamic changes during thiopental anesthesia in humans: Cardiac output, stroke volume, total peripheral resistance and intrathoracic blood volume. J. clin. Invest. 1955, **34**, 500.
28. Frye, R. L., and Braunwald, E. Studies on Starling's law of the heart. I. The circulatory response to acute hypervolemia and its modification by ganglionic blockade. J. clin. Invest. 1960, **39**, 1043.
29. Marshall, R. The physiology and pharmacology of the pulmonary circulation. Progr. cardiovasc. Dis. 1959, **1**, 341.
30. McGaff, C. J., Jose, A. D., and Milnor, W. R. Pulmonary, left heart and arterial volume in valvular heart disease (abstract). Clin. Res. 1959, **7**, 230.
31. Dock, D. S., Kraus, W. L., Woodward, E., Dexter, L., and Haynes, F. W. Observations on pulmonary blood volume in man. Fed. Proc. 1959, **18**, 37.
32. van der Feer, Y. The measurement of circulation time by means of an indicator. Phys. in Med. Biol. 1958, **3**, 157.
33. Newman, E. V., Merrell, M., Genecin, A., Monge, C., Milnor, W. R., and McKeever, W. P. The dye dilution method for describing the central circulation: An analysis of factors shaping the time-concentration curves. Circulation 1951, **4**, 735.
34. Pearce, M. L., McKeever, W. P., Dow, P., and Newman, E. V. The influence of injection site upon the form of dye-dilution curves. Circulat. Res. 1953, **1**, 112.
35. Emanuel, R. W., Lacy, W. W., and Newman, E. V. Relative effects of heart chambers, lungs and mitral insufficiency on the shape of indicator dilution curves. Circulat. Res. 1959, **7**, 141.
36. Wang, Y., Shepherd, J. T., and Marshall, R. J. Evaluation of the slope-volume method as an index of pulmonary blood volume. J. clin. Invest. 1960, **39**, 466.