

TOTAL RED CELL VOLUME, PLASMA VOLUME, AND SODIUM SPACE IN CONGESTIVE HEART FAILURE¹

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A large volume of literature has accumulated in the past 15 years dealing with the importance of hypervolemia in the pathologic physiology of congestive heart failure. Most of the series of blood volumes reported to date on this question have been measured with the dye T-1824 (1-4), although other dyes have been used (5-7). The errors in the dye methods have been repeatedly pointed out (8-16). Chief among these are the early and significant disappearance of the dye-albumin complex into: (1) the lymphatic system; (2) the reticulo-endothelial system; and (3) the bile. In reality, therefore, the dye space is not synonymous with plasma volume but includes a part of the volume of the lymphatic system, biliary and reticulo-endothelial systems. The degree to which these latter will be included depends on: (1) individual mixing and diffusion factors, and (2) the time at which one concludes from the dilution curve that mixing has become complete.

In most of the above-mentioned studies, patients with definite signs of congestive failure have been found, almost without exception, to have significant elevation of their blood volume, amounting in some cases to as much as 300% above established normal values for the method. These likewise have been noted to return to the established normal levels upon return to the compensated state. However, it should be noted that Wollheim (7), using a modification of the dye method of Keith and Rowntree, (17), noted two types of congestive failure; the first with high and the second with low blood volumes. In both groups the blood volume returned toward normal as compensation was achieved.

The relative magnitude and time relationships of total red cell volume and the plasma volume

during congestive failure were also examined (1-4). Gibson and Evans (1) found that total red cell volume was elevated to a greater degree than plasma volume. In contrast, Seymour and his associates (2) found that the plasma volume rose more than did the total red cell volume. Other groups (3, 4) noted an equal rise in these components of blood volume. There was general agreement, however, that plasma volume was definitely more labile than total red cell volume, falling considerably more rapidly as compensation proceeded. This resulted in a temporary rise of the hematocrit, which returned to normal as the excess red blood cells were destroyed.

The relation between the severity of failure, as indicated objectively by venous pressure, and degree of hypervolemia represents a point of disagreement among the above-mentioned investigators. Gibson and Evans (1) found a direct and definite correlation between increasing venous pressure and rising blood volume, which Meneely and Kaltreider (3) did not confirm.

Since the development of methods utilizing red cells labeled with P³² (18) or Iron⁵⁹ (19), blood volume determination would appear to be on a theoretically sounder basis, the chief advantage being the localization of the labeled red blood cells in the vascular system and a consequent plateau level of radioactivity for a finite period of time (approximately one hour with P³²) (20) following mixing. During this time a sample can be withdrawn to determine accurately the degree of dilution which has taken place.

There is one possible objection to the determination of the total blood volume by the tagged red cell method; namely, that the hematocrit in peripheral veins may differ significantly from the "total body" hematocrit. Good evidence is lacking on this point, and the degree of difference depends on the method of approach to the problem. Ebert

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and Stead (21) removed an ordinary venous sample from the antecubital vein for hematocrit, hemoglobin and protein content, then applied a tourniquet to the upper arm at 300 mg. Hg pressure, removed all the available blood, this blood presumably representing that in the larger vessels. Thereafter, an Esmarch bandage was applied to the forearm from the wrist up and any remaining blood in the arm was thus "milked" out. This blood was thought to come from the minute vessels of the arm. When compared, the hemoglobin concentration of the last samples were from 0.8 gm. to 1.89 gm./100 cc. less than the original venous sample. They concluded that venous blood is richer in cells and poorer in plasma than the blood contained in minute vessels. From their figures, the value of small vessel hematocrit is approximately 10% lower than that in the peripheral veins. Furthermore, the total estimated amount of blood in the minute vessels is from 10% to 17% (22, 23). Therefore, the maximum difference between venous hematocrit and total body hematocrit brought about by the blood in the minute vessels could not exceed 1.5% unless a very large percentage of the blood was in the capillaries. The concept that the "total body hematocrit" differs from the venous hematocrit (24-27) has largely arisen because the total red cell volume as determined by labeled red cells has been shown consistently to be less than the total red cell volume as calculated from the plasma volume determined with T-1824 and the venous hematocrit. However, as pointed out above, the dye methods are subject to error, giving falsely high plasma volumes and in turn falsely high calculated red cell volumes. In fact, even the various modifications of the dye method by the Louisville group (28-30) were not satisfactory in that the total red cell volume as determined by the dye was still higher than when methemoglobin labeled red cells were used. Therefore, the total body hematocrit concept, at least from this standpoint, rests on questionable experimental evidence. Since the total body hematocrit depends upon the plasma volume, a falsely high plasma volume calculation would lead to a falsely low total body hematocrit.

$$\left(\begin{array}{l} \text{Total body hematocrit} \\ = \frac{\text{Total red cell volume}}{\text{Total plasma} + \text{total red cell volume}} \end{array} \right)$$

From the available evidence we do not believe that the total body hematocrit differs significantly from the venous hematocrit. We therefore believe the labeled red cell method for determining blood volume to be accurate. No positive data have been produced to support this concept. But the weight of evidence against varying hematocrits, when viewed as a whole (16), certainly lends credence to it.

Nylin and Hedlund (20) studied seven patients in congestive failure using P^{32} labeled red cells; their results are not in complete agreement with the previous studies with the dyes. The data of these authors differed from the dye studies in that with primary left-sided failure with pulmonary congestion and high venous pressure, blood volume was found to be practically normal and to remain practically constant with return of compensation. They found no correlation between venous pressure and blood volume in their cardiac patients. Recently Ross, Baka and Freis (31) have studied a group of patients with congestive failure with P^{32} labeled cells, and found that there was no significant increase in circulating blood volume in patients with congestive failure as compared to controls. The types of cardiac abnormalities studied were not stated in this abstract.

METHODS

The blood volume was determined with P^{32} labeled cells in 27 patients with congestive heart failure by the method of Hevesy and Zerahn (18) as modified in this laboratory (32, 33).³ With labeled red blood cells, the total red cell volume is determined and is independent of the hematocrit. The plasma volume and blood volume are calculated from the total red cell volume and the venous hematocrit. Since, as pointed out above, it is unlikely that venous hematocrit differs significantly from the "total body hematocrit," the calculation of blood volume and plasma volume by this method should not lead to error.

Serum sodium was determined by the zinc uranyl acetate method (34). The normal range of serum sodium concentration using this method is 135-148 meq./liter. For the determination of total exchangeable body sodium, patients were given approximately 100 μ c. of Na^{24} and the radioactivity of a plasma sample 18 hours after adminis-

³ Blood samples for determination of dilution were taken 20 minutes after administration of P^{32} labeled cells. Nylin and Hedlund (20) have shown that mixing of red cells is complete well within this time in patients with congestive failure.

tration was determined in the same manner as were the P^{23} samples (32).

$$\text{Total exchangeable body sodium space} = \frac{\text{Disintegration/min. Na}^{24} \text{ injected} - \text{Disint./min. Na}^{24} \text{ excreted in urine}}{\text{Disint./min. Na}^{24} \text{ cc. of plasma}}$$

This calculation assumes a homogeneous concentration of the sodium. Since sodium is not homogeneously distributed but is present in high concentration in bone and in low concentration in cells, the value obtained by calculation is virtual rather than actual. However, "sodium space" measurements are of considerable value when used comparatively. Total exchangeable sodium is then determined by the following equation, assuming that at the end of 18 hours the specific activity of Na is uniform throughout the body.

$$\text{Serum sodium concentration in meq./liter} \times \frac{\text{"Sodium space" in liters}}{\text{Total sodium in meq.}} = \text{Total sodium in meq.}$$

Where the 18-hour plasma samples contained both Na^{24} and P^{23} , the following method was used to delineate the amount of activity of each:

(1) The 18-hour plasma sample was counted initially, and one equation set up: $\text{Na}^{24} + P^{23} = \text{initial count}$.

(2) The same sample was counted 24 hours later, and a second equation set up: $\% \text{ remaining Na}^{24} + \% \text{ remaining P}^{23} = \text{count at 24 hours}$.

The per cent remaining of each isotope at any given time was calculated from their well-established physical half-lives. There are then two simultaneous linear equations with two unknowns which can easily be solved for both unknowns.

The criteria for heart failure are the usual; namely, evidence of cardiac abnormality by history, physical examination and/or laboratory means. In addition, the presence of all or several of the following were required: dyspnea, orthopnea, cyanosis, pulmonary congestion and edema, peripheral edema, and fluid in the thoracic or abdominal cavities. Details of therapy are not outlined for each patient because Table III describes the exact clinical status of the patient on the day the blood volume was determined, as evaluated by examination at that time.

The symptoms and physical signs of each patient are given in Table III. The data are expressed in terms of "wet" and "dry" cc./kilo. Wet weight includes edema fluid. Dry weight indicates body weight when patient had returned to partial or fully compensated state. Where only one determination was done, we have arbitrarily subtracted 6 kilos and used the resulting figure as "dry" weight. The expression of volumes as cc./kilo of "dry" weight was used in order to avoid getting falsely low values, expressed as cc./kilo, because of excess weights. Admittedly, a certain percentage of patients will have more than 6 liters of edema fluid, so that our correction factor will be inadequate. However, even assuming they contain 12 liters excess, the values expressed in cc./kilo in a 70-kilo individual would be only 8.5% too low. Furthermore, the majority of patients studied had minimal to moderate edema, only four being classed as 4+ in degree. Warner and his co-workers (35) have recently observed the correlation between edema and *excess* "sodium space." They found that 1+ edema in an average individual (1.73 m²) corresponded to an excess of roughly 3 liters while 4+ edema represented approximately 13 liters, with gradations as expected between these limits. These figures further validate our 6-

TABLE I
Group with normal blood volumes

Name	Date	Age	Weight		Total blood volume (cc.)	Total blood volume (cc./kilo)		Total red cell volume (cc./kilo)		Plasma volume (cc./kilo)		Hemato-crit
			Wet	Dry		Wet	Dry	Wet	Dry	Wet	Dry	
*R. W.	8-23-50	40	—	61.4	4,236	—	68.9	—	28.1	—	40.0	41
M. S.	7-25-50	74	78.6	72.6	3,598	45.8	49.6	26.1	28.2	19.2	20.8	51
1) C. R.	8-17-50	38	68.6	—	3,740	54.5	—	23.3	—	30.7	—	43
2) C. R.	8-31-50	38	—	54.5	4,199	—	77.0	—	33.1	—	43.2	43
*H. R.	7- 6-50	59	—	81.8	3,755	—	45.9	—	20.2	—	25.2	44
C. P.	7-18-50	71	59.5	53.5	3,481	58.5	75.6	24.6	31.8	33.3	43.1	47
*W. M.	11-17-50	84	—	81.8	5,387	—	65.8	—	26.3	—	38.9	40
*F. G.	7-26-50	74	—	102.3	4,239	—	41.4	—	14.5	—	26.5	35
M. Gr.	8- 9-50	53	61.4	55.4	4,354	70.9	79.2	29.8	33.2	40.4	46.0	47
M. G.	5-22-50	47	64.5	59.5	3,380	52.4	58.8	27.7	30.3	24.7	28.5	53
1) A. G.	6-14-50	62	73.1	—	4,605	62.9	—	32.1	—	30.2	—	51
2) A. G.	6-22-50	62	—	68.1	5,196	—	76.3	—	38.1	—	37.4	50
1) *S. C.	12- 7-49	34	—	52.2	2,694	—	51.5	—	20.6	—	30.0	40
2) S. C.	8-18-50	34	—	52.2	3,012	—	57.9	—	24.8	—	32.3	43
1) T. A.	5-12-50	62	106.3	—	4,084	37.7	—	23.4	—	14.2	—	61
2) T. A.	9-27-50	62	—	99.1	6,793	—	68.5	—	34.9	—	32.9	51
Mean values		58.3	73.1	68.8	3,962.7	54.7	62.8	26.7	28	27.5	34.2	44.5

* Patient too ill to be weighed. Therefore, either the patient's usual weight prior to illness was used; or, when available, the weight was determined after recovery.

TABLE II
Group with high total red cell volume, plasma volume or total blood volume

Name	Date	Age	Weight		Total blood volume (cc.)	Total blood volume (cc./kilo)		Total red cell volume (cc./kilo)		Plasma volume (cc./kilo)		Hemato-crit
			Wet	Dry		Wet	Dry	Wet	Dry	Wet	Dry	
A. Patients with Rheumatic Valvulitis												
1/R. S.	9-14-50	50	56.4	—	5,113	90.7	—	41.7	—	49.0	—	46
2/R. S.	10-16-50	50	—	50.9	4,500	—	88.4	—	41.4	—	45.9	47
L. S.	11-21-50	61	48.2	42.2	4,255	88.3	101.0	37.1	42.3	51.2	58.7	42
I. R.	12- 1-50	34	43.6	37.6	4,505	103.3	120.0	46.5	54.0	56.8	66.0	45
P. D.	11-16-50	47	70.0	64.0	6,768	96.7	100.6	46.4	50.7	49.7	49.9	48
C. E.	1-29-51	45	60.0	54.0	4,969	82.8	91.8	40.6	45.1	41.4	46.0	49
C. C.	1- 2-51	48	57.7	51.7	5,000	86.7	96.7	39.8	44.5	45.8	51.2	46
M. B.	1-29-51	46	47.3	41.3	3,447	73.0	83.4	35.7	40.6	36.4	41.7	49
Mean		47.2	56.4	48.8	4,865	88.7	97.4	41.1	45.5	47.1	51.3	46.4
B. Nonrheumatic Patients												
S. W.	8-31-50	43	55.5	49.5	3,377	60.8	68.0	17.0	19.5	42.6	47.6	28
W. N.	12- 5-50	64	60.0	54.0	3,706	61.8	68.5	14.8	16.5	46.3	52.0	24
H. M.	8- 3-50	44	81.8	75.8	6,319	77.2	83.3	19.4	20.8	57.8	62.5	25
D. M.	8- 2-50	61	54.5	49.5	3,533	64.8	73.0	37.0	41.5	27.8	31.5	57
1/M. K.	7-13-50	34	51.7	—	4,469	86.4	—	27.7	—	57.9	—	32
2/M. K.	7-27-50	34	—	45.9	4,588	—	99.9	—	39.0	—	60.9	39
*M. H.	12- 8-50	83	—	39.5	2,629	—	66.5	—	37.2	—	28.6	56
*A. G.	11-30-50	74	—	59.5	4,421	—	74.3	—	18.5	—	54.9	25
B. K.	12- 8-50	70	49.1	43.1	4,417	90.0	102.5	40.5	46.2	48.6	55.4	45
Mean		57.5	60.6	53.4	4,065	73.4	79.5	26.0	29.9	46.8	49.1	32.9

* See footnote to Table I.

kilo correction factor for patients, most of whom had minimal to moderate edema.

Venous pressures were determined by measuring the height of a column of saline in a spinal fluid manometer, the arm being leveled by means of external landmarks at a point approximating the entrance of the superior vena cava into the right auricle. Arm to tongue circulation times were determined with 5 cc. of "decholin."

RESULTS

The results are summarized in the Tables I-III and Figures 1-3.

DISCUSSION

For purposes of discussion it should be noted that the normal total red cell volume and plasma volume values in males and females expressed in cc./kilo are as follows (33, 36) : In males the total red cell volume averages 29.9 (range 22.8 to 35.8) and the plasma volume, 38.7 (range 32.6 to 45.1). In females the total red cell volume averages 27.0 (range 21.1 to 32.7) and the plasma volume, 37.0 (range 27.3 to 46.6).

Table I includes all patients who had entirely normal or low total red cell volume, plasma volume and blood volume while in failure. Twelve patients are in this group, or 44.5% of the total; six are males and six females. This group can be divided into three clinical categories: a) Primarily

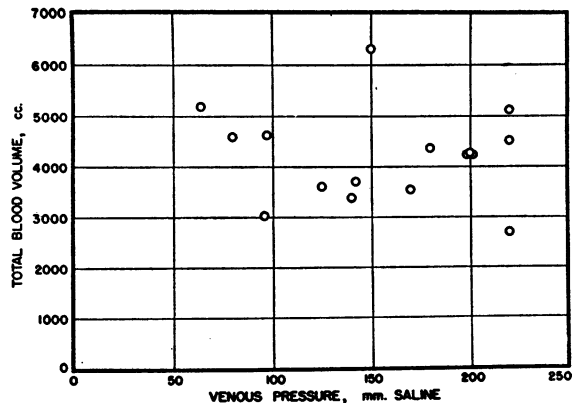


FIG. 1. RELATIONSHIP OF BLOOD VOLUME TO VENOUS PRESSURE, IN TOTAL CC.

TABLE III

	R. W.	M. S.	C. R. (1)*	C. R. (2)*	H. R.	C. P.	W. M.	F. G.
Age	40	74	38	38	59	71	84	74
Sex	M	F	F	F	F	M	M	M
Diagnosis	HCVD†	HCVD Diabetes mellitus	HCVD	HCVD	Myocardial infarction ASHD†	ASHD	Myocardial infarction HCVD	ASHD Myocardial infarction
B. P.	138/120	190/100	144/102	—	110/60	150/80	214/118	140/105
Pulse	90	92	100	66	60	80	88	90
Respiration	30	28	26	18	28 Shallow	30	34	32
Heart	Enlarged, Grade III mitral systolic, gallop rhythm	Enlarged, regu- lar. Grade III mitral systolic murmur	Enlarged, gallop rhythm. No murmurs	Enlarged, gallop rhythm. No murmurs	Sl. enlarged, frequent extra systoles, tones distant	Enlarged, regu- lar. Soft mitral murmur	Enlarged, regu- lar, distant tones	Enlarged, regu- lar, distant tones
Lungs	Basal rales right hydro- thorax	Rales through- out both lung fields	Clear	Clear	Crepitant rales both bases	Rales lower 2/3, both lungs	Moist rales lower 2/3, semile emphysema	Crepitant rales, both bases
Liver	Two fingers below costal margin	0	Questionable due to ascites	Two fingers below costal margin	0	Questionable due to dyspnea and orthopnea	Not felt	Four fingers below costal margin
Ascites	0	0	Very marked	None	0	0	0	0
Peripheral edema	0	++ Feet and ankles	None	None	0	Extensive sacral genitalia	Minimal sacral	0
Duration of illness	Three weeks. Repeated failures one year	Two weeks	Nine days. Repeated failures past three years	Two weeks later	Three weeks progressive. EKG myocar- dial infarction	Gradual. One year. Rapid progress— 3-4 weeks	Acute myocar- dial infarction— 2 days	Increasing dysp- nea one week. Infarction of myocardium 1 day
V. P.	200	125	Not done	Not done	Not done	Not done	Not done	200

TABLE III—Continued

	M. Gr.	M. G.	A. G. (1)	A. G. (2)	S. C. (1)	S. C. (2)	T. A.	R. S. (1)
Age	53	47	62	62	34	34	63	50
Sex	F	F	M	M	F	F	M	M
Diagnosis	HCVD	RhHD, § Auric fibrillation	HCVD	HCVD	HCVD due to chronic glomerulonephritis	HCVD due to chronic glomerulonephritis	HCVD Obesity	RhHD with mitral stenosis and constrictive pericarditis
B. P.	180/120	110/70	200/170	—	260/160	210/130	160/100	110/80
Pulse	96	128	120 Sl. cyanosis	80	130	80	80	90
Respiration	24	26	24	20	24 Labored	20	26	22
Heart	Very large. Frequent extra systoles. Grade III aortic murmur	Enlarged, fibrillating, loud mitral systolic murmur	Enlarged, regular, with mitral systolic and diastolic murmurs	Enlarged, regular, with mitral systolic and diastolic murmurs	Enlarged, regular	Enlarged, regular	Enlarged, regular. No murmurs	Enlarged, fibrillating, mitral systolic and diastolic murmurs
Lungs	Systolic murmur. Crepitant rales throughout both lungs	Crepitant and moist rales lower halves	Bilateral crepitant basal rales	Clear	Loud bubbling rales throughout	Clear	Moist rales left base	Crepitant and moist rales, lower halves bilaterally
Liver	Four fingers below costal margin. Tender	Three fingers below costal margin	Two fingers below costal margin	Not definitely palpable	Questionable due to dyspnea and orthopnea	0	Questionable due to obesity and ascites	Four fingers down
Ascites	0	Marked	Moderate	None	None	0	Moderate	Marked
Peripheral edema	0	++++ General anasarca	+++ to ++++ extending up to mid thigh	None	Minimal, feet and ankles	0	Moderate of feet, ankles and calves. Gradually progressive	+++ to ++++ lower extremities
Duration of illness	Repeated failures for two years; present episode 1-2 weeks	Progressive dyspnea and edema, 2 weeks. 25 years known RhHD	Rapidly progressive 1 week	Two weeks later	Chronic glomerulonephritis—6 years. Several previous failures	Done when patient fully compensated before present failure	Two months, 11 days treatment before first blood volume was done	Repeated failure since 1920. Five hospitalizations. Progressive failure for past month
V. P.	180	Not done	97	64	Not done	96	Not done	220

TABLE III—Continued

	R. S. (2)	L. S.	I. R.	P. D.	C. E.	C. C.	M. B.	S. W.
Age	50	60	34	47	45	44	45	40
Sex	M	F	F	M	F	M	F	F
Diagnosis	RhHD with mitral stenosis and constrictive pericarditis	RhHD with mitral stenosis and insufficiency HCVD	RhHD with mitral stenosis and insufficiency	RhHD with mitral stenosis and insufficiency	RhHD with mitral stenosis and insufficiency	RhHD with mitral stenosis and insufficiency	RhHD with mitral stenosis and insufficiency	HCVD
B. P.	110/80	210/110	120/70	110/70	118/80	126/90	128/110	175/105
Pulse	66	78	130	80	78	50	70	104
Respiration	18	18	32	22	28	20	24	24
Heart	Enlarged, fibrillating, mitral systolic and diastolic murmurs	Enlarged, regular, mitral systolic and diastolic murmurs	Enlarged, fibrillating, mitral systolic and diastolic murmurs	Enlarged, fibrillating, loud systolic mitral murmur	Enlarged, fibrillating, mitral systolic and diastolic murmurs	Enlarged, regular, mitral systolic and diastolic murmurs	Enlarged, fibrillating, mitral systolic and diastolic murmurs	Enlarged, regular. No murmurs
Lungs	Crepitant rales left base. Right lung clear	Crepitant rales both bases	Crepitant rales lower thirds bilaterally	Crepitant rales lower thirds bilaterally	Rales, right base. Left hydrothorax	Rales, left base	Rales left base. Right hydrothorax	Crepitant rales, both bases
Liver	One finger down	Four fingers down	Five fingers down	Three fingers down. Tender	Five fingers down	Four fingers down	Six fingers down	Two fingers down
Ascites	None	None	None	0	0	0	Slight	Questionable, slight
Peripheral edema	Negative	None	None	+++ to knees	+++ to umbilicus	0	Negative	++ feet and ankles
Duration of illness	Four weeks later	Progressive failure for 2 weeks. Several previous failures	Recurrent failures. Present acute episode began 2 days ago	Known RhHD since age 15. Many previous failures. Present episode 2 weeks progressive	Acute rheumatic fever, age 13. First failure 1939. Fairly well until 2 weeks ago. Progressive failure since then	Chronic mild failure 2 years requiring maintenance mercurials. Progressive failure 3 weeks	Chronic failure 4 years. Hospitalization much of the time	One-two months with increasing dyspnea and ankle edema
V. P.	Not done	200	225	Not done	Not done	Not done	Not done	140

TABLE III—Continued

	W. N.	H. M.	D. M.	M. K. (1)	M. K. (2)	M. H.	Al. Gonz.	B. K.
Age	64	44	61	34	34	78	74	70
Sex	M	F	F	F	F	F	M	M
Diagnosis	HCVD	HCVD	Cor. pulmonale. Diffuse pulmo- nary fibrosis	HCVD	HCVD	ASHD	HCVD	HCVD
B. P.	190/110	250/120	130/90	230/130	200/100	125/60	210/100	180/100
Pulse	80	90	100	84	76	120	120	76
Respiration	30	30	26 Cyanosis of lips and fingers	28	18	30	30	28
Heart	Enlarged, regular. No murmurs	Enlarged, gallop rhythm. No murmurs	Enlarged, regular. No murmurs	Enlarged, regular rhythm. Grade IV mitral systolic murmur	Enlarged, regular rhythm. Grade IV mitral systolic murmur	Enlarged, regular. No murmurs	Enlarged, rapid regular; loud systolic aortic murmur	Enlarged, regular. Grade I mitral systolic murmur
Lungs	Bilateral basal rales	Crepitant rales both bases	Coarse rales, lower halves, bilaterally	Crepitant rales lower thirds bilaterally	Clear	Moist rales lower halves	Crepitant rales both lower thirds	Rales both bases
Liver	One finger down	Three fingers down	0	Five fingers down	Two fingers down	Two fingers down	Two fingers down	Two fingers down
Ascites	Slight amount (autopsy)	Questionable slight	0	0	0	0	0	0
Peripheral edema	++ feet and ankles	+++ lower extremities	Massive extend- ing to nipple line	0	0	+++ to thighs	0	0
Duration of illness	Gradual pro- gressive dysp- nea, orthopnea; lower extremi- ties, edema for past 3 months	Weeks, three previous failures in past 5 years	Increasing edema for 2 weeks. Respi- ratory symp- toms minimal	Severe hyper- tension past 10 years, picked up in pregnancy. Urine clear. Present episode 2-3 weeks	Two weeks later	Increasing failure past month	"Leaky heart" for years. Tachycardia 1 month. In- creasing failure for 4 days	Intermittent failure, 6 years. Present episode progressive for past 3 weeks
V. P.	142	150	170	Not done	80	Not done	Not done	Not done

* (1) and (2) represent clinical findings during failure and after compensation had returned.

† HCVD—Hypertensive Cardiovascular Disease.

‡ ASHD—Arteriosclerotic Heart Disease.

§ RhHD—Rheumatic Heart Disease.

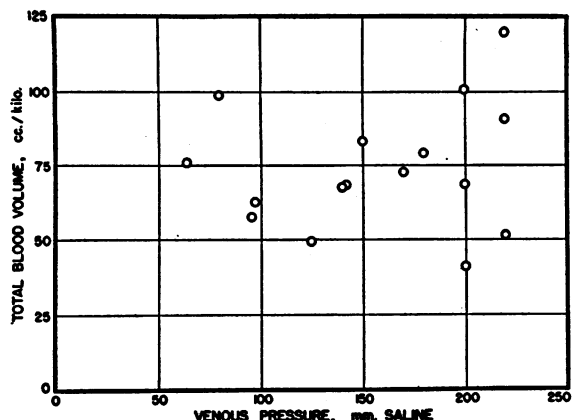


FIG. 2. RELATIONSHIP OF BLOOD VOLUME TO VENOUS PRESSURE, IN CC./KILO

right-sided failure, *b*) primarily left-sided failure, *c*) failure of both sides of heart to a significant degree. We recognize the fact that failure of the right ventricle rarely occurs in the absence of failure of the left, or vice versa. However, the clinical picture is very often determined by marked failure of one side and minimal failure of the other, or marked failure of both sides. Accordingly, the patients have been separated into the above categories. Patients were put in Group A when peripheral edema, liver engorgement, or ascites were marked while dyspnea and pulmonary engorgement played a minor role. They were placed in Group B under circumstances just the reverse of Group A. Group C comprised those patients with significant degrees of failure in the greater and lesser circuits. One patient was in Group A, four in Group B, and seven in Group C.

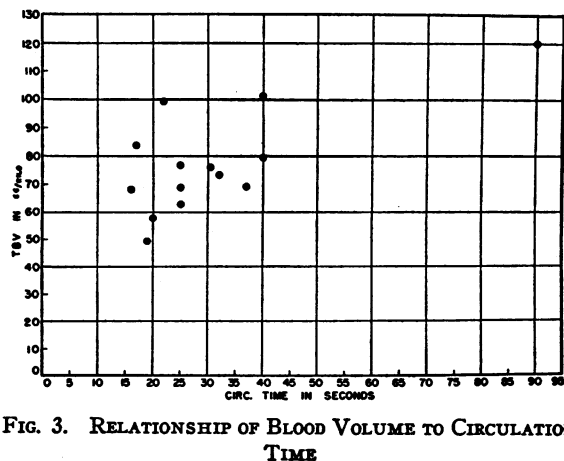


FIG. 3. RELATIONSHIP OF BLOOD VOLUME TO CIRCULATION TIME

It is thus seen that in this group of patients with congestive heart failure and normal blood volume there is not a predominance of left-sided failure. In fact, they comprise only one third of patients designated in Table I. It should be noted that in this group, 11 of the patients were in failure as a result of either arteriosclerotic or hypertensive heart disease and that only one patient had rheumatic heart disease.

All types of failure were found in the group with normal blood volumes. Also to be noted among those in Table I were the four patients where repeat blood volumes were done when compensation had returned. In every case there was a significant rise in blood volume as compensation returned. In three of these patients the total red cell volume and plasma volume rose to an equal degree. The fourth patient showed a much greater increase in plasma volume than total red cell volume.

Table II includes all patients with any elevation of total blood volume, total red cell volume or total plasma volume. There are 15 patients in this group, or 55.5% of the total. There are nine females and six males. This group has been divided into: (A) those whose failure has been caused by old rheumatic valvulitis; (B) others—principally arteriosclerotic heart disease and hypertensive cardiovascular disease. Of the patients in Table II, all had significant involvement of both greater and lesser circulation. No patients with early acute left ventricular failure were available for study during this investigation.

It will immediately be seen that the mean values for the total blood volume and its components in Group B border very closely on normal. It will be noted that four patients in this group were definitely anemic; the anemias being, as far as could be determined, on an azotemic basis. It has been observed that a low total red cell volume may be accompanied by a high plasma volume, presumably a compensatory mechanism through which normal total blood volume is maintained. Therefore, it is not unlikely that these individuals were thrown into the high volume group because of their anemia with compensatory high plasma volumes, rather than as a result of heart failure. Nevertheless, three out of four have normal total blood volumes. Again a rise in blood volume with compensation occurred in one repeat study. In

contrast, the first subgroup, the rheumatics, show strikingly high volumes. The mean value of their blood volume expressed in cc./kilo is 17.9 cc. greater than the mean of the total group in Table I, the total red cell volume and plasma volume being increased to an approximately equal degree. One repeat study done in this group revealed a moderate fall in blood volume when compensation returned, total red cell volume expressed as cc./kilo remaining the same, but plasma volume falling 3.1 cc./kilo. This was the only instance in a total of six repeat determinations in both groups, in which the blood volume did not rise when compensation returned.

As a group, therefore, the rheumatics have a much higher blood volume than those patients without rheumatic heart disease. Nevertheless, one patient with rheumatic heart disease and in failure had an entirely normal blood volume and two patients with nonrheumatic heart disease had very high volumes. In one of these two patients the increase in total blood volume was caused by equal increments of total red cell volume and plasma volume. The other patient had a greater rise in plasma volume than in total red cell volume.

In agreement with Meneely and Kaltreider (3), and as shown by the scatter diagrams in Figures 1 and 2, no correlation was found between either venous pressure or circulation time and blood volume. However, as previously noted, our blood volume data differed markedly from theirs. Using the product moment method, the coefficient of correlation between venous pressure and total blood volume was 0.17. It was not possible to correlate blood volume and venous pressure separately in the right-sided and left-sided failure groups because almost all patients in whom venous pressure was measured had significant failure of both sides of the heart.

The finding of a normal or only minimally increased blood volume in most (18 of 27) patients in frank cardiac decompensation requires a re-examination of some of the current concepts of the pathologic physiology of cardiac decompensation as regards blood volume, particularly in patients with arteriosclerotic heart disease, hypertensive cardiovascular disease, or myocardial infarction, etc.

Of interest are the serum sodium values measured in seven of these patients (Table IV). Three

TABLE IV
Serum sodium and total body sodium values

Patient	Serum sodium (meq.)	Total sodium		Sodium space (liters)	% Body weight
		(meq.)	(gm.)		
1/C. P.	145.7	4,939	113.6	33.9	57.0
2/C. P.	143.0				
A. G.	145.5				
1/M. K.	143.0	3,147	72.4	22.0	42.5
2/M. K.	140.0				
1/C. R.	147.8	5,084	116.9	34.4	50.0
2/C. R.	142.0				
H. M.	147.0				
M. G.	146.0	3,720	85.6	25.5	41.5
C. W.	148.0				

of these seven patients were restudied after complete or partial compensation had occurred. In agreement with previous reports (37) we found no patients with serum sodium concentration elevated beyond the range of normal.⁴ In those with repeat studies after compensation, no significant fall in serum sodium values (average of 3 meq.) was found. Total exchangeable body sodium determinations were done in four of these patients using Na²⁴ and invariably high values were found in failure. Sodium has been found to equilibrate rapidly between plasma and extracellular fluid (39, 40). Any increase in sodium level of the body results in concomitant expansion of the sodium (approximately extracellular) space rather than a rise in sodium concentration. Contrary to the suggestion of Warren and Stead (41) the plasma volume did not rise as the interstitial space expanded, nor vice versa, in five out of six cases studied during and after failure. In fact, just the opposite occurred. As compensation returned, with edema disappearing, the plasma volume rose. From these observations it appears that plasma volume is not controlled directly by rise and fall of the volume of the interstitial space.

CONCLUSIONS

(1) The blood volume has been determined with P³² labeled red blood cells in 27 patients in congestive failure.

⁴ Total exchangeable body sodium determinations and serum Na concentrations have been done in approximately 30 patients in congestive failure by Warner and his associates (35) in this laboratory using Na²⁴ and the flame photometer method (38). They also have found markedly elevated total exchangeable body sodium levels, and serum sodium concentrations which vary from normal to low.

(2) Twelve of 27 patients had normal blood volume, total red cell volume and plasma volume. In 11 of these patients the failure was due to arteriosclerotic heart disease or hypertensive cardiovascular disease; in one, a result of old rheumatic valvulitis.

(3) Fifteen of the 27 patients had either an elevated blood volume, total red cell volume, or plasma volume. These 15 patients were divided into two groups: (A) those with rheumatic valvulitis, seven; and (B) those with hypertensive cardiovascular disease or arteriosclerotic heart disease, eight. In Group A the total blood volumes were markedly increased, total red cell volume and plasma volume rising in equal degrees; in Group B, only slightly increased, the degree of rise in total red cell volume and plasma volume varying markedly from patient to patient.

(4) In five of six instances studied, the blood volume increased when compensation occurred. In the sixth patient, blood volume decreased with return of compensation.

(5) Serum sodium concentration did not change markedly during heart failure, but total body sodium rose to a marked degree.

REFERENCES

- Gibson, J. G., 2nd, and Evans, W. A., Jr., Clinical studies of the blood volume. III. Changes in blood volume, venous pressure and blood velocity rate in chronic congestive heart failure. *J. Clin. Invest.*, 1937, 16, 851.
- Seymour, W. B., Pritchard, W. H., Longley, L. P., and Hayman, J. M., Jr., Cardiac output, blood and interstitial fluid volumes, total circulating serum protein, and kidney function during cardiac failure and after improvement. *J. Clin. Invest.*, 1942, 21, 229.
- Meneely, G. R., and Kaltreider, N. L., A study of volume of the blood in congestive heart failure. Relation to other measurements in 15 patients. *J. Clin. Invest.*, 1943, 22, 521.
- Waller, J. V., Blumgart, H. L., and Volk, M. C., Studies of blood in congestive heart failure, with particular reference to reticulocytes, erythrocyte fragility, bilirubinemia, urobilinogen excretion and changes in blood volume. *Arch. Int. Med.*, 1940, 66, 1230.
- Brown, G. E., and Rowntree, L. G., The volume and composition of the blood, and the changes incident to diuresis, in cases of edema. *Arch. Int. Med.*, 1925, 35, 129.
- Thompson, W. O., Studies in blood volume. I. The blood volume in myxedema with a comparison of plasma volume changes in myxedema and cardiac edema. *J. Clin. Invest.*, 1925-26, 2, 477.
- Wollheim, E., Die zirkulierende Blutmenge und ihre Bedeutung für Kompensation und Dekompensation des Kreislaufs. *Ztschr. f. klin. Med.*, 1931, 116, 269.
- Peters, J. P., The role of sodium in the production of edema. *New England J. Med.*, 1948, 239, 353.
- Cardozo, E. L., The disappearance of the blue dye T-1824 from the blood stream into the thoracic duct lymph. *Arch. néerl. de physiol.*, 1941, 25, 410.
- Wish, L., Furth, J., and Storey, R. H., Direct determinations of plasma, cell and organ-blood volumes in normal and hypervolemic mice. *Proc. Soc. Exper. Biol. & Med.*, 1950, 74, 644.
- King, B. G., Cole, K. S., and Oppenheimer, E. T., Disappearance curves of the dye T-1824 after its injection into the blood stream. *Am. J. Physiol.*, 1943, 138, 636.
- Smith, H. P., Studies on vital staining. II. The removal of brilliant vital red from the blood stream. Distribution of dye between blood stream and body tissues. *J. Exper. Med.*, 1930, 51, 379.
- Smith, H. P., Studies on vital staining. III. The simultaneous ingestion of two dyestuffs by phagocytes. The question of "blockade of the reticulo-endothelial system." *J. Exper. Med.*, 1930, 51, 395.
- Smith, H. P., The fate of an intravenously injected dye (brilliant vital red) with special reference to its use in blood volume determination. *Bull. Johns Hopkins Hosp.*, 1925, 36, 325.
- Ferrebee, J. W., Leigh, O. C., and Berliner, R. W., Passage of the blue dye T-1824 from the blood stream into the lymph. *Proc. Soc. Exper. Biol. & Med.*, 1941, 46, 549.
- Berlin, N. I., and Grossman, L. M., A critique of the use of the dye methods for the determination of blood volume and the concept of total body hematocrit. To be published.
- Wollheim, E., Die Bestimmung der zirkulierende Blutmenge. *Ztschr. f. klin. Med.*, 1928, 108, 463.
- Hevesy, G., and Zerahn, K., Determination of the blood corpuscle content. *Acta physiol. Scandinav.*, 1942, 4, 376.
- Hahn, P. F., Balfour, W. M., Ross, J. R., Bale, W. F., and Whipple, G. H., Red cell volume circulating and total as determined by radio iron. *Science*, 1941, 93, 87.
- Nylin, G., and Hedlund, S., Weight of the red blood corpuscles in heart failure determined with labeled erythrocytes during and after decompensation. *Am. Heart J.*, 1947, 33, 770.
- Ebert, R. V., and Stead, E. A., Jr., Demonstration that the cell-plasma ratio of blood contained in minute vessels is lower than that of venous blood. *J. Clin. Invest.*, 1941, 20, 317.
- MacLeod, J. J. R., *MacLeod's Physiology in Modern Medicine*, edited by Bard, P. C. V. Mosby Co., St. Louis, 1941, 9th ed.

23. Gibson, J. G., 2nd, Seligman, A. M., Peacock, W. C., Aub, J. C., Fine, J., and Evans, R. D., The distribution of red cells and plasma in large or minute vessels of the normal dog determined by radioactive isotopes of iron and iodine. *J. Clin. Invest.*, 1946, **25**, 848.
24. Hahn, P. F., Balfour, W. M., Ross, J. F., Bale, W. F., and Whipple, G. H., Red cell and plasma volumes (circulating and total) as determined by radio iron and by dye. *J. Exper. Med.*, 1942, **75**, 221.
25. Gibson, J. G., 2nd, Peacock, W. C., Seligman, A. M., and Sack, T., Circulating red cell volume measured simultaneously by the radioactive iron and dye methods. *J. Clin. Invest.*, 1946, **25**, 838.
26. Meneely, G. R., Wells, E. B., and Hahn, P. F., Application of the radioactive red cell method for determination of blood volume in humans. *Am. J. Physiol.*, 1947, **148**, 531.
27. Nachman, H. M., James, G. W., III, Moore, J. W., and Evans, E. I., A comparative study of red cell volumes in human subjects with radioactive phosphorus tagged red cells and T-1824. *J. Clin. Invest.*, 1950, **29**, 258.
28. Lawson, H. C., Overbey, D. T., Moore, J. C., and Shadle, O. W., Mixing of cells, plasma and dye T-1824 in the cardiovascular system of barbitalized dogs. *Am. J. Physiol.*, 1947, **151**, 282.
29. Lawson, H. C., Overbey, D. T., Shadle, O. W., and Moore, J. C., Effect of plasma injection on dye and cell content of arterial blood. *Am. J. Physiol.*, 1947, **151**, 303.
30. Moore, J. C., Shadle, O. W., and Lawson, H. C., Measurement of the circulating red cell volume with methemoglobin-tagged cells. *Am. J. Physiol.*, 1948, **153**, 322.
31. Ross, J. F., Baka, W. H., and Freis, E. D., The blood volume in congestive heart failure. *J. Clin. Invest.*, 1950, **29**, 842.
32. Berlin, N. I., Huff, R. L., Van Dyke, D. C., and Hennessy, T. G., The blood volume of the adult rat as determined by Fe⁵⁹ and P³² labeled red cells. *Proc. Soc. Exper. Biol. & Med.*, 1949, **71**, 176.
33. Berlin, N. I., Lawrence, J. H., and Gartland, J., The blood volume in chronic leukemia as determined by P³² labeled red blood cells. *J. Lab. & Clin. Med.*, 1950, **36**, 435.
34. Arnold, E. A., and Pray, A. R., A colorimetric method for the determination of sodium. *Indust. & Engin. Chem., Analyt. Ed.*, 1943, **15**, 294.
35. Warner, G. F., Dobson, E. L., Rodgers, C. E., Johnston, M. E., and Pace, N., The measurement of total "sodium space" in normal subjects and in patients with cardiac edema. *Circulation*, in press.
36. Berlin, N. I., Hyde, G. M., Parsons, R. J., Lawrence, J. H., and Port, S., Blood volume in the normal female as determined by P³² labeled red cells. *Proc. Soc. Exper. Biol. & Med.*, 1951, **76**, 831.
37. Fox, C. L., Jr., Friedberg, C. K., and White, A. G., Electrolyte changes in congestive heart failure: effects of administration of potassium and sodium salts. *Am. J. Med.*, 1949, **6**, 511.
38. Hald, P. M., Determinations with flame photometer, in *Methods in Medical Research*. Year Book Publishers, Chicago, Vol. IV, 1951.
39. Reaser, P. B., and Burch, G. E., Radiosodium tracer studies in congestive heart failure. *Proc. Soc. Exper. Biol. & Med.*, 1946, **63**, 543.
40. Threefoot, S., Burch, G., and Reaser, P., The biologic decay periods of sodium in normal man, in patients with congestive heart failure and in patients with the nephrotic syndrome as determined by Na²² as the tracer. *J. Lab. & Clin. Med.*, 1949, **34**, 1.
41. Warren, J. V., and Stead, E. A., Jr., Fluid dynamics in chronic congestive heart failure; interpretation of mechanisms producing edema, increased plasma volume and elevated venous pressure in certain patients with prolonged congestive failure. *Arch. Int. Med.*, 1944, **73**, 138.