STUDIES IN CONGESTIVE HEART FAILURE: *I. The Effect of Edema on Oxygen Utilization*

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STUDIES IN CONGESTIVE HEART FAILURE

I. The Effect of Edema on Oxygen Utilization *

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The cardinal symptoms of heart disease are dyspnea, edema, and pain. The recent important publication of Keefer and Resnik (1928) has done much to remove the subject of cardiac pain from the realm of controversy, and to lead to a better understanding of the mechanism by which it is produced, and hence, to a clearer clinical concept of its significance. Unlike cardiac pain, edema and dyspnea are ordinarily indications of congestive heart failure and although these two symptoms have been the subject of many valuable studies there is not yet entire agreement as to the exact physiological disturbances which lead to their production.

The observations to be presented in this paper are the first of a series of investigations devoted to the subject of heart failure. Therefore, it seems appropriate to mention briefly the various modern theories as to the mechanism by which the important symptoms are produced.

1. Inadequate cardiac output: According to this conception, all the symptoms of heart disease are to be explained by the inadequacy in the amount of blood pumped by the heart (Mackenzie, 1925). This hypothesis has been widely accepted in English-speaking countries. Thus: "The efficiency of the heart is nothing else than the volume of blood that it can pump in relation to the oxygen requirement of the body. This applies to the athlete, the man of sedentary habits, and to the cardiac patient. The index of efficiency is therefore the arteriovenous difference during rest and varying degrees of muscular exertion" (Henderson, Haggard and Dolley, 1927). Similarly, Meakins and Long (1927) state: "Circulatory failure may be defined as a state in which the volume of blood circulated per unit of time is not adequate for the physical needs of the moment." The proponents of the "inadequate cardiac output" theory have usually not stated just how the inadequacy produces edema. Increased capillary permeability has been suggested but has not been clearly demonstrated until recently when Landis (1928) showed that anoxemia did tend to make fluid pass out of the capillaries more readily. Martin Fischer (1921) believed that diminished blood flow led to the accumula-

tion of acid in the tissue cells, thereby increasing their water-binding power, and he attributed cardiac edema to this cause.

2. Slowing of the circulation: Plesch (1926) reported prolonged circulation time, increased blood volume and increased minute output in heart disease (*"Bei Herzkranken ist im allgemeinen das Minutenvolumen erhöht"*). He showed that the circulation time is prolonged and believed that this led to increased permeability of the capillary walls, which caused edema. Blumgart and Weiss (1927) observed diminished velocity of blood flow in cardiac decompensation. They did not conclude definitely, however, that this was the essential cause of the edema.

3. "Back-pressure:" In Germany and in France many observers seem to believe that the symptoms of heart failure are essentially dependent on a damming of blood in, and back from, a dilated heart. Krehl (1917) may be cited as one of the leading advocates of this view. Vaquez (1924) distinguishes sharply between left and right ventricular failure and, like Krehl, regards pulmonary congestion as secondary to the former and peripheral congestion to the latter. In each instance he seems to consider "back-pressure" as the essential factor. This is different from the conception of Mackenzie who regarded pulmonary edema as due to inability of the "enfeebled" right ventricle to pump blood through the lungs, and considered peripheral congestion and edema as due to similar failure of the left ventricle.

4. Lack of balance between the ventricles: This is essentially a modification of the "back-pressure" theory, in as much as the ventricle which is working under the greatest handicap is considered as failing to keep pace in output with the other less hampered ventricle and consequently congestion as occurring "back" of the failing side of the heart. This concept was applied to cardiac asthma by Eppinger, von Papp, and Schwarz (1924). Robinson (1927) and Harrison and Leonard (1926) have attempted to explain other circulatory phenomena of heart failure on this basis.

5. A combination of the above-mentioned theories: Certain authors believe that different patients present different types of circulatory derangement. Thus, Burwell (1928) believed that dyspnea on exertion in compensated cardiacs might be due to relative inability to increase the cardiac output, whereas edema could be explained by lack of ventricular balance.

Wiggers (1925) has compared cardiac failure in man to the conditions in animals poisoned by chloroform or other drugs which "depress" the heart. He believed that "back-pressure," when it occurred was secondary to decreased output due to myocardial weakness. Gibson (1927) believed that both diminished output and "back-pressure" were causative factors in the production of edema.

6. Disturbances of lactic acid metabolism: In 1927 Eppinger, Kisch and Schwarz published a monograph in which a new point of view was stated and very important data were presented concerning heart failure. These authors do not believe that cardiac failure can be explained by hemo-dynamics alone. Briefly summarized, their theory is that there is a disturbance in the resynthesis of lactic acid in heart disease. More than the usual one-fifth of the lactic acid produced has to be

burned, to accomplish which, oxygen consumption at rest and during exercise would have to be increased. When such compensation is inadequate the accumulation of lactic acid in the tissues leads to diminished buffering power. At first, the carbon dioxide tension of the blood is increased and this causes cardiac dilatation and increased output. Later, due to the excessive loss of bicarbonate, a state of acapnia supervenes and this causes slowing of the circulation, with diminished output, which produces edema and cyanosis. More recently Eppinger, Laszlo, and Schürmeyer (1928) have found that in animals in a state of shock, and with diminution of the circulating blood volume, the oxygen requirement for a given amount of work is increased. They believe that in congestive heart failure the circulating blood volume is similarly decreased because of the stagnation of large portions of the blood in various depots of the body. The circulation through the muscle is therefore diminished, as in acute circulatory collapse, and the state of oxygen lack thereby produced leads to the abnormal chemical processes in the muscles.

This short summary states the main points in each of the more important hypotheses of cardiac failure. Without a more detailed discussion, it is sufficient here to point out that the currency of so many theories suggests the need for further work.

It has seemed to us that a study of the symptoms of the cardiac patient offered the best approach to the problem. Consequently, this and succeeding papers to appear at an early date are concerned with cardiac edema. In the present publication our observations concerning the effect of edema on the circulation are presented.

METHOD

If one assumes constancy of oxygen consumption in a given portion of the body, then the more blood which flows through it per minute the less will be the amount of oxygen removed from each unit of blood. Likewise, when blood flow is decreased the amount of oxygen taken out per unit of blood will be correspondingly increased. Therefore, the oxygen utilization or arteriovenous difference of blood from given vessels affords, subject to the assumption mentioned, a general index to the amount of blood passing through the corresponding portion of the body.

Other investigators have studied the arteriovenous difference in the arms of patients suffering from cardiac disease. Lundsgaard (1918) observed increased utilization in all individuals with congestive failure and in "compensated" patients when the rhythm was markedly irregular. Harrop (1919) found that the arteriovenous oxygen differ-

ence of blood drawn from the arm was usually greater when failure was present than when it was absent. On the other hand, Eppinger, von Papp, and Schwarz (1924) frequently found normal or low values for oxygen utilization in their patients with congestive failure.

Instead of using blood from an arm vein we have studied the blood from the the femoral vein. The arms are rarely edematous in cardiac failure; the legs usually are. Hence, the state of the blood drawn from the legs may be expected to be a better index of the blood flow through edematous tissues. The only previous studies on the femoral venous oxygen are those of Blalock (1929) who found low utilization in patients with varicose veins. His results were rather surprising and led us to undertake a similar study in patients with heart disease.

Our observations were made after the patient had been lying quietly for twenty minutes or more in a semi-recumbent posture. This position was necessary because the subjects were often too short of breath to lie flat and because femoral venepuncture is difficult when the subject is sitting upright. The skin was sterilized in the usual manner, the femoral arterial pulsation felt and the puncture made at a point about three centimeters below Poupart's ligament and one centimeter medial to the point of maximal arterial pulsation. The needle was inserted vertically for a distance of two to five centimeters, depending on the size of the patient and the amount of fat. With a little practice the procedure was found to be easily carried out. The patients complained of no more pain than from an ordinary venepuncture.

The blood was drawn into a syringe containing oil and immediately expelled into a one-ounce bottle containing a small amount of oxalate and 10 cc. of oil. Oxygen determinations were made in duplicate on the Van Slyke-Neill (1924) manometric apparatus. In most instances analyses for carbon dioxide content were made also.

Arterial blood was drawn in the usual manner from the brachial or from the femoral artery.

A few observations were made on individuals with no disease of the heart or blood vessels, and a number of patients with edema due to some cause other than heart disease were studied. The cardiac patients represented all grades of congestive failure. In most instances the same patient was investigated with various degrees of edema.

The degree of edema of the legs has been judged according to the extent of distribution. The term "marked edema" has been used to describe those cases in which the entire lower extremity was involved. When the entire leg below the knee was swollen but the thighs were not, the cases were considered to have "moderate" edema. Edema confined to the ankles and feet has been called "slight." Since the presence of edema in a given spot had to be determined by "pitting," and since it is well known that a leg may contain a liter or more of excess fluid without demonstrable "pitting," it is obvious that what we have called "no edema" was really, in some instances, unrecognized edema.

It soon developed from our studies that digitalis intoxication had a marked effect on the femoral venous oxygen content. Therefore, it became necessary to adopt certain definite criteria for classifying our patients in this regard. Accordingly, any individual who had been receiving digitalis was considered to be suffering from over-dosage whenever he developed (*a*) nausea, (*b*) vomiting, or (*c*) pulsus bigeminus, provided that the toxic symptoms disappeared within three days after the administration of the drug was stopped.

Diminished alkali reserve of the blood was also found to be frequently associated with unusual changes in the oxygen utilization. It became necessary, therefore, in analysing our results to fix an arbitrary level below which our patients would be considered as acidotic. We have classified all individuals with an arterial carbon dioxide content of forty volumes per cent or less as having acidosis. In a few instances the arterial carbon dioxide content was not determined and in such cases, normal values have been assumed.

The patients studied were all adult males. Two of them had congestive heart failure caused by syphilitic aortic insufficiency. The others had congestive failure without valve lesions. (During the six months in which these studies were carried out we have not had a single adult male with congestive heart failure of rheumatic origin in the Vanderbilt University Hospital. This illustrates the rarity of rheumatic heart disease in the southern states as compared with other parts of the country (Harrison and Levine, 1924).)

Some of the cardiac patients had regular rhythm, others had auricular fibrillation, and a third group had ectopic beats.

RESULTS

The *oxygen capacity* exhibited no constant change, as the edema disappeared, in those individuals who had had edema for a long time. However, two of our patients (McC. and G. C.) had been edematous for only a few days when they came to the hospital. In those individuals diuresis was accompanied by a sharp rise in oxygen capacity. In their cases true hydremia (i.e., edema of the blood stream) seems to have been present. In two patients (C. H. and M. E.) who suffered from chronic pulmonary infections, a gradual sight fall in oxygen capacity was noted during several months of observations. Presumably, this anemia was due to the infectious process.

The *arterial saturation* was usually within normal limits or only slightly abnormal. Patients who had chronic pulmonary disease, acute severe pulmonary edema or acute pneumonia had low arterial saturations. The lowest value which we found was 47.5 per cent in (H. C.) dying of acute bronchopneumonia superimposed upon a rather severe degree of pulmonary edema. In one patient with uncomplicated pulmonary edema, an arterial saturation of 79 per cent was found twenty hours before death.

Our most striking instance of arterial anoxemia occurred, however, in a man (M. E.) with chronic bronchitis, atelectasis and bronchiectasis of extreme degree. This case will be reported elsewhere in detail. It is sufficient to state here that he lived for a period of several months with an arterial saturation below 75 per cent, and that he lived at least one month with his arterial blood less than 60 per cent saturated.

In general, it may be said that severe arterial anoxemia in patients with acquired cardiac disease occurs only in the presence of (*a*) acute or chronic pulmonary infection or (*b*) severe pulmonary edema. Slight degrees of anoxemia are common in patients with senile emphysema or moderate congestion and edema of the lungs. Many patients who have marked pulmonary congestion, as revealed by their vital capacities, accompanied or not by slight or moderate pulmonary edema, as judged by râles over the bases of the lungs, have arterial saturations within normal limits. These conclusions are similar to those arrived at by Meakins (1923) and by Eppinger, Kisch and Schwarz (1927).

The femoral venous oxygen content and the oxygen utilization of the legs: As our findings in this connection appear to be new and not with-

out significance they will be presented in some detail. In table 1 are shown the results of twelve analyses of blood from the femoral veins of several hospital patients who were selected at random and who had no edema and no disease of the heart or blood vessels. The

TABLE 1

The resting oxygen utilization of individuals with no disease of the circulatory system and no edema

Subject	Arterial oxygen content	Femoral venous oxygen content		Arteriovenous difference		Oxygen capacity	Percentage arterial saturation	Arterial carbon-dioxide content	Remarks
		Right	Left	Right	Left				
	volumes per cent	*volumes per cent*	*volumes per cent*	*volumes per cent*	*volumes per cent*	*volumes per cent*		*volumes per cent*	
B. M.	12.96	6.18	6.67	6.78	6.29	14.40	92.0	45.4	Convalescent from repair of inguinal hernia
H. R.	15.45	6.81		8.64		18.77	84.1	42.5	During mild attack of bronchial asthma
T. F.	13.80	7.09		6.71		15.30	92.9	42.5	Carcinoma of stomach
G. T.	17.45	6.89	8.00	10.56	9.45	18.95	94.2	41.2	Balanitis (temperature 39.8°C.)
N. S.	15.92	3.26	5.92	12.66	10.00	17.24	94.5	45.2	Injury of eye
C. A.	15.30	7.00	11.03	8.30	4.27	17.08	91.6	44.2	Amebic dysentery
D. S.	14.60	9.72	10.55	4.88	4.05	16.00	93.3	42.2	Convalescent from suprapubic cystostomy
F. R.	14.61	9.14		5.47		16.80	89.1	41.9	Peptic ulcer
C. L.	12.00	9.03		2.97		13.80	89.2	47.8	Lung abscess
J. W.	14.71	12.21		2.50		15.80	95.2	41.1	Diabetes mellitus

Lowest arteriovenous difference: 2.50. Highest arteriovenous difference: 12.66. Average arteriovenous difference: 6.90.

highest, lowest and average arteriovenous differences were 12.66, 2.50 and 6.90 volumes per cent, respectively.

Similar studies on patients with marked edema due to congestive heart failure are depicted in table 2. The highest, lowest and average utilization values in sixteen observations on seven patients were 9.00, 1.26 and 4.08 volumes per cent, respectively.

In table 3 are shown the studies on five individuals with moderate edema. In these eleven observations the figures for utilization vary

TABLE 2

The resting oxygen utilization of individuals with cardiac disease and marked edema*

Subject	Date	Arterial oxygen content	Femoral venous oxygen content		Arteriovenous difference		Oxygen capacity	Percentage arterial saturation	Arterial carbon-dioxide content	Remarks
			Right	Left	Right	Left				
		volumes per cent	*volumes per cent*	*volumes per cent*	*volumes per cent*	*volumes per cent*	*volumes per cent*		*volumes per cent*	
McC.	August 13, 1928	15.95	9.93	10.64	6.02	5.31	17.25	94.5	43.5	White, male, 72, hypertension, arteriosclerosis, regular rhythm
G. C.	September 8, 1928	12.22	10.90	10.96	1.32	1.26	14.00	87.4	45.7	Negro, male, hypertension, arteriosclerosis, regular rhythm
C. H.	July 21, 1928	13.08	8.53	9.66	4.55	3.42	14.25	93.8		White, male, 42, syphilitic aortic insufficiency, empyema, regular rhythm
	July 24, 1928	12.96	10.42	9.89	2.52	3.07	13.79	95.9		
H. C.	August 5, 1928	13.66	10.39	11.10	3.27	2.56	17.18	81.6	61.4	Negro, male, syphilitic aortic insufficiency, acute broncho-pneumonia, regular rhythm
R. P.	August 2, 1928	17.45	13.68	14.85	3.77	2.60	18.16	98.1	42.9	White, male, 58, hypertension, arteriosclerosis, auricular fibrillation
M. E.	September 5, 1928	12.30		8.55		3.75	20.00	63.5	58.5	White, male, 42, bronchiectasis, atelectasis, regular
T. B.	November 23, 1928	17.80	12.30		5.50		19.26	94.5	45.8	Negro, male, 74, hypertension, arteriosclerosis, auricular fibrillation
	November 25, 1928	17.52		10.16		7.36	19.33	92.6	47.9	
	November 28, 1928	17.18	8.18		9.00		18.28	96.0	41.0	

Lowest arteriovenous difference: 1.26. Highest arteriovenous difference: 9.00. Average arteriovenous difference: 4.08.

* Patients with "pitting" of the entire leg and thigh have been classified as having marked edema.

TABLE 3

The resting oxygen utilization of individuals with cardiac disease and moderate edema*

Subject	Date	Arterial oxygen content	Femoral venous oxygen content		Arteriovenous difference		Oxygen capacity	Percentage arterial saturation	Arterial carbon-dioxide content	Remarks
			Right	Left	Right	Left				
		volumes per cent	*volumes per cent*	*volumes per cent*	*volumes per cent*	*volumes per cent*	*volumes per cent*		*volumes per cent*	
F. H.	December 15, 1928	14.55	10.42		4.13		16.25	91.6	48.6	Negro, male, 58 hypertension, arteriosclerosis, auricular fibrillation
C. H.	July 29, 1928	13.00	8.44	7.37	4.56	5.63	13.79	96.3		See table 2
R. P.	August 6, 1928	16.70	11.00	11.60	5.70	5.10	17.61	97.0	43.8	See table 2
	August 8, 1928	15.75	10.64	11.00	5.11	4.75	16.31	98.6	40.4	
M. E.	November 16, 1929	8.77		2.90		5.87	16.63	54.7		See table 2
	November 23, 1928	11.63		5.76		5.87	18.90	83.5	59.1	
J. R.	August 30, 1928	13.65	7.78	9.62	5.87	4.03	14.00	99.5	52.0	White male, 57, hypertension, arteriosclerosis, numerous ectopic beats

Lowest arteriovenous difference: 4.03 volumes per cent. Highest arteriovenous difference: 5.87 volumes per cent. Average arteriovenous difference: 5.15 volumes per cent.

* Patients with "pitting" of the entire leg below the knee but with very slight or no pitting of the thigh have been classified as having moderate edema.

TABLE 4

The resting oxygen utilization of individuals with cardiac disease and slight edema*

Subject	Date	Arterial oxygen content	Femoral venous oxygen content		Arteriovenous difference		Oxygen capacity	Percentage arterial saturation	Arterial carbon-dioxide content	Remarks
			Right	Left	Right	Left				
		volumes per cent	*volumes per cent*	*volumes per cent*	*volumes per cent*	*volumes per cent*	*volumes per cent*		*volumes per cent*	
A. A.	February 2, 1929	13.73	4.80		8.93		14.70	95.4	42.1	White male, 35, hypertension, regular
M. E.	September 10, 1928	15.47		11.42		4.05	20.68	76.9	56.6	See tables 2 and 3
	November 27, 1928	12.44		4.71		7.73	18.05	70.9	57.2	
R. P.	August 13, 1928	16.80	12.88	13.12	3.92	3.68	17.70	97.0	42.4	See tables 2 and 3
	August 22, 1928	17.02	11.80	11.92	5.22	5.10	17.48	99.2	41.0	
C. H.	August 11, 1928	11.20	5.53	5.18	5.67	6.02	12.12	94.6	51.3	See tables 2 and 3
McC.	August 17, 1928	18.54	10.57	12.35	7.97	6.19	19.58	96.7	45.2	See table 2
G. C.	September 12, 1928	14.86	12.48	14.03	2.38	0.83	17.57	86.7	41.3	See table 2
	September 14, 1928	15.05	10.15	11.33	4.90	3.72	16.82	91.5		
	September 19, 1928	15.19	9.60	10.82	5.59	4.37	17.14	90.7	45.7	
F. H.	December 23, 1928	14.84	8.76	8.16	6.08	6.68	16.17	93.8	43.4	See table 3
	August 27, 1928	13.04	4.98		9.06		14.38	90.6	44.6	
T. B.	December 6, 1928	17.02	9.97		7.05		18.02	96.4	45.8	See table 2

Lowest arteriovenous difference: 0.83 volumes per cent. Highest arteriovenous difference: 8.93 volumes per cent. Average arteriovenous difference: 5.44 volumes per cent.

* Patients with pitting of the ankles and feet only have been classified as having slight edema.

TABLE 5

The resting oxygen utilization of individuals with cardiac disease and no edema*

Subject	Date	Arterial oxygen content	Femoral venous oxygen content		Arteriovenous difference		Oxygen capacity	Percentage arterial saturation	Arterial carbon-dioxide content	Remarks
			Right	Left	Right	Left				
		volumes per cent	*volumes per cent*	*volumes per cent*	*volumes per cent*	*volumes per cent*	*volumes per cent*		*volumes per cent*	
J. R.	September 6, 1928	15.56	8.34		7.22		16.40	97.0	45.3	See table 3
M. E.	September 17, 1928	16.24		10.78		5.46	20.60	80.9		See tables 2, 3 and 4
	October 2, 1928	13.90		7.98		5.92	18.50	77.2		
R. P.	September 8, 1927	16.90	10.30	9.11	6.60	7.79				See tables 2, 3 and 4
McC.	August 23, 1928	18.04	12.33	12.82	5.71	5.22	18.95	97.4	43.4	See tables 2 and 4
	August 30, 1928	19.18	11.86	11.02	7.32	8.16	20.47	95.8	45.5	
	September 6, 1928	19.20	10.62	10.86	8.58	8.34	19.54	98.4	43.9	
G. C.	September 29, 1928	15.11	9.84	10.20	5.27	4.91	16.66	92.8		See tables 2 and 4
F. H.	September 29, 1928	14.04	8.32	8.44	5.72	5.60	14.49	97.0	42.6	See tables 3 and 4

Lowest arteriovenous difference: 4.91. Highest arteriovenous difference: 8.58. Average arteriovenous difference: 6.52.

* No edema, as here used, means no pitting.

between 4.03 and 5.87 with an average value of 5.15 volumes per cent. Similarly, in eight patients with slight edema, twenty-one observations, table 4, showed values of 0.83 to 8.93 volumes per cent with an average of 5.44. Six cardiac patients who had previously had edema

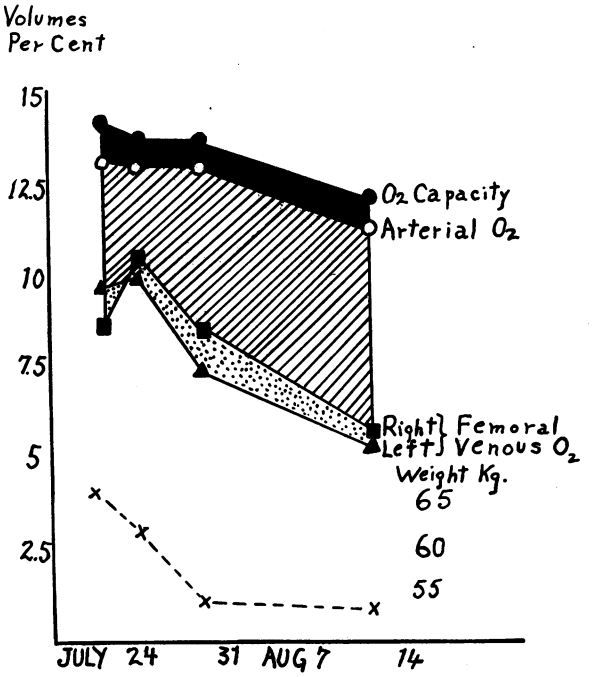

FIG. 1. SUBJECT C. H.

As the edema diminished the utilization (shaded and dotted areas) increased. The arterial oxygen saturation was within normal limits. The oxygen capacity did not rise as edema diminished. The edema had been present for more than six months.

but who had no perceptible edema at the time the blood samples were drawn, were found in fifteen observations to have femoral utilizations of 4.91 to 8.58 with an average of 6.52 volumes per cent (table 5).

In figures 1, 2, and 3, individual patients have been charted. In each individual the utilization was low when edema was present and rose as edema disappeared.

The type of heart disease made no difference in the results. The two patients with syphilitic aortic insufficiency and the patient with heart failure secondary to bronchiectasis reacted in the same way as did the larger group of individuals with hypertensive heart disease. Patients who had auricular fibrillation showed the same changes as did those with sino-auricular rhythm.

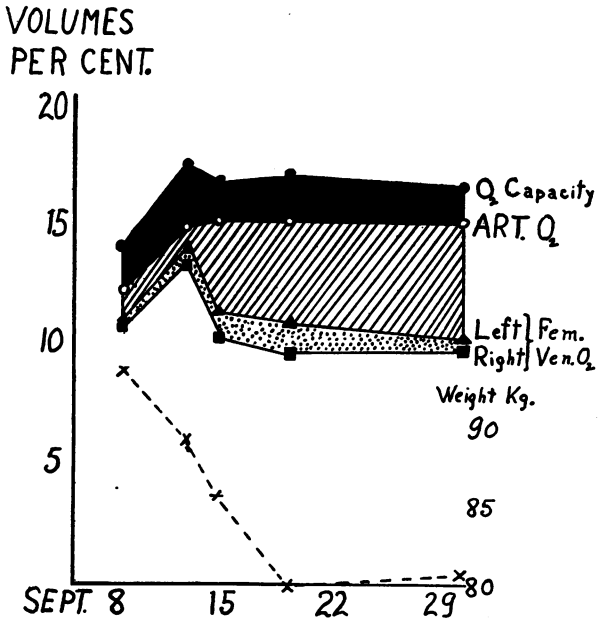

FIG. 2. SUBJECT G. C.

As edema diminished the utilization increased. The utilization, when he was edema free, was approximately four times as great as when he had marked edema. He had had edema for only two weeks when he entered the hospital. Improvement was associated with a sharp rise in oxygen capacity. The arterial saturation was slightly subnormal.

As a general rule, then, it may be stated that patients with hypertensive or syphilitic heart disease as well as patients with cardiac failure secondary to chronic pulmonary disease usually have, when edema of the legs is present, a high venous oxygen and a low femoral arteriovenous difference (utilization). The degree of diminution in oxygen utilization is roughly proportional to the amount of the edema.

There are, however, at least two important exceptions to these generalizations. One of these is seen in patients with digitalis intoxication and the other can be noted in individuals who are in a state of acidosis. In table 6, data from patients who were suffering from

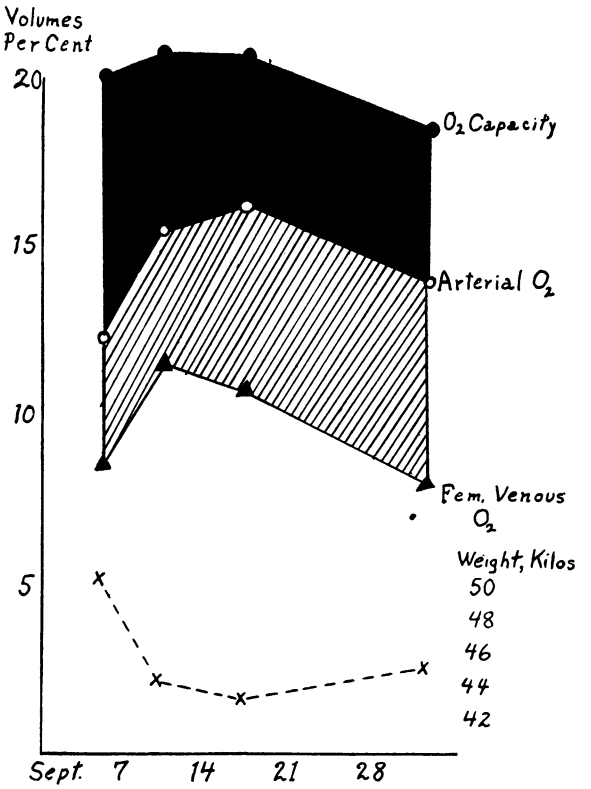

FIG. 3. SUBJECT M. E.

As edema diminished the utilization increased. The arterial saturation was very low. The patient had bronchiectasis and atelectasis.

digitalis over-dosage are presented. It will be noted that regardless of the amount of edema, such patients have femoral venous oxygen contents which are lower and femoral oxygen utilizations which are higher than those seen in any of the groups which have been considered. The values for utilization are even higher than those found

in control indiyiduals. In six observations on four patients the figures for lowest, highest and average arteriovenous oxygen differences were 6.10, 11.1 and 9.12 volumes per cent, respectively.

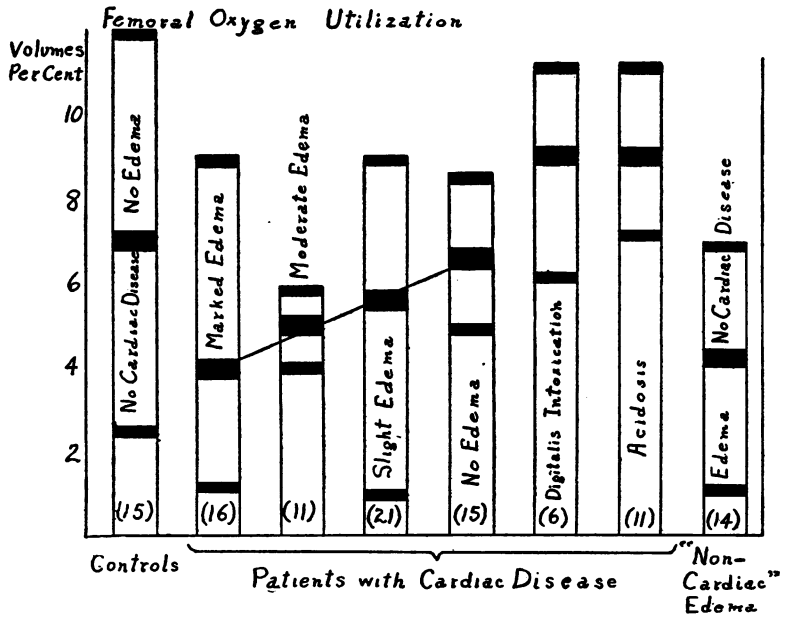

FIG. 4

In each column the highest and lowest narrow bars indicate the highest and lowest utilization, respectively. The broader middle bars represent the average utilizations for the group. It can be noted that subjects within each group show rather marked variations in utilization. The average values are consistent, however. The average utilization in the cardiac patients is almost an inverse linear function of the amount of edema. The cardiac patients with no edema had utilization values almost as high as did the control group. The utilization was very high in patients with acidosis or digitalis intoxication. The individuals with noncardiac edema had low arteriovenous differences, also, indicating that the diminution in utilization is not specifically associated with heart disease but is related to edema *per se*. The figures in parentheses at the bottom of each column refer not to the number of patients in each group but to the number of observations of utilization.

In patients with acidosis (arterial CO_2 40 volumes per cent) similar findings were noted. These are shown in table 7. Here the lowest

TABLE 6

*The resting oxygen utilization of individuals with cardiac disease and digitalis intoxication**

Subject	Date	Arterial oxygen content	Femoral venous oxygen content		Arteriovenous difference		Oxygen capacity	Percentage arterial saturation	Arterial carbon-dioxide content	Amount of edema	Remarks
			Right	Left	Right	Left					
		volumes per cent	*volumes per cent*	*volumes per cent*	*volumes per cent*	*volumes per cent*	*volumes per cent*		*volumes per cent*		
M. E.	October 11, 1928	10.32		2.28		8.04	17.65	60.5	51.3	Moderate	See tables 2, 3, 4 and 5
R. P.	July 30, 1928	17.30	6.80	6.20	10.50	11.10	18.50	95.6	34.7	Marked	See tables 2, 3, 4 and 5
				6.32		10.98					
C. H.	July 19, 1928	13.49		5.53		7.96	16.15	85.5		Marked	See tables 2, 3 and 4
F. H.	December 12, 1928	15.04		8.94		6.10	17.17	89.6	51.4	Marked	See tables 3, 4 and 5

Lowest arteriovenous difference: 6.10 volumes per cent. Highest arteriovenous difference: 11.10 volumes per cent. Average arteriovenous difference 9.12 volumes per cent.

* Patients were classified as suffering from digitalis intoxication only when all of the following conditions were fulfilled.

a. The patient was receiving the drug in adequate dosage.

b. The patient had nausea, vomiting, or pulsus bigeminus.

c. The symptom disappeared within three days after the drug had been discontinued.

TABLE 7

*The resting oxygen utilization of individuals with cardiac disease and acidosis**

Subject	Date	Arterial oxygen content	Femoral venous oxygen content		Arteriovenous difference		Oxygen capacity	Percentage arterial saturation	Arterial carbon-dioxide content	Amount of edema	Remarks
			Right	Left	Right	Left					
		volumes per cent	*volumes per cent*	*volumes per cent*	*volumes per cent*	*volumes per cent*	*volumes per cent*		*volumes per cent*		
C. T.	December 4, 1928	12.95	4.94		8.01		13.75	96.2	31.1	Moderate	White, male, 56, hypertension, arteriosclerosis, ectopic beats
H. C.	August 4, 1928	15.62	7.14	7.39	8.48	8.32	18.92	84.6	31.1	Marked	See table 2
A. R.	August 27, 1928	11.97	4.50	4.26	7.47	7.71	14.45	84.9	33.0	Marked	Negro, male, 33, hypertension, aortic syphilis, marked pulmonary edema. Before receiving 20 grams $NaHCO_3$ by mouth
		11.74		4.38		7.36	14.80	81.4	39.3		After
T. B.	November 21, 1928	13.25		3.51		9.74	15.06	90.0	40.0	Marked	See tables 2 and 4
	December 5, 1928	16.12		7.86		8.26	16.19	99.6	38.7	Slight	
R. P.	July 30, 1928	17.30	6.80	6.20 6.32	10.50	11.10 10.98	18.50	95.6	34.7	Marked	Digitalis intoxication. See tables 2, 3, 4, 5 and 6

Lowest arteriovenous difference: 7.36 volumes per cent. Highest arteriovenous difference: 11.10 volumes per cent. Average arteriovenous difference: 8.87 volumes per cent.

* Patients having an arterial carbon dioxide content of 40 volumes per cent or less have arbitrarily been classified as having acidosis.

TABLE 8

The resting oxygen utilization of individuals with edema but no cardiac disease

Subject	Date	Arterial oxygen content	Femoral venous oxygen content		Arteriovenous difference		Oxygen capacity	Percentage arterial saturation	Arterial carbon-dioxide content	Degree* of edema	Remarks
			Right	Left	Right	Left					
		volumes per cent	*volumes per cent*	*volumes per cent*	*volumes per cent*	*volumes per cent*	*volumes per cent*		*volumes per cent*		
N.	December 5, 1928	12.48	9.85	9.80	2.63	2.68	12.48	100.0		Moderate	Pellagra, edema apparently due to anemia and undernutrition
N.	January 4, 1929	13.55	8.72	10.17	4.83	3.38	15.60	87.0	49.1	Slight	
M. V.	January 9, 1929	14.66	9.70	9.70	4.96	4.96				Moderate	Nephrosis
C. M.	September 17, 1928	16.35	9.65	11.57	6.70	4.78	16.44	99.5	31.5	Moderate	Diabetes, acidosis on September 17. No acidosis on September 20
	September 20, 1928	16.08	10.92	10.92	5.16	5.16			42.8	Slight	
I. J.	September 21, 1928	15.96	11.88	10.56	4.08	5.40	17.40	93.8	45.0	Slight	Chronic eczema
R. G.	September 18, 1928	12.37	10.74	11.16	1.63	1.21			47.4	Moderate	Arsphenamine dermatitis

Lowest arteriovenous difference: 1.21 volumes per cent. Highest arteriovenous difference: 6.70 volumes per cent. Average arteriovenous difference: 4.10 volumes per cent.

If the last two subjects in whom the edema was associated with inflammation and the observation on C. M. at the time he had acidosis are omitted the values are: lowest arteriovenous difference: 2.63 volumes per cent; highest arteriovenous difference: 5.16 volumes per cent; average arteriovenous difference: 4.22 volumes per cent.

* The criteria used in classifying edema as to degree were the same as those stated in tables 2, 3 and 4.

utilization was 7.36, the highest 11.10 and the average 8.89 volumes per cent. (One patient had acidosis and digitalis intoxication simultaneously and was therefore included in both tables 6 and 7.)

The next question which arose was whether the results found in cardiac patients with edema were specifically due to heart disease or whether the findings were caused by edema. The answer to this question was sought through observations on patients with edema due to causes other than heart disease. In table 8 are shown the results of fourteen observations on five patients. The findings were striking.

TABLE 9

The resting oxygen utilization of the blood from the antecubital vein in patients with cardiac disease and edema of the arms

Subject	Date	Arteriovenous difference of blood from right cubital vein	Degree of edema of arm	Remarks
		volumes per cent		
R. P.	July 30, 1928	9.30	Moderate	Digitalis intoxication and acidosis (arterial CO_2 34.7)
	August 2, 1928	2.1	Moderate	No digitalis intoxication
	August 6, 1928	2.7	Slight	No acidosis
	August 8, 1928	3.7	None	
	August 22, 1928	4.6	None	
C. H.	July 19, 1928	2.5	Slight	Vomiting from digitalis
	July 21, 1928	1.1	Slight	No evidence of digitalis intoxication
	July 29, 1928	2.8	None	

The greatest utilization was less than the average value for individuals without edema. (It is of some interest to note that this value was found in an individual with diabetic acidosis.) The lowest utilization, 1.21 volumes per cent, approached the lowest value found in the cardiac patients with edema. The average arteriovenous difference, 4.10 volumes per cent, was slightly less than two-thirds of the average figure for individuals with no edema.

The objection may be raised that the two last subjects in table 8 had edema of an inflammatory nature and hence would be expected to have a low utilization. If one omits them from consideration and

also omits the observations on C. M. when he was acidotic, (as was done in compiling tables 2, 3, 4, and 5) the values for highest, lowest and average arteriovenous differences in non-inflammatory, non-cardiac edema are 5.16, 2.63, and 4.22 volumes per cent, respectively.

The oxygen utilization in the arm was studied in two patients who had congestive heart failure and edema of the upper extremities. Inspection of table 9 reveals the fact that the oxygen utilization in the antecubital veins is less when edema is present than when it is absent. However, in the presence of digitalis intoxication and acidosis the utilization is high. It may therefore be stated that the antecubital

TABLE 10

The carbon dioxide gained by one hundred cubic centimeters of blood in passing from the femoral artery to the femoral vein

	I. Patients with cardiac disease and:						II. Patients with no cardiac disease and no edema	III. Patients with edema but no cardiac disease
	a. Marked edema	b. Moderate edema	c. Slight edema	d. No edema	e. Digitalis intoxication (and edema)	f. Acidosis (and edema)		
Number of observations	12	8	16	9	5	12	12	7
Least amount of CO_2 gained, *cc.*	0.6	1.2	0.9	3.4	3.5	4.8	3.2	0.9
Greatest amount of CO_2 gained, *cc.*	8.2	5.7	9.2	8.6	6.4	10.9	9.0	6.0
Average amount of CO_2 gained, *cc.*	3.0	4.3	4.0	6.1	5.2	6.4	6.7	3.1

and femoral venous oxygen contents behave similarly under similar conditions.

The antecubital venous oxygen was determined also in several patients who had edema of the legs but none of the arms. No definite conclusions were arrived at, as the results were conflicting. In some instances a rise in venous oxygen occurred with improvement. Such cases corresponded in this respect to those reported by Lundsgaard and by Harrop. We found, as did Eppinger, von Papp and Schwarz that in other patients improvement was associated with a fall in antecubital venous oxygen. As a rule, the changes were very variable and consequently these observations are not presented in detail.

The carbon dioxide content of the blood was determined in most of the cases. The values for arterial carbon dioxide content are shown in the tables. As has been mentioned, abnormally low carbon dioxide contents were found to be associated with low venous oxygen and high utilization of oxygen. We do not propose to enter here into a detailed discussion of cardiac acidosis, which is being investigated in a separate study. It is of interest to state, however, that the values for venous CO_2 minus arterial CO_2 correspond well with the arteriovenous oxygen difference. This is shown in table 10.

DISCUSSION

The data which have been presented show clearly that edema of the legs, whether due to cardiac diseases or not, is usually accompanied by a tendency toward high femoral venous oxygen content and low oxygen utilization. This low utilization is not, as in the case of the antecubital venous oxygen content of Lundsgaard's patients, to be ascribed to improvement. Our patients were studied in various stages: (*a*) during improvement, (*b*) when the condition was static, and (*c*) when edema was accumulating. The degree of diminution in utilization was in proportion to the amount of edema present at the time of observation, and was independent of the rate at which edema was being gained or lost.

If one makes the assumption that the femoral vein drains the same proportion of the leg in edematous and non-edematous subjects, then there are only three possible explanations of our results: (1) the oxygen consumption of edematous tissues is very much decreased; (2) the blood flow through edematous tissues is increased; or (3) both these factors are active.

We do not think the findings can be explained by diminished oxygen consumption alone, for the following reasons:

a. A priori, it is unlikely that the oxygen consumption could be diminished to the degree required. Consider the case of G. C. This man, (fig. 2) when edematous, had oxygen utilization values of 1.32, 1.26, 0.83, and 2.38 volumes per cent. When he had no edema, values of 5.27 and 4.91 volumes per cent were found. If the changes in oxygen utilization were dependent solely on differences in oxygen consumption

(oxygen used per unit of time), one must assume that the patient's legs used only one-fourth as much oxygen when edematous as when edema-free.

b. The lower extremities constitute a fairly large proportion of the body weight, and contain an even larger fraction of the total body muscle. It is likely, therefore, that the oxygen consumption of the legs is a definitely appreciable fraction of the total oxygen consumption of the body. Were the oxygen consumption of the legs and the other edematous tissues markedly diminished (unless there is compensatory increased utilization elsewhere), one should expect the oxygen intake of the body as a whole to be decreased. But this is not usually the case, as illustrated by the reports of Peabody, Meyer, and Dubois (1916) and Eppinger, Kisch and Schwarz, who found normal or increased resting oxygen consumption in decompensated patients. (We have determined the oxygen consumption of several of the patients in whom oxygen utilization was studied. When edema was present the oxygen consumption was not less than when the subject was edema-free)

For these reasons, it seems probable to us that the blood flow through the legs of cardiac patients is greater when edema is present than when it is absent. Such a conclusion seems paradoxical in view of some of the prevailing concepts of heart failure, but the data given make it desirable to consider such an interpretation.

The view that the blood flow through the legs is increased in cardiac patients with edema is not contrary to the important observations of Blumgart and Weiss. These observers found diminished velocity of blood flow through the lungs in the presence of congestive failure. In the first place, the legs and the lungs are different parts of the body In the second place, velocity of flow and amount of flow are not the same thing.

The presence of increased blood flow through edematous tissues is further substantiated by the results of a separate study by Blalock, Pilcher and Harrison (1929) who observed the effect of injecting large quantities of saline solution into one of the hind legs of a dog They found that the utilization of oxygen was lower in the "edematous" leg and that the volume outflow from the cannulated femoral vein on the "edematous" side was one and one-half to three times that from the non-edematous side. The objection may be raised that the fluid intro-

duced from the outside was not edema which has a different cause. However, we have already shown (table 8) that the low utilization is due to edema *per se* and, since the utilization in the injected legs of the dogs was also diminished, it seems only logical to attribute the low utilization in both cases to a common cause—increased blood flow. These results are further substantiated by those of Barcroft and Kato (1915), who found an increased volume flow and increased oxygen content (as much as ninety per cent saturation) of venous blood from edematous muscle.

Further evidence that edema *per se* can cause an increase in local blood flow may be found in a consideration of the analogy between edema of the lungs and edema of the peripheral tissues.

It is well known that pulmonary edema causes an increased pulmonary ventilation and hence a rise in the alveolar oxygen pressure. On the other hand, in severe cases at least, the oxygen tension in the arterial blood is decreased. In other words, edema in the lungs acts as a barrier to the passage of oxygen into the blood. The alveolar oxygen tension is normally only a little higher than the arterial tension. When edema is present, however, a greater pressure difference is necessary to "drive" oxygen through the (functionally) thickened capillary wall. (It is true that active secretion of oxygen by the pulmonary epithelium might, if it occurred, modify the course of events as depicted here. However, the possibility of oxygen secretion seems to have been disproved by the work of Barcroft and his associates. Similarly, it seems extremely unlikely that the systemic capillaries secrete oxygen.) If one assumes (and we know of no evidence contrary to such an assumption) that edema in the tissues also acts as a barrier to the passage of oxygen from the blood to the body cells, then the oxygen tension in the cells will be lowered. Oxygen lack in a tissue ordinarily causes capillary dilatation and increase in local blood flow (Krogh, 1924, Hilton and Eichholtz, 1925). Arterial—and hence general—anoxemia, if severe enough, causes increased output of the heart (Harrison and Blalock, 1927; Harrison, Wilson, Neighbors and Pilcher, 1927; Harrison, Blalock, Pilcher and Wilson, 1927).

Increase in the local blood flow through edematous tissues would raise the mean oxygen pressure in the capillaries and this would tend to raise the tissue oxygen tension toward, but not to, the normal.

This series of events which we believe takes place in the edematous tissues may be summarized as follows:

Edema (from whatever cause)→diminished tissue oxygen tension→ increased local blood flow and decreased utilization (oxygen consumption remaining constant)→increased oxygen tension in the blood→a rise in tissue oxygen tension toward, but not to, the normal level. This scheme seems less fanciful and more likely when it is compared with the cycle of events known to occur in severe pulmonary edema.

Edema in the lungs→decreased oxygen tension in the arterial blood →overventilation→increased alveolar oxygen tension→a rise in arterial oxygen tension, but not to the normal level.

In the absence of evidence that edema in the tissues behaves differently toward oxygen than does edema in the lungs, it seems permissible to draw the tentative conclusion that fluid in the tissues leads to oxygen deficiency in the tissues, oxygen excess in the blood and increase in blood flow through the edematous tisues.

What light does such a conclusion throw on the theories of heart failure which were mentioned in the introduction to this paper? Our findings concerned primarily as they are with the effects of edema, do not throw any light on the cause of edema, but they do offer evidence against the validity of the "diminished output" theory. Either our findings and conclusions are totally wrong, or the theory that edema in heart disease is essentially dependent on diminished cardiac output is no longer tenable.

Limitation of space prevents a full discussion of all the evidence *pro* and *con*, of the "diminished output" theory of congestive heart failure. This will be done at a future date.

One point concerned with the effect of digitalis must be mentioned because of its bearing on the results reported here following intoxication by that drug. Harrison and Leonard (1926) found that digitalis caused a diminution in the output of the heart of normal dogs, as well as a decrease in the size of their hearts, and suggested that the same effects probably resulted from the use of digitalis in patients with heart disease. Cohn and Stewart (1928) confirmed the findings of Harrison and Leonard, but objected to the latter authors' interpretation of them, basing their objection on the fact that they believe on the basis of their own studies that there is a two-fold action of digitalis: the one

effect being an increase of cardiac "tonus" (tending to decrease cardiac size and output) the other an increase of cardiac "contractility" (tending to increase cardiac output). They question the use of the term "sedative" by Harrison and Leonard to describe reduced cardiac output arising from what they consider to be increase of cardiac "tonus." They furthermore raise the question whether the decrease in size of a heart both diseased and enlarged in man is necessarily followed by the decreased cardiac output which both Harrison and Leonard and they themselves demonstrated following the administration of digitalis to normal dogs or to dogs with enlarged hearts but without signs of heart failure.

The fact that our patients with digitalis intoxication had, in spite of edema, high values for oxygen utilization in the femoral vein is suggestive, although not conclusive, evidence that Harrison and Leonard were correct in their belief that digitalis diminished cardiac output in patients with heart disease, as well as in normal dogs.

We were not certain whether the high utilization, and hence the (presumably) diminished blood flow through the legs of our patients with digitalis intoxication, was due to an action on the heart or, as was suggested to us by Dr. Laszlo of Freiburg, to an effect on the peripheral circulatory system. In any case, the findings are difficult to reconcile with the "diminished output" theory of heart failure.

The conclusion which we draw from this discussion of the action of digitalis is that its action in heart disease is not completely known but that the available evidence leads us to believe that it diminishes the output of the heart.

In those individuals who had diminished carbon dioxide content of the blood, the femoral oxygen utilization was found to be high even when edema was marked. At the present time we are not able to explain this finding.

It appears that edema *per se* may constitute a danger for the heart. Assuming its occurrence, the increased blood flow through the edematous tissues would be almost certain to cause a local increase in capillary and venous pressure. But a rise in capillary pressure tends, *ceteris paribus*, to produce edema. Thus a vicious cycle would be formed, the edema tending to increase in amount, unless restricted by other factors.

When only a small proportion of the body tissues is edematous, the effect on the general circulation would probably be small. But when a large proportion, such as all of both lower extremities is edematous, it seems likely that the circulation to the body as a whole would be seriously affected. Compensation might be affected in one or both of two ways. Either (1) the blood flow through the edematous tissues being increased and the minute output of the heart remaining constant, the remainder of the body may receive less than the normal quota of blood, or (2) the blood flow through the edematous portions being increased and the remainder of the body receiving its normal quota of blood, the minute output of the heart must be increased. In the first case, compensation has been established at the expense of the vital tissues of the body; in the second instance, an additional load has been thrust on the already overburdened heart.

Our work, like that of Eppinger, Kisch and Schwarz, leads to the conclusion that not only circulation but also utilization is altered in heart disease. These authors, however, believed edema to be the ultimate result of inadequate utilization, whereas, our observations lead us to believe edema to be its cause. We nevertheless agree with these authors that patients with congestive heart failure suffer not so much from insufficiency of the heart as from the inefficiency of the circulation.

This statement must not be interpreted as indicating that we believe the cardiac output to be normal or greater than normal in all cases of heart disease. There is evidence that the minute cardiac output may be seriously diminished in certain disorders of the heart. The clinical picture in such cases resembles that of acute surgical collapse. (Such conditions have been discussed at more length in a paper shortly to be published by one of us.) We have called such cases *hypokinetic* (or insufficient) circulation, in order to distinguish them from *dyskinetic* (or inefficient) circulation. The studies reported in the present paper seem to us to mean that regardless of the level of cardiac output, the patient with congestive heart failure is suffering primarily from circulatory inefficiency (dyskinesia). It seems that the term "cardiac insufficiency," if it is to be retained, should be used to mean inability to maintain a small diastolic volume, rather than a normal output.

In order to test further the hypothesis that edema in the tissues

interferes with the passage of oxygen out of the capillaries a number of observations have been made before and immediately after standard exercise. These studies have been made since the data in this publication were tabulated and hence are not presented in the tables. The exercise consisted of alternately flexing and extending the thigh and leg a given distance at a rate of thirty times per minute, samples of blood from the femoral vein being obtained immediately before and within one half to one minute after the end of the exercise.

A priori, one would expect the cardiac patient to increase his utilization during exercise more than the normal man for the following reasons: (*a*) presumably the cardiac reserve and hence the maximum cardiac output is less in patients with heart disease; (*b*) moving an edematous leg calls for more work than does moving a normal leg the same distance; (*c*) the resting utilization is decreased in edematous subjects, and hence there is more "room" (the venous oxygen being higher) to increase it; (*d*) in a given exercise of the leg the femoral venous blood becomes more acid in the edematous cardiac patient (this finding will be reported in detail in a subsequent publication) and the consequent shift of the dissociation curve downward and to the right should facilitate the passage of oxygen into the tissues. For these reasons it seemed probable that the subject with edema would increase utilization more by exercise than the normal individual, unless edema *per se* interfered with such increase.

Five observations on subjects with no circulatory disease showed that the utilization after exercise was 0.3 to 2.8 volumes per cent greater than at rest. The average increase in this control series was 1.4 volumes per cent. In six observations in individuals with heart disease but with little or no edema, the increase in utilization after exercise was 0.4 to 4.7 volumes per cent, the average increase being 2.7 volumes per cent. Twelve observations were made in patients with outspoken edema. The lowest, highest, and average values for the increase in utilization during exercise were -1.7, 4.1 and 1.2 volumes per cent, respectively. One patient was studied repeatedly during various degrees of edema and in him there was a definite tendency for the utilization to be increased less by exercise when edema was marked than when edema was slight or absent.

From these findings one might be tempted to conclude that the edematous patient not only suffers from diminished utilization at rest, but is unable to increase his utilization by work and hence, has either to increase his blood flow more or to get a greater oxygen debt than when edema free. However, we do not feel that our data on exercise are sufficiently complete or convincing to justify such a conclusion. They do show clearly, however, that the edematous cardiac patient does not, as one might expect, increase his utilization more than does the normal subject during the type of exercise which has been studied. This fact seems to confirm our interpretation of the findings at rest—interference with the diffusion of oxygen into the edematous tissues. These findings may also throw some light on the question of the cause of the high oxygen debt in cardiac patients after exercise. Data concerning this point will be presented in our next publication.

Realizing as we do that the observations and conclusions which have been mentioned here will seem at first sight paradoxical to the majority of those who read them, we should like to point out a few simple clinical facts which are easily verifiable and which lend support to our view: (1) If the fingers and toes of an edematous, cyanotic patient be inspected it will usually be noted that the edematous portions are not cyanotic and vice versa. (This may be due, however, to the opacity of the edematous tissue.) (2) If one feel the legs of an edematous cardiac patient, the skin ordinarily is not cold to the touch. (3) Individuals with congestive heart failure often have dyspnea on slight exertion and paroxysms of dyspnea when they have no edema. But such patients rarely have continuous dyspnea at rest except when they have edema. One often observes that the administration of a diuretic with consequent diminution in edema is associated with marked improvement of the patient's dyspnea, even though one has done nothing to his heart and finds no obvious change in the physical signs of the lungs.

Clinical as well as experimental observations lead us to believe that, in cardiac disease edema is in itself a potent factor toward increasing the severity of the underlying condition which caused the edema. For this reason it seems wise to combat it by every possible measure, for in so doing, we are treating not only a symptom but a link in that chain of events which constitutes the vicious cycle of heart failure.

SUMMARY

The oxygen and carbon dioxide contents of arterial and femoral venous blood have been determined in patients with heart disease, in individuals with edema but no cardiac disease, and in subjects with no edema and no heart disease. The femoral venous oxygen content tends to be higher in patients with edema than in patients with no edema. The oxygen utilization tends to be lower in edematous legs. The changes found at a given time bear no relationship to the progress of the disease, but are proportional to the amount of edema present, regardless of whether the patient is gaining or losing edema.

When patients are in a state of digitalis intoxication or have diminished alkali reserve of the blood, the oxygen utilization tends to be high, regardless of the amount of edema.

The amount of carbon dioxide gained by the blood parallels, in general, the amount of oxygen lost by the blood in the various conditions which have been mentioned.

As these studies have been concerned with the blood from edematous tissues they are believed to have a value in the interpretation of edema as a symptom not possessed by studies which have been made by others of venous blood from the body which were not edematous.

These studies have led us to believe the following:

1. That edema causes an increased local blood flow. This seems to be brought about in the following manner: Edema (acting in the tissues, as in the lungs, as a barrier to the diffusion of oxygen)→ diminished tissue oxygen tension→increased local blood flow and decreased oxygen utilization.

2. That the symptoms of congestive heart failure are not primarily and essentially due to diminished minute output of the heart. Since utilization is faulty it is possible for the cardiac output to be increased and at the same time inadequate.

3. That edema, itself a symptom of congestive heart failure, throws an additional load on the heart and is thus secondarily a further cause of "heart failure."

4. That the patient with "heart failure" suffers, when at rest, from circulatory inefficiency rather than from cardiac insufficiency.

We are indebted to Dr. C. S. Burwell for encouragement and helpful advice. It is a pleasure to express our appreciation to him and to Dr. Alfred Blalock, whose method of investigation and findings in patients with varicose veins first led us to undertake this study.

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