

STUDIES ON VEM AND VDM IN BLOOD IN RELATION TO RENAL HEMODYNAMICS AND RENAL OXYGEN EXTRACTION IN CHRONIC CONGESTIVE HEART FAILURE^{1, 2}

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The inadequate cardiac output of chronic congestive heart failure is accompanied by a general increase in peripheral resistance—reflected by the maintenance of normal blood pressure—and an even more marked renal vasoconstriction, which results in a disproportionate decrease in renal blood flow. Neurogenic factors seem to be excluded as the major reason for the renal ischemia, since presumptive functional denervation by high spinal anesthesia (1) does not affect the vasoconstriction. Merrill's (2) demonstration of an increased concentration of renin in the renal venous blood of congestive failure patients suggests the possible role of this humoral factor in the renal and peripheral vascular adjustments of heart failure.

We have directed our attention to a newly described vasotropic system consisting of the renal vasoexcitor, VEM, and the hepatic vaso-depressor, VDM, whose vascular effects are such as to suggest that they constitute a homeostatic regulatory mechanism for the peripheral circulation (3). VEM has been shown (4) to be regularly released *in vivo* from kidneys whose blood flow has been reduced by partial clamping of the renal artery, or after acute ischemia; and to be produced by kidney cortex *in vitro* under conditions of hypoxia. Similarly, VDM is produced by the liver *in vivo* under conditions of reduced blood

flow as in shock, and by normal liver *in vitro* on exposure to hypoxia.

The present studies on congestive heart failure have been concerned with (a) the appearance of these vasotropic principles in the blood stream during the course of the syndrome, (b) the relationship between hepatic and renal hypoxia and the production of these principles, and (c) the possible significance of VEM and VDM for the altered renal hemodynamics and excretory phenomena in this condition.

METHODS

Two groups of patients, 12 with chronic congestive heart failure, secondary to rheumatic valvular disease, without hypertension or demonstrable organic renal disease, and 14 non-cardiac controls were studied. Due to technical difficulties, complete studies were obtained on only 22 of the 26 patients. The cardiac subjects were equally distributed as to sex and averaged 44 years of age. In the control group, complete studies were obtained on eight males and four females, and the average age was 35 years.

The studies were carried out in the resting, post-absorptive state with no sedation. An indwelling needle was placed in the femoral artery under local metycaïne anesthesia. A multiple-holed urethral catheter was passed into the bladder and measurements of renal clearances of p-aminohippurate (PAH) and either thiosulfate, mannitol, or inulin by the constant infusion technique of Smith and associates (5) were begun.

Blood was obtained by venous catheterization, under fluoroscopic control, from the right renal vein and a right hepatic vein during one or more clearance periods. Clotting in the catheter was prevented by a slow infusion of isotonic saline or 5 per cent glucose in water, containing 2 to 3 cc. of 10 per cent heparin per liter. After the position of the catheter in the right renal vein had been confirmed by determining the extraction of PAH, heparinized blood for renal clearance determination and vasotropic assay was collected simultaneously from the femoral artery and the renal vein. Immediately thereafter, samples for oxygen and hematocrit determinations

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were drawn simultaneously from the same vessels into freshly prepared syringes in which the dead space was filled with bubble-free heparin-sodium fluoride mixture. The syringes were sealed with mercury and stored in an ice bath until analyzed. Either before or after the renal vein catheterization, blood for the same determinations was drawn simultaneously from the femoral artery and hepatic vein.

The chemical analyses were performed by the following methods: thiosulfate as described by Newman, Gilman, and Philips (6), modified by Elliott and Scott (7); PAH,⁴ inulin, and mannitol as described by the New York University group (8) with acetylation of PAH, if mannitol was present, as suggested by Barker and Clark (9); oxygen content and capacity manometrically according to Van Slyke and Neill (10) on 1 cc. samples (duplicate analyses agreed within 0.1 volume per cent); hematocrits were determined in Wintrobe tubes, centrifuged at 3000 r.p.m. for at least 30 minutes. No correction was made for trapped plasma.

Iced samples of heparinized plasma taken from the femoral artery, renal vein, and hepatic vein were sent coded to the Cornell-New York Hospital group (B.W.Z. and E.S.) for assay of vasotropic activity by the rat mesoappendix technique described in detail by Zweifach (11). The origin of the plasma samples was unknown to the assayer. The assay is based on the changes in the reactivity of the terminal arterioles and precapillaries to topically applied epinephrine following the intravenous injection of test samples. For the test, 100-125 gm. rats are anesthetized with sodium pentobarbital and the triangular flap of mesentery lying between the cecum and the terminal ileum is exteriorized. The exposed tissue is kept both warm and moist by continuous irrigation with a Ringer gelatin solution, rigidly maintained at body temperature. The most satisfactory vessels for the assay of vasotropic principles were found to be the precapillary vessels leading directly into the capillary bed. Quantitation is based on the determination of the minimal effective concentration of epinephrine which produces a given type of constrictor response. This is arrived at by making successive topical applications of increasing concentrations of epinephrine until a concentration is reached which induces a narrowing of the precapillaries just sufficient to slow markedly the blood flow through the capillaries and the tributary venules. Because of its strategic location, the precapillary vessel can effect, by a slight narrowing of its sphincter, a sharp reduction in blood flow in its branches. The sample to be assayed is injected intravenously by way of the tail vein, about 0.5 cc. being used routinely. The reactivity of the terminal arterioles and precapillaries is then tested at three to four minute intervals. Blood samples producing no changes in vascular reactivity are called neutral.

⁴ To increase the amount in the sample analyzed, PAH in renal vein plasma was determined on a 1 to 5 dilution and on a 1 to 15 dilution to which a known amount of PAH was added. The results were identical.

With active samples, the vascular effects generally appear within two to three minutes and persist for as long as 40 minutes. These were classified either as vasoexcitators (potentiators) or vasodepressors (inhibitors) of the epinephrine response. Vasoexcitator activity (VEM) is measured both by the duration of the response and by the amount of dilution of epinephrine required to produce the control type of vasoconstrictor response. The vasodepressor activity (VDM) is measured by noting the period during which there is a depression of the reactivity of the vessels to the initially determined minimal effective concentration of epinephrine. In several instances a toxic effect prevented the discrimination of the vasotropic activity of the samples. The toxic side effects in the test rat consisted of markedly increased reactivity of the venules and arterioles which appeared without the application of epinephrine and which have been found in the past to be ascribable to the release of potassium and other cellular breakdown products into the blood stream.

Calculations

The renal extraction of PAH was calculated as:

$E_{PAH} = \frac{A - V}{A}$, where A and V = the concentration (mg. per cc.) of PAH in arterial and renal venous blood respectively. Applying this extraction ratio, the true or corrected renal plasma flow was calculated as:

$$RPF = \frac{\text{Clearance PAH}}{\text{Extraction PAH}}; \text{ and renal blood flow}$$

$$RBF = \frac{RPF}{1 - \text{hematocrit}}$$

In these and subsequent calculations, the average renal hemodynamic data for three or more consecutive 10 to 40 minute periods were used rather than the values for the single period during which, generally, extraction studies were completed. That this is valid was established by the observation that PAH and oxygen extraction in humans remained constant for four to five hours.

The renal oxygen consumption (Q_{O_2}) in cc. per minute was calculated as the product of the renal blood flow (RBF) in cc. per minute and the difference in oxygen content (cc. O_2 per cc. of blood) of the femoral artery (FA) and the renal vein (RV) blood samples drawn simultaneously. Thus, $Q_{O_2} = RBF \times (O_{2FA} - O_{2RV})$. Like others (12) we have found that in man, unlike the dog, oxygen capacities and hematocrits in simultaneously drawn renal venous and femoral arterial blood rarely differ and, therefore, the correction factors suggested by Phillips and his associates (13) were not applied.

Oxygen saturations were calculated from the content and capacity data by applying the usual corrections (14) for physically dissolved oxygen. The mean renal capillary oxygen saturation was calculated by Lundsgaard's formula, $\frac{A + V}{2}$, where A = arterial and V = the renal venous oxygen saturation.

RESULTS

The complete data on the cardiac and control patients, corrected to a body surface area of 1.73 sq. m., are summarized in Table I. Variables such as sex difference, sodium content of diet, nutrition, and age may have influenced some of the results to an indeterminate degree. Vasotropic activity studies alone were done on two additional cardiacs and two control subjects.

The glomerular filtration rate in the cardiacs was about one-half that of the controls, 65.7 ± 29.0 cc. per minute and 128.8 ± 22.7 cc. per minute, respectively. One cardiac, H. T., with an enlarged tender liver but no peripheral edema, had a thiosulfate clearance of 124 cc. per minute, which was confirmed one week later with an inulin clearance. Other experimental findings on H. T., however, fell within the range of the cardiac group.

The effective renal plasma flow was 188 ± 76 cc. per minute in the cardiacs, as compared to 659 ± 174 cc. per minute in the controls. The mean PAH extraction, which was 90 and 86.5 per cent in the cardiacs and controls, respectively, did not differ significantly in the two groups. It should be noted that control subjects H. F. and H. M. were being treated for syphilis with depot penicillin. Their relatively low PAH extraction may represent competitive depression by penicillin of tubular extraction of PAH (15) rather than contamination of the samples with non-renal blood, since the catheter tip was radiologically observed to be several centimeters to the right of the inferior vena cava.

The true or corrected renal plasma flow, the effective renal plasma flow corrected for PAH extraction, was 207.4 ± 80.1 cc. per minute in the cardiacs and 766 ± 233 cc. per minute in the controls. The true renal blood flow was 366 ± 113 cc. per minute in the congestive failure group, in contrast to 1280 ± 367 cc. per minute in the controls, or an average reduction of 71 per cent in the cardiacs.

The filtration fraction, presented in Table I as the ratio of mean glomerular filtration rate and mean true renal plasma flow, checked to within ± 10 per cent of that obtained by the renal extraction of thiosulfate or inulin. The latter was omitted from the table because the inherent analytical error in determining the smaller renal A-V

difference of these filtered substances results in a greater variability. The mean filtration fraction was 31.9 ± 7.4 per cent in the congestive failure patients and 17.5 ± 3.3 per cent in the non-cardiac subjects. Only one cardiac, R. F., had a normal filtration fraction.

The arterial oxygen saturation was 88.4 ± 5.9 per cent in the cardiacs and 93.0 ± 1.1 per cent in the controls. This difference is not statistically significant. In contrast, the difference in the renal venous oxygen saturation in the two groups was statistically highly significant ($P < 0.001$). Thus, the mean renal venous oxygen saturation was 69.9 ± 8.0 per cent in the cardiacs in contrast to 86.1 ± 3.1 per cent in the controls. Similarly, there was a significant difference in the mean renal oxygen uptake (Figure 1) with the cardiacs having a mean renal A-V oxygen difference of 3.53 ± 1.09 volumes per cent, and a range of 2.21 to 5.50 volumes per cent, and the controls having a mean oxygen difference of 1.29 ± 0.31 volumes per cent, and a range of 0.78 to 1.72 volumes per cent (Table I). The mean renal capillary oxygen saturation was 89.5 per cent for the control patients and 79.1 per cent for the cardiacs.

The renal oxygen consumption (renal blood flow \times renal A-V oxygen difference) averaged 12.0 ± 1.8 cc. per minute in the cardiacs and 15.8 ± 3.6 cc. per minute in the controls. This difference is statistically significant ($P < 0.01$). There was no significant correlation between glomerular filtration rate and oxygen consump-

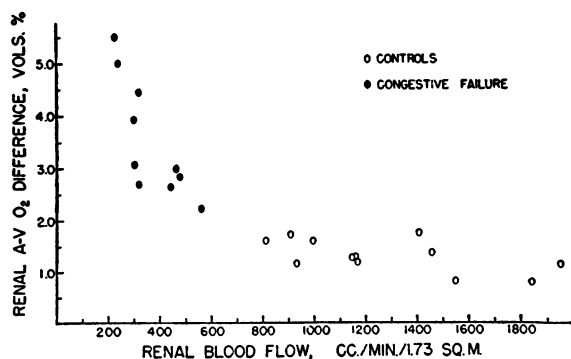


FIG. 1. THE RENAL A-V O₂ DIFFERENCE IN RELATION TO THE RENAL BLOOD FLOW IN CONTROLS AND IN PATIENTS WITH CONGESTIVE HEART FAILURE

The sharp contrast between the two groups in these functions is evident.

TABLE I
Summary of data

Pa- tient	Age	Sex	Surface area* sq. m.	Diagnosis*	Renal data†						Oxygen data						Rat mesoappendix assay					
					Plasma flow‡ cc. per min.	PAH extrac- tion per cent	Corr. plasma flow§ cc. per min.	Hema- tocrit per cent	Blood flow cc. per min.	Corr. filtra- tion fraction	Femor. artery Con- tent vol. per cent	Satu- ration per cent	Renal vein Con- tent vol. per cent	Satu- ration per cent	Renal A-V differ- ence vol. per cent	Renal O ₂ con- sump- tion ml. per min.	Hepatic vein Con- tent vol. per cent	Satu- ration per cent	Renal vein VE (6x)	Hepatic vein VD	Femor. artery VD	
J. W.	41	M	1.60	R. H. D.	67.5	227	88	257	443	26.3	17.37	94.0	14.73	79.2	2.64	11.7	9.24	49.6	VE 38' (5.3x)	VD 24'	VD 16'	
E. G.	40	F	1.59	R. H. D.	56.0	137	87	158	319	35.4	16.74	85.5	14.05	72.2	2.69	8.6	9.57	49.0	VE 28' (6x)	VD 27'	VE 19' (2x)H	
M. S.	43	F	1.52	R. H. D.	60.3	171	93	184	317	32.8	15.16	88.0	10.73	62.4	4.43	14.0	5.12	29.5	VE 46' (6x)	VD 32'	VE 30' (5x)H	
B. D.	50	F	1.41	R. H. D.	91.0	270	90	298	479	30.5	14.69	88.0	11.87	71.8	2.82	13.5	7.94	47.6	VE 15**	VD 32'	VD 20'	
S. O.	42	F	1.41	R. H. D.	68.5	150	92	163	299	42.0	17.56	93.7	13.64	73.0	3.92	11.7	11.36	60.6	VE 29' (4x)	VD 22' ††	VE 22' (2.5x)	
D. C.	56	M	1.62	R. H. D.	86.9	316	93	342	566	25.4	16.06	90.7	13.85	78.7	2.21	12.5	9.81	55.4	e	d	N	
J. B.	30	M	1.70	R. H. D.	31.3	87	86	101	228	31.0	19.10	87.2	13.60	62.2	5.50	12.5	4.52	19.8	VE 40' (4x)	toxic	toxic	
R. F.	60	F	1.45	R. H. D.	31.6	145	84	172	304	18.4	16.06	91.5	12.99	75.4	3.06	9.3	8.08	48.4	N	VD 40'	VD 32'	
H. T.	28	M	1.73	R. H. D.	124.0	263	96	276	464	44.9	14.03	90.5	11.03	70.6	3.00	13.9	4.27	27.3	VE 27' (4.5x)	VD 30'	N	
J. F.	57	M	1.61	R. H. D.	40.0	112	91	123	240	32.5	16.34	75.2	11.34	53.4	5.00	12.0	5.38	24.4	VE 20' (3x)	VD 27'	VD 21'	
					Mean	187.8	90.0	207.4	365.9	31.9		88.4		69.9	3.53	11.97		41.2				
					Standard deviation	29.0	76.0	80.1	113.2	7.36		5.89		8.04	1.09	1.80		14.4				
					Standard error	9.2	24.0	25.3	35.8	2.33		1.86		2.54	0.34	0.57		4.56				

A. Patients with congestive failure

* Surface area in the cardiacs is estimated from weight which is ideal for a subject of given height, sex, and age rather than the actual surface estimated from the weight and height at the time of observation (28). R. H. D. = rheumatic heart disease.

† All renal clearance figures are corrected to a body surface area of 1.73 sq. m.

‡ Clearance of PAH uncorrected for extraction.

§ Corrected plasma flow is the plasma flow measured as mg. PAH excreted per min./mg. PAH extracted from one cc. of plasma. The corrected filtration fraction is the ratio of the glom. fil. rate and the corrected plasma flow.

|| Three categories of vasotropic activity are recorded:

** Patient sedated with phenobarbital and codeine; test rat gasping.

†† Plasma diluted one-half.

1. Neutral = N

2. Vasoexcitor = VE

3. Vasodepressor = VD

e = trace or mild vasoexcitor

d = mild vasodepressor.

TABLE I—Continued

Pa-tient	Age	Sex	Surface area* sq. m.	Diagnosis*	Renal data†						Oxygen data							Rat mesoappendix assay				
					Ultra-tion rate cc. per min.	Plasma flow‡ cc. per min.	PAH extrac-tion per cent	Corr. plasma flow§ cc. per min.	Hema-tocrit per cent	Blood flow cc. per min.	Corr. filtra-tion fraction	Femor-al artery Con-tent	Femor-al artery Satu-ration	Renal vein Con-tent	Renal vein Satu-ration	Renal A-V differ-ence vol. per cent	Renal O ₂ con-sump-tion per min.	Hepatic vein Con-tent	Hepatic vein Satu-ration	Renal vein	Hepatic vein	Femor-al artery
A. A.	29	M	1.75	syphilis	161	705	87	809	42.6	1409	19.9	18.80	94.5	17.25	87.0	1.55	21.8	14.40	70.0	N	N	N
H. F.	28	F	1.55	syphilis	126	760	78	974	37.3	1550	13.0	15.10	94.2	14.28	89.5	0.82	12.7			N	N	N
H. M.	23	M	1.91	syphilis	162	890	82	1085	41.0	1840	14.9	16.04	93.5	15.26	88.5	0.78	14.4			N	N	N
C. C.	18	M	1.77	undesc. testicle	161	1002	82	1220	37.6	1955	13.2	16.58	94.2	15.46	89.0	1.12	21.8			VE 18' (2x)	VD 16'	N
A. S.	41	M	1.73	duod. ulcer	120	706	85	832	43.0	1460	14.5	19.01	95.0	17.64	88.7	1.37	20.0			VE 19'	VD 16'	N
O. S.	40	M	1.67	multiple sclerosis	103††	615	91	675	42.4	1170	15.2	17.69	92.0	16.52	86.0	1.17	13.7			e	VD 16'	N
A. S.	50	M	1.91	parasis	93††	396	90	440	46.0	815	21.2	18.52	90.8	16.92	83.3	1.60	13.0			N	N	N
S. P.	31	M	1.73	duodenal ulcer	126	475	89	534	42.8	935	23.6	18.97	94.8	17.81	89.5	1.16	10.9			N	N	N
C. D.	34	F	1.67	cardio-spasm	116	513	88	584	35.9	910	19.8	14.92	91.8	13.20	81.0	1.72	15.6			N	N	N
A. W.	37	M	1.74	cerebellar degener.	114	518	90	576	43.0	1001	19.7	18.86	91.0	17.26	84.8	1.60	16.0			N	VD 14'	N
M. P.	48	F	1.52	neuritis	120	670	86	730	33.0	1165	15.3	10.42	92.5	9.13	81.0	1.29	15.1			e		
R. S.	47	F	1.70	buraitis	143	660	90	733	36.5	1154	19.4	15.80	92.0	14.50	85.0	1.30	15.0			N		N
				Mean	128.8	659.2	86.5	766		1280	17.5	93.0	86.1			1.29	15.83					
				Standard deviation	22.7	173.5	4.04	233		367	3.3	1.12	3.07			0.31	3.56					
				Standard error	6.6	50.1	1.16	67.2		106	0.95	0.09	0.89			0.09	1.03					

† Control patients without congestive failure

Samples with depressor activity are indicated by D together with a figure indicating the duration in minutes of the depressed response to epinephrine. Samples with excitor activity are indicated by E together with a figure indicating the duration in minutes of the potentiated response to epinephrine. The figure in parenthesis refers to the maximum dilution of epinephrine which produced the control response. Samples with neutral activity do not produce any demonstrable change in the reactivity of the capillary vessels to epinephrine.

†† Mannitol clearance times 1.10.
 §§ Datum obtained from a study one month previously.
 || Pyrogen reaction.

tion in the two groups, considered separately or combined.

The *hepatic venous oxygen saturation* in the cardiacs was 41.2 ± 14.4 per cent as compared to 69.4 ± 4.0 per cent in the seven controls in which it was determined. This marked difference between the two groups is highly significant ($P < 0.001$). The cardiacs with the greatest renal venous unsaturation, with few exceptions, had the greatest hepatic venous oxygen unsaturation.

Increased vasoexcitor activity was present in the *renal venous blood of the cardiacs* as compared to the controls. In eight of the 10 cardiacs listed in Table I there was a marked VEM reaction which lasted as long as 46 minutes and required as much as a six-fold dilution of the epinephrine to give the control response. In two additional cardiacs not included in Table I (R. S. and B. R.) there were vasoexcitor reactions which lasted 33 and 40 minutes, respectively, and required diluting the epinephrine to the same extent as in the other congestive failure patients. In only one cardiac, R. F., did the renal venous blood give a neutral vasotropic reaction. It is of interest to note that R. F. also had a normal filtration fraction, a most unusual finding in chronic heart failure. Whether her congestive failure was complicated by intrinsic renal disease is not known. One other cardiac, D. C., had renal venous blood which gave only a mild excitor reaction. The clinical status of this patient, the renal blood flow of 566 cc. per minute, and a renal A-V oxygen difference of 2.21 volumes per cent, all suggested that he was in less severe failure than the others of the group. The semiquantitative character of the biological test did not permit conclusions as to whether there was any direct relationship between the degree of vasotropic activity in the renal venous blood, and the reduction in renal blood flow, increase in renal oxygen extraction or change in renal oxygen utilization in the cardiac group.

A *marked vasodepressor reaction*, which lasted from 24 to 40 minutes, was found in the *hepatic venous blood* in 10 of the 12 *congestive failure patients*. The plasma sample of patient J. B., who was probably in the most severe failure of the group, gave a toxic reaction in the test rat, preventing a proper assay. The hepatic venous plasma of patient D. C. showed only a mild de-

pressor reaction. As mentioned previously, this patient was in less severe congestive failure than any of the other cardiacs, and his renal venous plasma also showed only a mild vasoexcitor reaction.

In the 12 samples of *femoral arterial plasma* from the cardiac group there was an excitor reaction in five, a depressor reaction in four, a neutral reaction in two, and in one patient a toxic reaction which precluded accurate assay. In no instance did the peripheral blood have a depressor or excitor reaction greater than or equal to the corresponding hepatic or renal venous plasma sample. The vasotropic effects produced by the femoral arterial plasma represent the resultant of varying amounts of VEM and VDM.

In contrast, vasotropic activity in the blood of control patients was infrequent and mild when present. Thus, in 14 renal venous samples there was a neutral reaction in 10. Two controls, M. P. and A. S., had a trace of VEM in the renal venous plasma. One other control, C. C., developed a pyrogen reaction during the sampling and his renal venous plasma exhibited a mild excitor reaction which lasted 19 minutes. We have no adequate explanation for the presence of another mild excitor reaction in the renal venous plasma of H. M., which lasted 18 minutes.

There was a neutral reaction in the hepatic venous plasma in nine of 12 controls. Mild depressor activity was present in the hepatic venous samples of three patients (C. C., A. S., and A. W.), two of whom showed the greatest oxygen unsaturation. No statement can be made with regard to A. W., since oxygen and vasotropic studies were not done simultaneously.

A neutral reaction was obtained in all 13 instances in which peripheral arterial plasma was assayed in control subjects.

DISCUSSION

In the cardiac group, the renal hemodynamic data are characteristic of chronic congestive heart failure, showing a decreased glomerular filtration rate, a more marked decrease in renal plasma flow, and a resultant elevated filtration fraction (16, 17). The one cardiac, H. T., with a normal glomerular filtration rate—the first patient in our series of 83 cardiacs to exhibit this finding—also

had a reduced renal plasma flow. Others (16, 18, 19) have reported similar exceptional cases.

The presence of markedly increased concentration of vasotropic substances in the blood of the cardiacs suggests a possible role of these principles in the altered renal and peripheral hemodynamics of chronic congestive heart failure. It also raises the question of the various interrelationships between the reduced renal circulation and oxygen transport and the production of these substances. The decreased renal blood flow is accompanied by an increase in renal oxygen extraction, which is not, however, sufficiently great to maintain a normal oxygen consumption. Congestive failure appears to be unique among conditions involving reduced renal blood flow in that the renal arteriovenous oxygen difference is elevated. In contrast, in chronic glomerulonephritis and nephrosclerosis (12), during abdominal compression in man (20), and in experimental renal hypertension in the dog (21), the renal arteriovenous oxygen difference remains unchanged so that there is a fall in renal oxygen consumption parallel with the fall in renal blood flow. In hemorrhagic shock in dogs, there is also a proportional reduction in oxygen consumption with the renal ischemia until the renal blood flow has fallen to low levels, at which time the renal oxygen extraction increases (22). In acute and subacute glomerulonephritis there is likewise a decrease in renal oxygen consumption. In these conditions, however, renal blood flow is reported to be within normal limits, whereas oxygen extraction is significantly reduced (12).

It should be emphasized that the measured arteriovenous oxygen difference may vary from 5 to 25 per cent and when individual subjects, normals or cardiacs, are compared, the renal oxygen consumption may differ as much as 65 to 100 per cent. Moreover, since the noncardiac subjects have a smaller renal arteriovenous oxygen difference, contamination of renal venous blood with more unsaturated caval blood will produce greater apparent increases in renal oxygen extraction and, consequently, oxygen consumption in these patients.

The mean oxygen consumption of our control patients of 15.8 ± 3.56 cc. per minute is comparable to the mean of 16.0 ± 2.9 cc. per minute reported by Cargill and Hickam (12). Clark and Barker (23) found a mean of 6.1 cc. per 100

gm. of kidney tissue per minute, or 18.3 ± 2.27 cc. per minute assuming 300 gm. of kidney tissue for 1.73 sq. m. of surface area. In five normal patients, Bradley and Halperin (20) found a low renal oxygen consumption ranging from 6.0 to 14.2 cc. per minute. In Warren's group (24) of eight patients without congestive failure (two with low arterial oxygen contents) the mean renal arteriovenous oxygen difference was 2.3 volumes per cent with a range of 1.9 to 2.6 volumes per cent, which is significantly greater than in other reported normals.

Despite the overlap in renal oxygen consumption of some individuals in the two groups, the mean of the cardiac patients, 12.0 ± 1.8 cc. per minute, was significantly lower than that of the normals. Calculation of the only other available data on renal oxygen consumption in congestive failure, reported by Merrill in nine patients yields a mean renal oxygen consumption of 14.0 cc. per minute with a range of 9.6 to 21.0 cc. per minute. The mean renal arteriovenous oxygen difference, 3.51 volumes per cent with a range of 2.4 to 5.5 volumes per cent, is essentially the same as that of the present study.

The physiological significance of the reduced renal oxygen consumption of congestive failure is not clear. In chronic renal disease such reduction is to be expected since the mass of functioning nephrons is diminished (25a). This consideration does not apply to congestive failure in which no evidence of organic renal disease has been demonstrated. In fact, unpublished data from this laboratory indicate that the functional renal mass as measured by T_{mPAH} and T_{mG} is normal (25b). Therefore, the reduced renal oxygen consumption may represent a generalized decrease in renal parenchymal metabolism if no significant number of nephrons has been excluded. It should be emphasized, however, that chance sampling error as discussed above will tend to produce or to increase a difference in renal oxygen consumption between the two groups.

Since in the cardiacs the renal venous oxygen saturation was lower, there was an equivalent reduction in the mean renal capillary oxygen saturation which was 79.1 per cent as compared to 89.5 per cent in the controls. On the oxygen dissociation curve at an assumed pH of 7.4, these figures correspond to mean renal capillary oxygen

tensions of 44 mm. Hg and 62 mm. Hg, respectively. If corrections were made for the shift in the oxygen dissociation curve resulting from the increased carbon dioxide tension and lowered pH of the cardiac's blood, this difference between the two groups would be somewhat less but remain highly significant.

The release of the renal vasotropic principle, VEM, would seem to be related to reduction in oxygen tension rather than to low oxygen consumption, since all the cardiacs had definitely lowered renal oxygen tension, whereas several had a renal oxygen consumption in the normal range. That such a relationship exists *in vivo* is also suggested by the fact that normal kidney produces VEM *in vitro* when exposed to a decreased oxygen tension. However, the participation of both factors in the local genesis of VEM cannot be excluded on the basis of these data.

In an effort to evaluate the influence of reduced oxygen tension, the effect of breathing a 10 per cent oxygen mixture for 15 minutes was studied in two normal subjects. The data in Table II indicate that moderate titers of VEM were found in the renal venous blood during hypoxia, in contrast to a neutral reaction obtained during the breathing of room air. During the hypoxic period, the blood flow, the arteriovenous oxygen difference, and the oxygen consumption of the kidneys in patient C. D. did not change significantly, whereas the mean renal capillary oxygen tension was reduced from a control value of 56 mm. Hg to 37 mm. Hg. The influence of other factors, such as the gen-

eralized decrease in arterial oxygen saturation during the hypoxic period, is difficult to evaluate. However, the analogy between this *in vivo* study and the *in vitro* experiments in which reduced renal oxygen tension led to the production of VEM supports the conclusion that in man one of the possible mechanisms for the release of VEM is a decreased oxygen tension in the renal interstitial fluids. Apparently, the degree of hypoxia of the kidneys encountered in cardiac patients is not sufficient to produce manifest renal injury, at least as reflected by available tubular functional tests. However, since the oxidative enzyme systems of the tubular cells are sensitive to decreased oxygen tension (26), it is conceivable that the altered metabolism at such times may result in the liberation of substance(s) not normally demonstrable.

The marked hepatic venous oxygen unsaturation in the patients in congestive heart failure reflects the severe hypoxia of the liver. Myers and Hickam (27) have reported that this increased hepatic arteriovenous oxygen difference is sufficient to compensate for the reduction in blood flow, which is proportionate to the reduction in cardiac output, so that the hepatic oxygen consumption in congestive failure is normal. When liver slices are exposed to decreased oxygen tensions there is a release of VDM. By analogy, hepatic hypoxia *in vivo* such as occurs in congestive heart failure would appear to be responsible for the release of VDM.

The exact role played by VDM and VEM in the peripheral and renal circulations in congestive

TABLE II
The effect of low oxygen tension breathing on VEM formation

Inspired air	Arterial blood		Renal						
			Venous blood		A-V oxygen diff.	Blood flow	Oxygen consumption	Mean capillary PO ₂	Vasotropic activity
	Oxygen cont.	Oxygen satur.	Oxygen cont.	Oxygen satur.					
Atmosphere	vol. per cent 14.92	per cent 91.8	per cent 13.20	per cent 81.0	per cent 1.72	cc. per min. 910	cc. per min. 15.6	mm. Hg 56	neutral
10 per cent O ₂ 90 per cent N ₂ (15 min.)	12.10	74.0	10.45	64.3	1.65	1000	16.5	37	VEM-24' (3X)

The above data were obtained on patient C. D. In another patient, A. W., the determination of the oxygen content of the renal vein blood obtained during the hypoxic period was unsatisfactory due to technical difficulties. However, the vasotropic assay showed an excitatory reaction lasting 20 minutes, as compared to a neutral reaction obtained during the control period.

heart failure is still speculative. What has emerged from these studies is the regularity with which each factor appears in congestive heart failure in the venous blood of the organ to which its genesis has been traced. This would indicate that, as far as the liver and kidney are concerned, high concentrations of VDM and VEM, respectively, are present within the organ involved in their production. The specific relationship of the increased amounts of both factors to the local hemodynamics of each organ and to the renal excretory alterations in congestive failure remains a matter for future investigation.

SUMMARY AND CONCLUSIONS

1. The renal blood flow in a group of 10 patients in chronic congestive heart failure, due to rheumatic valvular disease, was measured by the direct Fick principle, employing p-aminohippurate, and found to be reduced about 70 per cent. The PAH extraction was normal, averaging 90.0 ± 3.7 per cent.

2. In the present series, the mean glomerular filtration rate in the cardiacs was reduced to about one-half of normal. The filtration fraction averaged 31.9 ± 7.36 per cent in the cardiacs and 17.5 ± 3.3 per cent in the controls.

3. There was an increased renal extraction of oxygen in the congestive failure patients. The mean renal A-V oxygen difference was 3.53 ± 1.09 volumes per cent in the cardiac group in contrast to 1.29 ± 0.31 volumes per cent in the control group.

4. The mean renal oxygen consumption was 12.0 cc. (with a range of 8.6 to 14.0 cc.) in the cardiac group, as compared to 15.8 cc. (with a range of 10.9 to 21.8 cc.) in the control group. The difference between the means was statistically significant.

5. The mean renal capillary oxygen tension was calculated to be 62 mm. Hg in the control group and 44 mm. Hg in the cardiac group.

6. Utilizing the rat mesoappendix assay method for vasotropic activity, high titers of vasoexcitator material, VEM, were demonstrated in the renal venous blood in 10 of 12 congestive failure patients in contrast to the presence of only trace amounts in three of 13 control subjects.

7. It is suggested that one of the possible mecha-

nisms for the release of VEM in the cardiac group was a decreased oxygen tension in the renal interstitial fluids. In two normal subjects breathing a 10 per cent oxygen: 90 per cent nitrogen mixture for 15 minutes resulted in increased VEM production by the kidney without significant change in the renal oxygen consumption or oxygen extraction.

8. The hepatic vein blood had high titers of vasodepressor material, VDM, in 10 of the 11 cardiacs. The 14 control hepatic vein samples assayed gave a mild depressor reaction in three; the remainder were neutral.

9. The peripheral arterial blood containing a mixture of VEM and VDM showed a predominance of VEM in five, predominance of VDM in four, and a neutral response in two of the cardiacs as compared to the 13 controls, all of whom showed a neutral reaction.

10. In the present state of our knowledge it is not possible to define the relationship between the production of VEM by the ischemic, hypoxic kidney and the marked renal vasoconstriction in congestive heart failure.

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