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Research Article

CEREBRAL HEMODYNAMICS IN PATIENTS WITH HEART FAILURE ASSOCIATED WITH HYPERTENSION AND THE RESPONSE TO TREATMENT[1]

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Cerebral blood flow and cerebral oxygen consumption are not altered in patients with uncomplicated hypertension (1). Scheinberg observed that in a mixed group of patients who had congestive heart failure, the cerebral blood flow was depressed (2). This suggests altered cerebral hemodynamics either as a primary abnormality or as a result of disturbances in the cerebral circulatory dynamics secondary to the cardiac failure. Novack, Goluboff, Bortin, Soffe, and Shenkin (3) studying the same problem concluded that the cerebral blood flow is not depressed to any greater extent in patients with heart failure than it would be in a similar group of patients of the same age group who were not in heart failure. Since cerebral blood flow and cerebral oxygen consumption are relatively normal (1, 4) in patients with essential hypertension which is uncomplicated by the co-existence of heart failure, it seemed worth making observations on cerebral hemodynamics in a group of patients with hypertension who had developed heart failure. Since all but three of these patients were under the age of sixty years, if a significant reduction in cerebral blood flow were found, it could then be considered to be a result of the heart failure rather than secondary to cerebral arteriosclerosis. In addition, observations were made on the cerebral hemodynamic response when twelve patients were given maximum therapy for heart failure. If cerebral blood flow and oxygen consumption were depressed because of heart failure, one might well have expected these functions to improve following treatment.

METHODS AND MATERIALS

Observations on cerebral hemodynamics and cerebral oxygen metabolism were made on twenty patients with hypertension complicated by heart failure and six patients with heart failure due to other causes. Similar observations were made from four days to one month later on fourteen of these patients after they had received maximum benefit from treatment for heart failure. Although all but one patient showed marked subjective and objective improvement of symptoms and signs following therapy, the circulation time and venous pressure had not returned to normal in all of them. Twelve of the fourteen patients who were studied before and after long-term therapy had hypertension. Treatment included digitalis, diuretic therapy, low-salt diet, and bed rest when indicated. Observations were also made before and one-half hour to two hours after rapid digitalization in five patients. Cerebral blood flow was measured by the nitrous oxide method (5). The jugular venous pressure was measured with a spinal fluid manometer using the level of the venopuncture site (jugular bulb) as the reference point. The mean arterial pressure (MABP) was measured by direct arterial manometry using the femoral artery. The methods and analytical procedures used have been described previously (4, 6). The partial pressure of carbon dioxide (pCO_2) was determined with the aid of a Van Slyke Nomogram (7). The cerebral oxygen consumption ($CMRO_2$) was determined by multiplying cerebral blood flow by the arteriovenous oxygen difference. The cerebrovascular resistance (CVR) as presented in the current study is a simple ratio of effective mean blood pressure divided by cerebral blood flow per 100 grams of brain per minute.

At the time of the initial study all of the patients had peripheral edema and some dyspnea associated with varying degrees of heart failure. Because of technical difficulties in carrying out the procedure, patients with very severe dyspnea were excluded from the study. The severity of disease in the twenty patients with hypertension varied from mild essential hypertension to severe malignant hypertension. In one patient (No. 6) the hypertension was associated with chronic glomerular nephritis. All of the studies were done with the patients in the supine position, although in several patients it was necessary to flex the neck and thorax because of moderate orthopnea. When this became necessary in order to complete the initial observations, the post treatment observations were made with the patient in the same position. Studies were also completed on six patients with heart failure due to causes other than hypertension. In addition to the twenty-six patients herewith reported, studies were attempted on five other patients, but the

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TABLE I

Clinical status of patients with heart failure and the effect of treatment *

Patient	Sex	Age	Clinical diagnosis	Degree of heart failure	Hematocrit (%) C	Hematocrit (%) D	Circulation time† (sec.) C	Circulation time† (sec.) D	Venous pressure mm. water C	Venous pressure mm. water D	Respiratory rate (per min.) C	Respiratory rate (per min.) D	Pulse rate (per min.) C	Pulse rate (per min.) D	Mean blood pressure‡ mm. Hg C	Mean blood pressure‡ mm. Hg D	Date of study C	Date of study D
a. Patients with hypertension on whom studies were done before and after treatment for heart failure																		
1.§	F	59	HCVD	2+	36	35	35	20	260‡‡	160‡‡	31	14	74	70	133	109	6-8	6-12
2.‖¶	M	56	HCVD	3+	36	36	20	15	241‡‡	132‡‡	34	21	110	94	155	130	5-15	5-29
3.	M	57	HCVD, SHD	2+	42	41	35	25	111	90	42	44	100	78	150	127	6-29	7-6
4.‖	F	51	HCVD	3+	35	38	28	15	103	62	17	19	110	96	160	135	9-5	10-2
5.§	F	56	HCVD	3+	42	40	50	22	180	100	48	18	86	78	172	127	9-12	9-25
6.**††	M	46	HCVD, CGN	2+	35	37	37	21	240‡‡	140‡‡	20	26	80	90	157	180	9-25	10-3
7.	F	46	HCVD	1+	28	33	28	20	230‡‡	130‡‡	20	20	86	72	150	133	6-10	6-30
8.	M	34	HCVD	1+	49	38	—	—	130	100	26	30	96	88	167	174	10-7	10-11
9.	M	65	HCVD	4+	42	49	—	—	250	196	29	20	98	62	152	140	4-17	5-1
10.	M	59	HCVD	3+	39	48	17	13	112	82	56	17	127	76	182	143	4-24	5-29
11.	M	50	HCVD	3+	38	36	—	—	—	191	24	—	90	92	173	135	8-10	8-14
12.	M	40	HCVD	2+	42	40	50	19	210	61	20	14	92	75	147	127	7-17	7-24
Mean		52			39	39	33	19	188	120	31	22	96	81	158	138		
% of control						100		58		64		71		84		87		
P<						0.50		0.01		—		0.10		0.01		0.01		
b. Patients with hypertension on whom post treatment studies were not done																		
13.	F	48	HCVD	1+	34		—		211		15		78		145			
14.	F	46	HCVD	1+	47		17		245		20		88		150			
15.	M	34	HCVD	1+	43		20		40		20		96		195			
16.	M	59	HCVD	1+	47		23		184		31		124		118			
17.	F	44	HCVD	4+	42		—		—		32		110		153			
18.	F	63	HCVD	3+	26		30		146		22		95		143			
19.	M	30	HCVD	3+	51		31		146		33		120		168			
20.	F	65	HCVD	3+	42		42		256		24		114		153			
Mean		49			42		27		175		25		103		153			
Grand Mean ±S.E.§§		50			40±1.5		31±2.8		183		28±2.4		99±3.4		156±3.8			
c. Patients in heart failure not associated with hypertension																		
21.	M	34	Etiology?	4+	38		34	24	170‡‡	110‡‡	26	20	100	92	93	105	3-6	3-20
22.	M	46	RHD, AI, MS	3+	55		55	25	200‡‡	140‡‡	22	16	104	88	58	58	4-27	5-22
23.	M	58	SHD, AI	3+	50		35	—	170‡‡	—	28	—	96		93			
24.	M	24	RHD, AI	1+	39		14		80		20		124		80			
25.	M	41	RHD, MS	2+	52		18		30		20		72		98			
26.	M	61	SHD, AI	2+	30		28		140		36		108		95			
Mean		44			44		31	25	132	125	25	18	101	90	86	82		
S.E.‖‖					4.0		6.0				2.5		7.0		6.2			

* C—Control.
D—After treatment of heart failure with digitalis, mercurials, etc.
HCVD—Hypertensive cardiovascular disease.
RHD—Rheumatic heart disease.
AI—Aortic insufficiency.
MS—Mitral stenosis.
SHD—Syphilitic heart disease.
CGN—Chronic glomerular nephritis.
† Decholin® circulation time in seconds.
‡ Mean blood pressure—direct arterial manometry.
§ Received NH_4Cl before and during studies.
‖ Azotemia—Patient 2—BUN = 34 mg. per cent 5/15 and 16 mg. per cent 5/29.
Patient 4—BUN = 27 mg. per cent during control study, 14 mg. per cent after treatment.
¶ Poor results with treatment.
** Hemoglobin = 10 gm.
†† Confused.
‡‡ Antecubital venous pressur ; all others are jugular bulb pressure.

§§ ±S.E. – Standard Error = $\sqrt{\frac{SX^2}{N(N-1)}}$. Standard error for patients 1 to 20.

‖‖ Standard error for patients 21 to 26.

procedure had to be discontinued because of dyspnea and discomfort when the mask was applied. The blood urea nitrogen was elevated in two patients (Numbers 2 and 4) apparently as a result of the heart failure, since there was no evidence of primary renal disease in these patients. The venous pressure was moderately elevated in fourteen of the twenty-four patients so studied, and the circulation time was increased in twenty of the twenty-one on whom this observation was made. The average age of the patients with hypertension was fifty years. The heart failure responded well to therapy in all but one of the patients (Number 2) who were treated. The two patients who were receiving ammonium chloride prior to therapy continued to receive this drug during the treatment period. The remainder of the patients did not receive acidifying salts before or during the study. About half of the patients had not previously received treatment for heart failure and the remainder had failed

to follow an adequate treatment program prior to these studies.

RESULTS

The clinical status of the patients and the mean blood pressure are presented in Table I. The cerebral hemodynamics and the response to treatment are presented in Table II.

Although the cerebral blood flow seemed to be lower than normal in a few instances, there was no significant difference in cerebral blood flow for the group of patients with heart failure associated with hypertension (51 ± 2.9 ml. per min.) than in normal subjects (5) or patients with hypertension (1, 4) who did not have heart failure. In

TABLE II

Cerebral hemodynamics and cerebral blood oxygen and carbon dioxide in patients with heart failure and the effect of treatment *

	Arterial CO_2 *volume %*		Venous CO_2 *volume %*		Arterial P CO_2 *mm. Hg*		Arterial O_2 *volume %*		Venous O_2 *volume %*		A-V O_2 *volume %*		Cerebral blood flow *ml./min.*		Cerebral O_2 uptake° *ml./min.*		CVR	
Patient	C	D	C	D	C	D	C	D	C	D	C	D	C	D	C	D	C	D
a. Patients with hypertension on whom studies were done before and after treatment of heart failure																		
1.†	29.5	31.9	35.0	38.5	—	—	17.6	16.6	10.8	9.7	6.8	6.9	37	50	2.5	3.5	3.6	2.2
2.‡‖	19.2	21.7	25.8	29.6	32	36	11.9	12.7	5.4	4.3	6.5	8.4	55	41	3.6	3.4	2.8	3.2
3.	37.4	37.0	45.9	44.9	—	—	15.6	17.8	7.4	9.2	8.2	8.6	32	43	2.6	3.7	4.7	3.0
4.‡	26.0	43.6	32.4	49.9	36	38	14.6	14.1	8.2	7.6	6.4	6.5	48	57	3.1	3.7	3.3	2.4
5.†	24.9	51.0	33.7	61.0	28	44	16.6	18.1	9.4	9.3	7.2	8.8	59	45	4.2	4.0	2.9	2.8
6.§¶	51.6	55.0	55.0	60.0	49	47	8.8	8.7	5.0	4.5	3.8	4.2	50	49	1.9	2.1	3.1	3.7
7.	39.4	37.2	45.3	43.5	36	33	16.0	15.9	10.8	9.9	5.2	6.0	74	70	3.8	4.2	2.0	1.9
8.	48.7	45.1	52.1	51.8	38	40	16.2	12.7	11.2	8.1	5.0	4.6	64	55	3.2	2.5	2.6	3.2
9.	39.8	40.8	47.5	46.1	32	38	16.8	20.7	10.3	11.8	6.5	8.9	53	36	3.4	3.2	2.9	3.9
10.	34.8	42.9	41.5	52.3	29	37	10.6	16.5	5.8	7.9	4.8	8.6	35	58	1.7	5.0	5.2	2.5
11.	29.0	31.4	35.8	37.4	—	—	15.1	16.8	8.5	8.3	6.6	8.5	63	48	4.2	4.1	2.7	2.8
12.	42.7	39.8	49.6	45.6	32	31	12.0	13.4	5.7	9.0	6.3	4.4	49	46	3.1	2.0	3.0	2.8
Mean	35.3	39.8	41.6	46.7	35	38	14.3	15.3	8.2	8.3	6.1	7.0	52	50	3.1	3.5	3.2	2.9
% of control		113		112		109		107		101		115		96		113		91
P<		0.30		0.10		0.10		0.20		0.50		0.10		0.50		0.40		0.30
b. Patients with hypertension on whom post treatment studies were not done																		
13.	29.6		33.2		31		16.2		7.2		9.0		43		3.9		3.4	
14.	38.4		45.3		38		16.0		10.8		5.2		56		2.9		2.7	
15.	44.6		51.8		31		14.7		9.1		5.6		38		2.1		5.1	
16.	26.4		31.9		—		16.8		11.8		5.0		65		3.3		1.8	
17.	32.1		36.5		—		15.6		5.8		9.8		47		4.6		3.3	
18.	41.0		45.0		38		13.5		8.0		5.5		40		2.2		3.6	
19.	34.6		42.3		30		18.8		8.7		10.1		32		3.2		5.3	
20.	39.8		49.5		32		16.8		10.3		6.5		73		4.7		2.1	
Mean	35.8		41.9		33		16.1		9.0		7.1		49		3.4		3.4	
Grand Mean ±S.E.**	35.5 ±1.92		41.8 ±2.65		34 ±1.0		15.0 ±0.64		8.5 ±0.48		6.5 ±0.38		51 ±2.9		3.2 ±0.20		3.3 ±0.23	
c. Patients in heart failure not associated with hypertension																		
21.	37.8	48.4	46.4	55.0	—		18.5	14.7	6.2	7.5	12.3	7.2	22	57	2.7	4.1	4.2	1.8
22.	29.5	31.9	35.0	38.5	—		17.6	16.6	10.8	9.7	6.8	6.9	37	50	2.5	3.5	1.6	1.2
23.	25.0	—	33.2	—	—		15.2	—	6.5	—	8.7	—	31	—	2.7	—	3.0	—
24.	41.6	—	48.5	—	37		15.8	—	9.1	—	6.7	—	38	—	2.5	—	2.1	—
25.	40.8	—	46.0	—	39		18.4	—	12.2	—	6.2	—	41	—	2.5	—	2.4	—
26.	20.7	—	28.0	—	—		12.7	—	8.0	—	4.7	—	46	—	2.2	—	2.1	—
Mean	32.6	40.2	39.5	46.8	38		16.4	15.7	8.8	8.6	7.6	7.1	36	54	2.5	3.8	2.6	1.5
Std. Error	3.30		3.40		1.0		0.92		0.97		1.08		3.4		0.24		0.37	

* C—Control.
D—After treatment for heart failure.
CVR—Cerebrovascular resistance = $\frac{\text{Mean Blood Pressure}}{\text{Cerebral Blood Flow}}$.
°—Cerebral blood flow in ml. per 100 grams of brain times Arterial-Venous Oxygen difference.
P CO_2—Partial pressure of carbon dioxide in mm. Hg.
A-V O_2—Arterial-Venous O_2.
† Received NH_4Cl before and during studies.
‡ Azotemia—Patient 2—BUN = 34 mg. per cent 5/15 and 16 mg. per cent 5/29.
Patient 4—BUN = 27 mg. per cent during control study, 14 mg. per cent after treatment.
§ Hemoglobin = 10 gm.
‖ Poor results with treatment.
¶ Mentally confused.

** ±Standard Error − Standard Error = $\sqrt{\frac{SX^2}{N(N-1)}}$. This is the standard error for patients 1 to 20.
S.E.—Standard Error.

four of the patients (Numbers 3, 10, 19, and 21) in whom the cerebral blood flow appeared to be depressed, dyspnea was marked. Under these circumstances one might anticipate a low pCO_2 due to hyperventilation which in itself could cause a reduction in cerebral blood flow (8) rather than on the basis of a reduction in cardiac output (2). However, a number of patients with marked dyspnea showed entirely normal cerebral blood flow and cerebral oxygen consumption. As in patients with hypertension (1) without heart failure, the cerebrovascular resistance was increased in these patients (3.3 ± 0.2). Cardiac failure did not appear to alter these dynamics. Both patients (Numbers 2 and 4) with azotemia had normal cerebral blood flow and cerebral oxygen consumption.

Treatment for heart failure in twelve of the patients with hypertension resulted in a significant reduction in mean blood pressure ($p < 0.01$). However, cerebral blood flow did not change significantly. It increased in four patients, decreased in five, and in three it was approximately the same after treatment as it was before therapy. The averages for the group before and after treatment were nearly identical (Table II). There was a slight increase in cerebral oxygen uptake for the group, but this response was neither great enough nor consistent enough to be statistically significant. The increase in arteriovenous oxygen difference was due primarily to increased oxygen content in the arterial blood, presumably a result of improved pulmonary oxygen exchange. There was an increase in both arterial ($p < 0.30$) and venous ($p < 0.10$) blood CO_2 content associated with an increase in partial pressure (pCO_2) ($p < 0.10$). These alterations were not statistically significant when analyzed by paired differences [2] but the changes were fairly consistent, and were probably a result of the relief of the hyperventilation associated with the pulmonary congestion. There was very little alteration in the arteriovenous blood CO_2 content.

Rapid digitalization with 0.68 to 1.4 mgm. of Strophanthin K given intravenously had no effect on cerebral blood flow or on cerebral oxygen uptake 30 to 120 minutes after administration of the drug in the five patients studied. For example, one patient with a low cerebral blood flow of 34 ml. per minute and 37 ml. per minute during successive control periods taken 30 minutes apart showed a cerebral blood flow of 30 ml. per minute one-half hour after Strophanthin K administration and 38 ml. per minute one and one-half hours later. The mean value for cerebral blood flow in five patients was 44 ml. per minute before rapid digitalization and 45 ml. per minute after it. The cerebral blood flow in six patients with heart failure due to diseases other than hypertension (syphilis, chronic rheumatic heart disease, and etiology unknown in one instance) was reduced significantly, although the age range was approximately the same as in the twenty patients with heart failure associated with hypertension (Table II).

[2] $t = \bar{x}\sqrt{\frac{N(N-1)}{Sx^2}}$

Statistics completed by Dr. R. A. Seibert.

COMMENTS

The current observations appear to support the contention that cerebral blood flow is not depressed in patients with heart failure (3) when the heart failure is due to hypertension. It appears that heart failure *per se* did not depress cerebral blood flow or cerebral oxygen consumption, since the average cerebral blood flow in this group of patients with heart failure was about the same as in normal subjects (5, 9) as well as patients with hypertension (1, 4). As Novack, Goluboff, Bortin, Soffe, and Shenkin (3) have pointed out, arteriosclerosis itself is frequently associated with a reduction in cerebral blood flow. When these patients develop heart failure cerebral blood flow will accordingly be lower than in normal young subjects. The fact that adequate and prolonged treatment with improvement of the heart failure in our patients did not increase cerebral blood flow or cerebral oxygen consumption, is further evidence that the cerebral blood flow was probably not depressed due to heart failure in the first place. Likewise, rapid digitalization with Strophanthin K did not alter cerebral hemodynamics. The patients with low values for cerebral blood flow before treatment were usually dyspneic and also exhibited low pCO_2 values, apparently a result of the hyperventilation (8). Patients with prerenal azotemia did not show a decrease in cerebral blood flow despite the low

pCO_2 and CO_2 content and acidosis exhibited by them. Similarly, the cerebral oxygen consumption was not altered.

Further observations are indicated on patients with cardiac failure due to causes other than hypertension before dogmatic and inclusive deductions can be made about congestive heart failure, irrespective of the etiology of the disease. The current observations on six patients (Numbers 21 to 26) suggest that cerebral blood flow is reduced in patients with rheumatic and syphilitic heart disease associated with heart failure. However, the reduction in cerebral blood flow in these cases may be due to the mechanics of the underlying cardiac disease (aortic insufficiency or mitral stenosis) resulting in a greater depression in cardiac output and may not be a result of the accompanying congestive heart failure.

In order to further elucidate this problem, cerebral blood flow determinations have been done before and after tourniquets were applied around the necks of three normal subjects and four patients with heart failure who had received adequate therapy. The tourniquet pressure was increased until the venous pressure in the jugular bulb was increased to 120 to 300 mm. Hg. Cerebral blood flow was not altered by this procedure (10). This indicates that cerebral blood flow is not reduced by increases in venous pressure within the limits present in patients with congestive heart failure. However, it is possible that cerebral hemodynamics and cerebral oxygen consumption may be altered in patients with severe pulmonary congestion associated with dyspnea due to severe heart failure. Under these conditions, it is impossible to do accurate cerebral blood flow determinations using the nitrous oxide technique.

SUMMARY

1. Observations have been made on cerebral hemodynamics and cerebral oxygen consumption in twenty patients with hypertension associated with heart failure. Cerebral blood flow and cerebral oxygen consumption were not altered in these patients.

2. Treatment for heart failure did not alter cerebral blood flow or cerebral oxygen consumption in patients with hypertension and associated cardiac failure.

3. Cerebral blood flow was depressed in six patients who had heart failure associated with aortic insufficiency or mitral stenosis.

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