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Research Article

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Similar studies were carried out in the external carotid artery of six patients. Within 10 sec after injection blood flow was markedly reduced, indicating a direct vasoconstricting action on this vascular bed.

Effect of Norepinephrine, Epinephrine, and Angiotensin on Blood Flow in the Internal Carotid Artery of Man

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ABSTRACT Internal carotid artery blood flow and arterial pressure were measured with a sine-wave electromagnetic flowmeter and a pressure transducer in 22 patients during control period and after the intravenous and intracarotid administration of norepinephrine, epinephrine, and angiotensin. Intravenous infusion of both norepinephrine and angiotensin was accompanied by an increase in cerebral vascular resistance. Administration of norepinephrine, epinephrine, and angiotensin into the internal carotid artery failed to alter blood flow immediately. However, when the systemic blood pressure increased, a concomitant passive rise in blood flow did not occur. Thus, at this time cerebral vascular resistance was significantly increased. It is concluded that these drugs do not have a direct action on the cerebral vessels, but that the increased cerebral vascular resistance after their administration is due to autoregulation or to a combination of autoregulation and reduced arterial carbon dioxide pressure (Pco_2) secondary to hyperventilation.

Similar studies were carried out in the external carotid artery of six patients. Within 10 sec after injection blood flow was markedly reduced, indicating a direct vasoconstricting action on this vascular bed.

INTRODUCTION

Several groups of investigators have demonstrated that an increase in arterial pressure after the systemic administration of norepinephrine to human subjects is accompanied by either no change or a slight reduction in cerebral blood flow (1–4). These data have been interpreted as indicating that this drug constricts cerebral vessels directly (5). However, the intracranial vessels probably have the capacity to autoregulate blood flow in response to changes in blood pressure (6, 7), and therefore an increase in vascular resistance after norepinephrine administration does not prove that the drug constricts these vessels directly. One technique for determining whether norepinephrine affects the cerebral vasculature is to inject this drug into the internal carotid artery while measuring blood flow and arterial pressure continuously. If flow decreases before a change in arterial pressure, then one can assume that this drug has a direct constricting action on the cerebral vessels. Similarly, the possible vasoconstricting actions of other drugs on the cerebral circulation can be evaluated. The effect of epinephrine on the cerebral vessels in man remains controversial (1, 3, 5), and to our knowledge, there are no data from human subjects which document the cerebrovascular action of angiotensin. Accordingly, this study was undertaken to determine the effects produced by intracarotid injections of norepinephrine, epinephrine, and angiotensin on blood flow and pressure in the internal carotid artery of human subjects. In order to provide comparative data similar measurements were obtained in the external carotid artery of a few of these subjects.

METHODS

Pressure-flow studies were carried out in 22 male patients who were hospitalized on the Neurosurgical Serv-

A portion of this data was presented at the Conference on Blood Flow through Organs and Tissues, 27–29 March 1967, Glasgow, Scotland.

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ice of the Durham Veterans Administration Hospital. The informed consent of each patient was obtained. In each patient subtotal resection of a supratentorial malignant brain tumor had been carried out from 10 to 20 days previously. At the time of the study, however, all of the patients were alert and showed no major neurologic deficit. The cerebrospinal fluid pressure was measured on the day of the study in 13 of these patients and was found to be less than 200 mm of H_2O in 11. The data described in this report were obtained during exposure of the carotid vessels so that an antitumor agent[1] could be infused directly into the internal carotid artery.

Before the surgical procedure the patients were premedicated with 50 mg of meperidine and 25 mg of promethazine. Local anesthesia was accomplished with injections of lidocaine. The common carotid artery and proximal portions of both the internal and external carotid arteries were exposed, and the small arterial branches in this area were ligated. The probe of an electromagnetic flowmeter (EMF)[2] was placed around the common carotid artery proximal to its bifurcation. The probe size was selected so that the vessel was not constricted more than was necessary to obtain an adequate flow signal. Since the EMF probe was on the common carotid artery, flow in either the internal or external carotid artery could be measured by occluding the other vessel with a nontraumatic arterial clamp. A short polyvinyl catheter[3] was inserted in the superior thyroid artery and the tip advanced to the common carotid artery. This catheter was connected to a strain gauge[4] and used for recording pressure. Drugs were administered through a 23-gauge needle connected to a short catheter which was inserted into either the internal or external carotid artery distal to the carotid sinus. The drug solutions were prepared with physiologic saline.

Both mean and pulsatile blood flow were recorded continuously with a Kolin-Kado type sine-wave EMF (8). The frequency-amplitude response of this instrument is flat $\pm$ 5% through at least 20 cycles/sec. The zero-flow reference was checked frequently during the procedure by temporarily occluding the vessel distal to the probe. The EMF was calibrated on multiple occasions by passing known quantities of physiologic saline through the probes in a given period of time. The instrument was found to be linear $\pm$ 2% through the range of flows encountered and the calibration factor, i.e., flow per unit EMF signal remained within a SD $\pm$ 6% during the period of this study. The catheter-transducer system used to measure arterial blood pressure had a frequency amplitude response of $\pm$ 5% through 20 cycles/sec. Both mean flow and mean arterial pressure were obtained by electrical integration of their respective pulsatile signals.

During both the control state and the infusion of drugs, arterial blood samples were obtained frequently for measurement of Pco_2.[5] Respiratory rate was recorded in some patients with a pneumotachograph. An electrocardiogram was obtained throughout the procedure on each patient. All recording of data was carried out on a direct writing oscillograph at paper speeds of 2.5, 50, or 100 mm/sec.[6]

Although not all drugs were given to each patient, the general protocol was as follows. Continuous measurements of both pulsatile and mean blood pressure and flow were obtained in the internal carotid artery during a control period and after the intravenous administration of norepinephrine[7] (3.0 μg/min) for a 5 min period. Both blood pressure and flow were allowed to return to control levels before the infusion of another drug. Angiotensin[8] (1.0 μg/min) was given intravenously for a second 5 min period.

After this infusion intra-arterial injections of norepinephrine, begining initially with a small quantity, 0.25 μg, were given in increasing doses every 3–5 min until the systemic arterial pressure increased. Usually 8.0 μg of norepinephrine was required to achieve a suitable response. In a similar manner increasing amounts of epinephrine[9] and finally angiotensin were given into the internal carotid artery. The maximum single dose of epinephrine administered was 5.0 μg. The largest amount of angiotensin given was 1.0 μg. After the injection of each drug internal carotid arterial pressure and flow were monitored for at least a 2 min period.

In six patients the internal carotid artery was clamped temporarily. The occlusion was never maintained for longer than a 3 min period, and during this time the neurologic status of the patient was tested frequently. Norepinephrine (1.0 μg), epinephrine (1.0 μg), and angiotensin (0.25 μg) were injected into the external carotid artery sequentially after suitable control periods and blood pressure and flow monitored for a 2 min period.

Although blood pressure and flow were recorded continuously, only selected periods were chosen for analysis. Control pressure-flow data were calculated as the average values of five consecutive heart beats just before the administration of drugs. Data recorded 5 min after beginning the intravenous infusion of norepinephrrine and angiotensin were analyzed. After the intraarterial injection of drugs, pressure-flow data were measured at 10, 20, and 30 sec and at 1 min. Both the mean flow and arterial pressure were read directly from the oscillographic recordings. The peak and nadir values of the flow pulse as well as the systolic and diastolic blood pressures were measured. The vascular resistances of both the internal

[1] S-112 (a chlorethylthioacetamide) 0.08 mg/kg of body weight.

[2] Model K-2000, Statham Instruments, Inc., Los Angeles, Calif.

[3] No. VX-044, Becton-Dickinson & Co., Rutherford, N. J.

[4] Model P23dB, Statham Instruments, Inc., Puerto Rico.

[5] Model 113, Instrumentation Laboratory Inc., Boston, Mass.

[6] Model 850, Sanborn Co., Cambridge, Mass.

[7] Norepinephrine, Winthrop Laboratories, New York.

[8] Angiotensin, Ciba Pharmaceutical Co., Summit, N. J.

[9] Epinephrine, Parke, Davis & Co., Detroit, Mich.

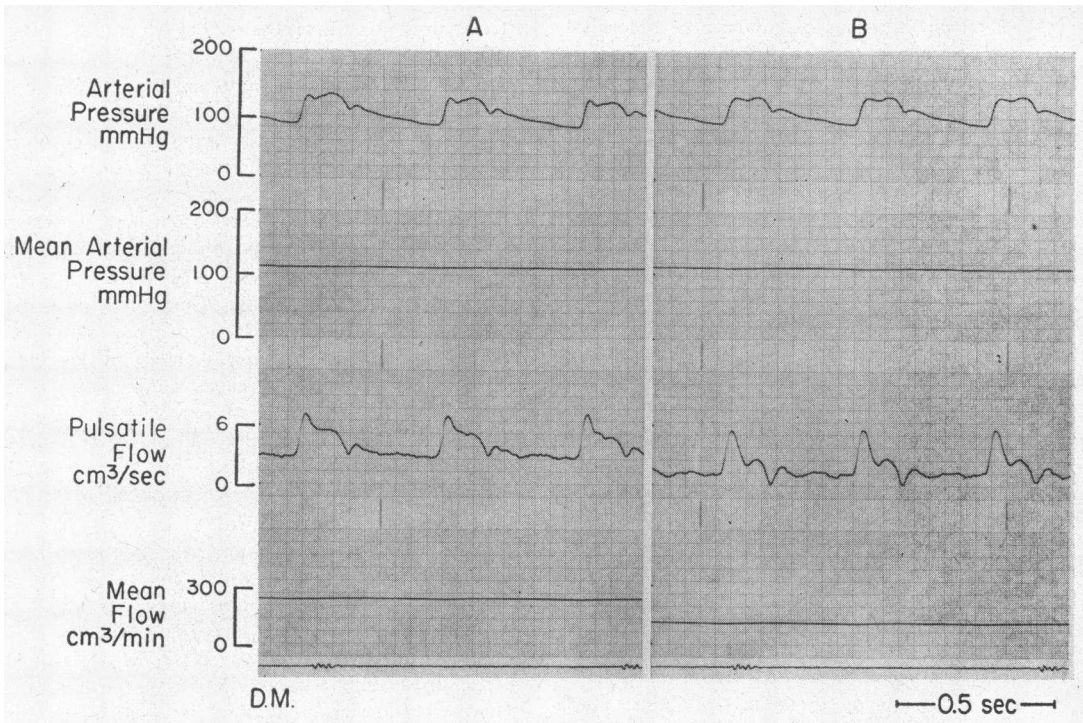

FIGURE 1 Typical recordings of blood pressure (top) and flow (bottom) from both the internal (panel A) and external (panel B) carotid artery obtained during the control state. The peak-to-nadir amplitude of the flow pulses are similar. Flow in the internal carotid artery is maintained at a relatively constant and much higher level throughout diastole. Thus, a major portion of the blood flow in the internal carotid artery is nonpulsatile in nature.

TABLE I

Effects of Intravenous Norepinephrine on Internal Carotid Artery Blood Flow

	A*						B*					
	Blood flow		Blood pressure				Blood flow		Blood pressure			
Name	Max/min‡	Mean	Syst/diast§	Mean	CVR‖	Heart rate	Max/min	Mean	Syst/diast	Mean	CVR	Heart rate
	cm³/sec	*cm³/min*	*mm Hg*		*cm³/min per mm Hg*	*beats/min*	*cm³/sec*	*cm³/min*	*mm Hg*		*cm³/min per mm Hg*	*beats/min*
O.P.	4.2/0	165	132/88	103	0.624	89	3.6/0	126	148/96	113	0.897	80
G.H.	9.6/2.0	305	148/88	108	0.354	87	9.6/2.3	241	160/92	115	0.477	82
I.H.	8.7/1.6	219	128/64	85	0.388	84	8.7/1.6	198	152/72	99	0.500	78
S.B.	5.3/1.5	137	124/80	95	0.693	84	5.1/1.3	131	140/88	106	0.809	66
F.L.	7.6/1.8	154	120/80	93	0.604	96	7.4/1.8	145	148/90	109	0.751	84
J.G.D.	5.3/0.8	135	112/68	82	0.603	90	5.5/1.3	144	158/76	94	0.651	69
H.L.M.	6.5/1.8	236	156/100	119	0.505	72	7.2/1.8	252	170/110	130	0.516	63
J.P.F.	6.2/2.0	153	140/88	93	0.607	79	6.0/3.8	153	184/100	132	0.861	72
L.G.M.	9.1/3.0	220	120/92	108	0.490	90	9.6/2.3	200	146/100	127	0.635	80
D.M.	7.4/3.4	256	137/96	116	0.453	120	7.3/3.4	265	171/110	139	0.525	110
Mean	7.0/1.7	198	133/84	100	0.532	89	7.0/2.0	186	155/92	116	0.662	78
SE		± 18		± 4	±0.04	± 5		± 17		± 5	±0.11	± 5

* A, data recorded during control; B, 5 min after start of norepinephrine infusion.
‡ max/min, maximum and minimum values of pulsatile flow.
§ syst/diast, systolic and diastolic blood pressure.
‖ CVR, vascular resistance of the internal carotid artery.

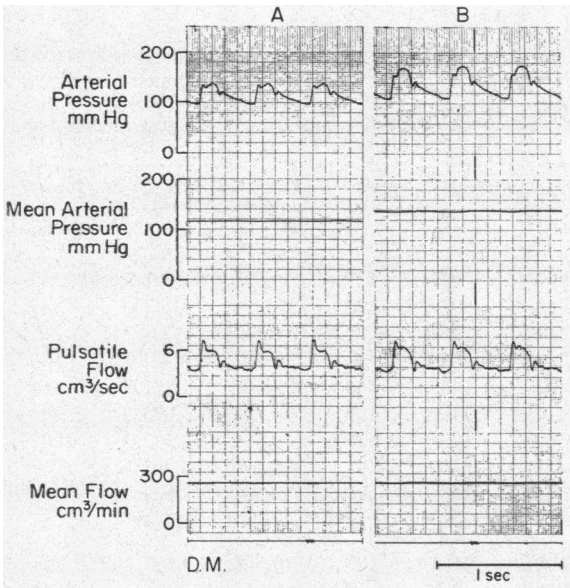

FIGURE 2 Typical pressure and flow recordings from the internal carotid artery obtained during control period (panel A) and during infusion of norepinephrine (panel B). The mean blood flow is approximately the same for both the control and postnorepinephrine periods. The peak amplitude of the flow pulse is unchanged after norepinephrine. Flow is maintained at a higher level during the the latter part of systole than in the control state.

and external carotid artery were calculated as the mean arterial pressure divided by mean blood flow in that vessel. Data were evaluated by using standard multivariate statistical techniques (Hotelling T^2).

RESULTS

The average value for mean blood flow in the internal carotid artery measured during the control state in the 22 patients was 194 ml/min, SE ± 9.7, and the average peak to nadir value for pulsatile flow was 7.1/1.8 ml per sec. Control mean arterial pressure was 102 mm Hg, SE ± 3.0. In the six patients the average control value for mean blood flow in the external carotid artery was 128 ml/min, SE ± 8.8, and the mean arterial pressure was 113 mm Hg, SE ± 4.8. Pulsatile flow in this vessel had an average peak-to-nadir value of 7.8/0.5 ml per sec. Typical examples of the blood pressure and flow pulse contours recorded during the control state from the internal carotid artery (panel A) and the external carotid artery (panel B) are illustrated in Fig. 1. Note that in the internal carotid artery a high value for flow is maintained throughout diastole; thus a major portion of the flow is nonpulsatile in nature. This finding is somewhat dependent on heart rate, i.e., the slower the rate the less the forward flow at the end of diastole. In contrast much less flow occurs during diastole in the external carotid artery. In both vessels flow reaches a peak value very early in systole which corresponds to the first peak in the arterial pressure. The amplitude of the flow pulse in the external carotid artery decreases rather sharply during the last half of systole. In the

TABLE II

Effects of Intravenous Angiotensin on Internal Carotid Artery Blood Flow

	A*						B*					
	Blood flow		Blood pressure				Blood flow		Blood pressure			
Name	Max/min‡	Mean	Syst/diast§	Mean	CVR‖	Heart rate	Max/min	Mean	Syst/diast	Mean	CVR	Heart rate
	cm³/sec	*cm³/min*	*mm Hg*		*cm³/min per mm Hg*	*beats/min*	*cm³/sec*	*cm³/min*	*mm Hg*		*cm³/min per mm Hg*	*beats/min*
L.A.	8.9/2.1	244	152/92	112	0.459	120	7.4/2.4	244	200/120	147	0.602	108
A.L.L.	5.6/1.6	178	128/88	103	0.578	72	4.9/2.0	188	156/103	120	0.639	60
G.L.N.	7.0/1.5	188	124/71	90	0.480	78	6.5/2.3	203	160/95	118	0.581	72
J.G.D.	6.7/1.2	145	120/60	77	0.531	90	4.7/1.3	144	138/80	100	0.693	66
H.L.M.	6.5/1.8	204	148/100	116	0.569	68	6.7/2.5	267	198/122	147	0.550	60
J.P.	6.0/1.4	139	104/58	76	0.548	88	4.8/1.8	151	152/79	100	0.663	68
J.P.F.	6.2/1.8	143	135/82	102	0.713	75	5.0/2.2	162	153/100	120	0.743	71
D.M.	7.2/3.4	261	144/104	124	0.475	128	7.5/3.2	269	180/115	146	0.543	116
Mean	6.7/1.9	188	132/82	100	0.544	90	5.9/2.2	204	167/102	125	0.627	78
SE		± 16		± 6	±0.09			± 18		± 7	±0.08	± 8

* A, data recorded during control; B, 5 min after start of angiotensin infusion.
‡ max/min, maximum and minimum values of pulsatile flow.
§ syst/diast, systolic and diastolic blood pressure.
‖ CVR, vascular resistance of the internal carotid artery.

TABLE III
Effects of Norepinephrine Injection

Name	A* Blood flow Max/min‡	A* Blood flow Mean	A* Blood pressure Syst/diast§	A* Blood pressure Mean	A* CVR‖	B* Blood flow Mean	B* Blood pressure Mean	B* CVR	C* Blood flow Max/min	C* Blood flow Mean
	cm³/sec	*cm³/min*	*mm Hg*		*cm³/min per mm Hg*	*cm³/min*	*mm Hg*	*cm³/min per mm Hg*	*cm³/sec*	*cm³/min*
L.A.	7.7/1.2	202	176/100	125	0.619	202	129	0.639	7.7/1.7	220
G.H.	9.2/2.1	292	142/86	105	0.360	292	108	0.370	9.2/2.6	318
I.H.	8.6/1.7	203	132/64	86	0.424	198	89	0.449	7.3/1.9	219
Z.L.	8.2/2.0	196	100/68	79	0.403	188	76	0.404	7.3/2.0	200
S.B.	5.3/1.5	148	126/80	95	0.642	144	96	0.667	4.5/1.6	144
R.J.	10.5/2.8	249	133/88	103	0.414	249	109	0.438	8.0/3.1	282
F.T.	6.4/1.9	193	145/90	108	0.560	193	113	0.585	6.2/2.0	197
R.M.	9.9/1.9	228	130/79	96	0.421	228	91	0.399	8.7/2.4	248
F.L.	7.3/1.8	150	124/80	95	0.633	146	97	0.664	7.1/2.0	159
D.M.	7.4/3.4	262	135/96	112	0.427	260	117	0.450	7.7/4.0	287
Mean	8.1/2.0	212	134/83	100	0.490	210	103	0.507	7.4/2.3	227
SE		± 15		± 4	±0.04	± 15	± 5	±0.04		± 18

* A, control data; B, 10 sec; C, 20 sec; D, 30 sec; and E, 1 min after injection of 4–8 mg of norepinephrine into the internal carotid artery.
‡max/min, maximum and minimum values of pulsatile flow.
§ syst/diast, systolic and diastolic blood pressure.
‖CVR, vascular resistance of the internal carotid artery.

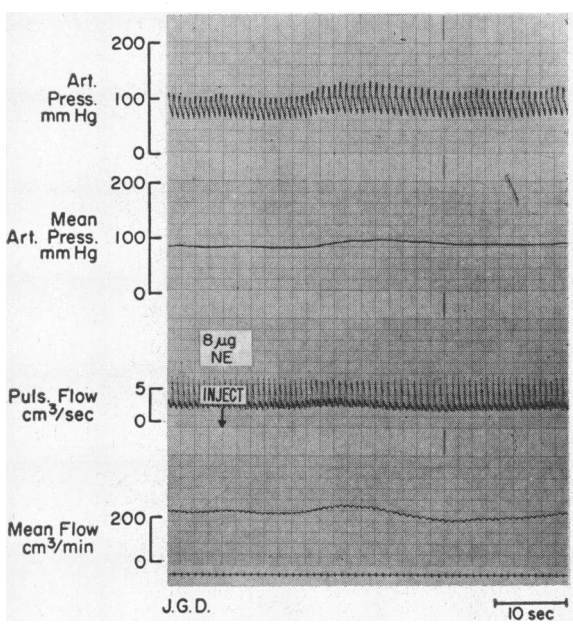

FIGURE 3 Recording of internal carotid artery pressure and flow obtained during the intracarotid injection of 8.0 µg of norepinephrine (*NE*). The time of injection is marked on the pulsatile flow recording. Note that blood flow is essentially unchanged for approximately 16 sec after the injection. Flow and pressure then increase. 35 sec after injection the flow falls below the control value.

internal carotid artery, however, flow is maintained at a fairly constant level until near the end of systole.

Pressure-flow data obtained in 10 patients during the control state (panel A) and 5 min after the intravenous administration of norepinephrine (panel B) are listed in Table I. A recording obtained from one of these patients is illustrated by Fig. 2. As shown in Table I, the control mean blood pressure for the group of 100 mm Hg, SE ± 4.0, increased to 116 mm Hg, SE ± 5.0. At the same time the control mean blood flow of 198 ml/min, SE ± 18.0, decreased to 186 ml/min, SE ± 17.0. The change in mean blood flow among the 10 patients was variable and not significant ($P > 0.1$); it increased in three, was unchanged in one, and decreased in six patients. The vascular resistance increased significantly ($P < 0.01$) from an average control value of 0.532 ml/min per mm Hg, SE ± 0.04, to 0.662 ml/min per mm Hg, SE ± 0.11. In five patients (Nos. 1–5, Table I), brachial arterial samples were obtained for Pco_2 determination. These samples were drawn at the same time that the data listed in panel B were recorded. The control value of arterial Pco_2 of 42.8 mm Hg, SE ± 1.1, decreased significantly ($P < 0.05$) to 39.9

C*			D*			E*				
Blood pressure			Blood flow	Blood pressure		Blood flow		Blood pressure		
Syst/diast	Mean	CVR	Mean	Mean	CVR	Max/min	Mean	Syst/diast	Mean	CVR
mm Hg		*cm³/min per mm Hg*	*cm³/min*	*mm Hg*	*cm³/min per mm Hg*	*cm³/sec*	*cm³/min*	*mm Hg*		*cm³/min per mm Hg*
204/112	143	0.650	166	125	0.753	7.4/1.3	193	184/107	133	0.689
168/100	123	0.387	258	109	0.422	9.6/2.0	280	148/88	108	0.386
164/84	111	0.507	178	92	0.517	8.3/1.6	194	140/68	92	0.474
116/80	92	0.460	181	83	0.459	9.2/1.3	173	108/68	81	0.468
156/88	115	0.799	110	96	0.873	4.8/1.5	131	132/86	101	0.771
175/110	132	0.468	224	117	0.522	10.2/2.5	232	146/92	110	0.474
164/104	124	0.629	152	113	0.743	6.0/1.6	166	153/94	114	0.687
164/88	113	0.456	228	113	0.496	10.1/1.7	219	136/76	96	0.438
164/96	119	0.748	127	98	0.772	7.1/0.1	118	134/80	98	0.831
174/116	132	0.460	276	124	0.449	7.4/3.1	252	116/84	108	0.429
165/98	120	0.556	190	107	0.601	8.0/1.7	196	140/84	104	0.565
	± 4	±0.05	± 17	± 4	±0.05		± 16		± 4	±0.05

mm Hg, SE ± 1.5. Inspection of Fig. 2 reveals little change in the contour of the flow pulse resulting from the infusion of norepinephrine except for a slight increase in the late systolic portion of the flow pulse. This finding is characteristic of the flow pulse contour recorded when the arterial pressure is elevated.

Data recorded from the internal carotid artery of eight patients during the control state (panel A) and 5 min after beginning an intravenous infusion of angiotensin (panel B) are listed in Table II. The control value of mean arterial blood pressure of 100 mm Hg, SE ± 6.0, increased to 125 mm Hg, SE ± 7.0, and the control blood flow of 188 ml/min, SE ± 16.0, increased to 204 ml/min, SE ± 18.0, an insignificant change ($P > 0.1$). The average peak-to-nadir amplitude of the flow pulse decreased from 4.8 ml/sec to 3.7 ml/sec. At the same time the vascular resistance increased significantly ($P < 0.01$) from a control value of 0.544 ml/min per mm Hg, SE ± 0.09, to 0.627 ml/min per mm Hg, SE ± 0.08. In five patients (Nos. 1–5, Table II) the control value for arterial Pco_2 (42.2 mm Hg, SE ± 2.2) did not change appreciably during infusion of angiotensin (42.1 mm Hg, SE ± 2.5).

Table III lists data from 10 patients obtained during the control state (panel A) and 10 sec (panel B), 20 sec (panel C), 30 sec (panel D), and 1 min (panel E) after the injection of 4.0–8.0 μg of norepinephrine into the internal carotid artery. A typical recording from one of these patients obtained during this procedure is illustrated in Fig. 3. From inspection of Table III it is apparent that 10 sec after the injection of norepinephrine there was no change in either the blood flow or arterial pressure. The cerebral vascular resistance was not significantly altered at this time ($P > 0.1$). 20 sec after injection the mean arterial pressure had increased from a control value of 100 mm Hg, SE ± 4.0, to 120 mm Hg, SE ± 4.0. At this time mean blood flow also increased significantly ($P < 0.01$) so that the control level of 212 ml/min, SE ± 15, increased to 227 ml/min, SE ± 18. The vascular resistance was also significantly elevated ($P < 0.01$) above the control values. Both at 30 sec and 1 min the arterial blood pressure was maintained slightly but significantly ($P < 0.05$) above control values. The mean blood flow at this time fell to a value significantly below the control levels ($P < 0.05$). The vascular resistance remained significantly above control levels ($P < 0.01$) during this time. In seven of these

TABLE IV

Effects of Injection of Epinephrine and

Name	A* Blood flow Max/min‡	A* Blood flow Mean	A* Blood pressure Syst/diast§	A* Blood pressure Mean	A* CVR‖	B* Blood flow Mean	B* Blood pressure Mean	B* CVR	C* Blood flow Max/min	C* Blood flow Mean
	cm³/sec	*cm³/min*	*mm Hg*		*cm³/min per mm Hg*	*cm³/min*	*mm Hg*	*cm³/min per mm Hg*	*cm³/sec*	*cm³/min*
Epinephrine										
I.L.E.	6.4/1.0	120	150/98	115	0.958	129	117	0.907	8.0/0.8	116
T.M.	7.4/2.0	200	168/96	126	0.630	209	128	0.612	7.1/2.3	180
C.M.	6.8/1.6	157	148/92	120	0.765	191	116	0.607	7.0/2.0	177
A.L.L.	5.4/2.0	179	120/81	95	0.530	173	92	0.532	5.3/1.6	185
G.L.N.	6.9/1.3	189	124/75	94	0.498	174	93	0.535	6.7/1.1	178
C.F.	6.3/2.8	255	130/82	106	0.416	241	104	0.432	7.0/2.9	271
D.M.	7.2/3.1	245	140/92	115	0.469	258	112	0.434	7.4/3.4	271
Mean	6.6/2.0	192	140/88	110	0.606	196	109	0.580	6.9/2.0	197
SE		± 18		± 5	±0.07	± 17	± 5	±0.06		± 21
Angiotensin										
L.A.	7.4/0.9	221	164/100	121	0.548	216	125	0.579	6.8/1.2	222
O.P.	1.0/0.3	175	136/88	100	0.571	165	100	0.609	1.0/0.4	175
A.L.L.	5.7/2.0	173	130/89	103	0.595	190	105	0.553	5.7/2.0	199
J.G.D.	5.7/1.0	137	106/62	81	0.591	144	80	0.556	5.2/1.3	144
C.F.	6.0/2.6	228	129/82	107	0.469	215	104	0.484	6.0/2.5	223
D.M.	7.4/3.2	258	141/91	116	0.450	256	113	0.441	6.8/3.2	257
Mean	5.5/1.7	198	134/85	105	0.537	198	105	0.540	5.3/1.8	203
SE		± 18		± 6	±0.08	± 16	± 6	±0.08		± 16

* A, control data; B, 10 sec; C, 20 sec; D, 30 sec; and E, 1 min after injection of 2–5 μg of epinephrine (top) or 0.50–1.0 μg of angiotensin (bottom) into the internal carotid artery.

‡ max/min, maximum and minimum values of pulsatile flow.

§ syst/diast, systolic and diastolic blood pressure.

‖ CVR, vascular resistance of the internal carotid artery.

patients the mean arterial P_{CO_2} had a control value of 40.9 mm Hg, SE ± 1.8, and 30 sec after intracarotid injection of norepinephrine the P_{CO_2} was 35.9 mm Hg, SE ± 2.1, representing a significant ($P < 0.01$) decrease.

In Table IV are listed pressure-flow data which were obtained from the internal carotid artery after the intra-arterial injection of 3.0–5.0 μg of epinephrine to seven patients (upper half) and 0.5–1.0 μg of angiotensin to six patients (lower half). Fig. 4 illustrates a recording from one of these subjects during the administration of epinephrine. 10 sec after epinephrine administration there was no significant change in either blood flow or pressure for the group with the exception of patient C.M. who did have an increase in flow in the internal carotid artery which was maintained for 30 sec. All patients were noted to become somewhat agitated and to experience hyperventilation beginning approximately 8 sec after the injection and persisting for about 1 min (see Fig. 4). In six patients 1 min after epinephrine administration the blood flow was attenuated significantly ($P < 0.05$) from a control value of 192 ml/min, SE ± 18, to 168 ml/min, SE ± 22.

10 sec after the intracarotid administration of angiotensin (lower half Table IV) there was no significant change in either mean arterial pressure or blood flow. After this period, the mean arterial blood pressure gradually increased ($P < 0.05$) from a control level of 105 mm Hg, SE ± 6, to 120 mm Hg, SE ± 9, 1 min after the drug was given. Thus, the increase in blood pressure was more gradual than that found after norepinephrine. The blood flow for the group did not change significantly during this period, since the individual responses were somewhat varied. In general, there was a slight increase in blood flow associated with

C*			D*			E*				
Blood pressure			Blood flow	Blood pressure		Blood flow		Blood pressure		
Syst/diast	Mean	CVR	Mean	Mean	CVR	Max/min	Mean	Syst/diast	Mean	CVR
mm Hg		*cm³/min per mm Hg*	*cm³/min*	*mm Hg*	*cm³/min per mm Hg*	*cm³/sec*	*cm³/min*	*mm Hg*		*cm³/min per mm Hg*
162/90	114	0.983	107	114	1.065	8.2/0	99	188/96	127	1.283
152/92	120	0.667	190	138	0.726	8.9/2.0	161	140/80	104	0.646
148/92	120	0.680	186	130	0.698	9.6/1.2	142	130/78	104	0.731
132/82	98	0.529	177	108	0.609	5.9/1.2	121	100/71	85	0.701
128/75	94	0.529	169	100	0.593	7.2/1.1	162	130/72	93	0.575
145/86	116	0.428	228	96	0.421	7.1/3.1	252	124/80	104	0.413
164/104	124	0.458	239	108	0.452	7.4/2.9	240	134/90	110	0.458
147/89	112	0.611	185	113	0.652	7.8/4.5	168	135/81	104	0.687
	± 5	±0.07	± 16	± 6	±0.08		± 22		± 5	±0.11
192/120	144	0.649	207	145	0.700	7.1/1.5	216	200/128	152	0.704
148/96	112	0.640	141	111	0.787	1.7/0.3	169	148/100	116	0.686
140/90	114	0.573	190	107	0.563	5.2/1.8	182	136/98	109	0.599
138/86	88	0.611	148	100	0.676	4.8/1.0	116	110/70	90	0.776
124/70	110	0.493	248	119	0.480	6.7/2.8	262	148/90	120	0.458
140/94	116	0.451	252	120	0.476	7.0/3.4	274	166/105	131	0.478
147/93	114	0.570	198	117	0.614	5.4/1.8	203	151/99	120	0.617
	± 7	±0.03	± 19	± 6	±0.05		± 24		± 9	±0.17

the initial increase in blood pressure. The cerebral vascular resistance for the group increased significantly ($P < 0.05$) from a control value of 0.537 ml/min per mm Hg, SE ± 0.08, to 0.617 ml/min per mm Hg, SE ± 0.17, 1 min after drug administration.

In Table V are listed the pressure-flow effects resulting from the injection into the external carotid artery of 1.0 μg of norepinephrine (6 patients), 1.0 μg of epinephrine (3 patients), and 0.25 μg of angiotensin (1 patient). Fig. 5 illustrates a recording from one patient during the infusion of 1.0 μg of norepinephrine. Within 10 sec after norepinephrine administration into the external carotid artery the blood flow was reduced markedly ($P < 0.01$) from a control value of 128 ml/min, SE ± 10, to 80 ml/min, SE ± 6. The peak-to-nadir value of the flow pulse, 6.5–1.2 ml/sec, at this time actually demonstrates retrograde blood flow occurring at the end of systole (see Fig. 5). During the period of observation the blood pressure did not change significantly from control levels, and the blood flow remained markedly reduced. Similar pressure-flow results were noted in two of the patients who received epinephrine (middle of Table V). In one patient (D.M.) the flow initially decreased at 10 sec and then transiently increased to near control levels at 20 sec and, finally, decreased markedly at 1 min after injection. Angiotensin injected into the external carotid artery in one patient reduced the flow at 10 sec without changing the blood pressure. Flow remained attenuated during the period of observation.

DISCUSSION

The values obtained for mean internal carotid artery blood flow in these 22 patients showed wide

TABLE V

Effects of Injection of Norepinephrine, Epinephrine,

Name	A* Blood flow Max/min‡	A* Blood flow Mean	A* Blood pressure Syst/diast§	A* Blood pressure Mean	A* PVR‖	B* Blood flow Max/min	B* Blood flow Mean	B* Blood pressure Syst/diast	B* Blood pressure Mean	B* PVR
	cm³/sec	*cm³/min*	*mm Hg*		*cm³/min per mm Hg*	*cm³/sec*	*cm³/min*	*mm Hg*		*cm³/min per mm Hg*
Norepinephrine										
C.M.	8.7/0	99	136/80	99	1.000	7.2/0	70	148/88	108	1.543
F.L.	8.1/0.4	114	126/88	101	0.886	6.6/−3.8	68	120/87	98	1.441
I.L.E.	7.0/0.8	120	146/98	114	0.950	6.4/−0.4	90	154/102	119	1.322
T.M.	6.3/0.6	120	164/96	128	1.070	5.7/−0.3	70	164/96	132	1.886
L.B.	9.0/−0.1	161	148/91	108	0.671	7.5/−2.0	82	147/94	112	1.366
D.M.	6.9/0.8	155	156/104	128	0.826	5.7/−0.4	102	154/104	128	1.255
Mean	7.7/0.4	128	146/93	113	0.901	6.5/−1.2	80	148/95	116	1.469
SE		± 10		± 5	±0.45		± 6		± 5	±0.09
Epinephrine										
I.L.E.	8.2/0.4	124	154/100	118	0.952	6.6/−1.2	56	152/100	117	2.089
T.M.	8.2/1.4	152	176/96	128	0.842	6.6/−1.1	61	176/96	126	2.066
D.M.	5.7/0.8	132	148/100	118	0.894	5.3/0.3	103	140/92	116	1.126
Mean	7.4/0.9	136	159/99	121	0.896	6.2/−0.7	73	156/96	120	1.760
SE		± 8		± 3	±0.03		± 15		± 3	±0.40
Angiotensin										
D.M.	6.5/0.5	123	144/95	114	0.927	6.2/0.3	106	140/92	112	1.056

* A, control data; B, 10 sec; C, 20 sec; D, 30 sec; and E, 1 min after injection of 1.0 μg norepinephrine (top), 1.0 μg epinephrine (middle), 0.25 μg angiotensin (bottom) into the external carotid artery.

‡ max/min, maximum and minimum value of blood flow; (−) before minimal flow denotes reverse flow.

§ syst/diast, systolic and diastolic blood pressure.

‖ PVR, resistance of the external carotid artery.

individual variation. These findings are consistent with similar measurements carried out in this laboratory previously (9). In some patients the control values for flow would appear to be low when compared to the total cerebral blood flow measured by the nitrous oxide technique (10). However, blood flow in only one vessel was measured in the present study, and one cannot assume that this value will represent the same per cent of the total cerebral blood flow for all patients. Although these patients had intracranial pathology at the time of study, the cerebrospinal fluid pressure was normal in the majority, and they were alert and had no major neurologic deficit. We feel that the conclusions regarding the effects of these drugs on the cerebral circulation are appropriate to the normal human subject.

The finding that there is a large diastolic flow component in the internal carotid artery is of interest. Thus, a major portion of flow in this vessel is nonpulsatile in nature, a finding suggesting that the brain, like the kidney, is perfused continually. In contrast the external carotid artery has little forward flow during diastole. The values for peak systolic flow in both vessels are quite similar. In general, elevation of the blood pressure tends to reduce the peak-to-nadir amplitude of the internal carotid artery flow pulse and to increase the nonpulsatile component of flow.

Although a single value for control mean blood flow is given for each patient in the tables, obviously the flow fluctuates around this mean value in a manner similar to the variations noted in blood pressure. We have found that in a man resting quietly with normal respiratory excursion the cyclic changes in flow are in the order of ± 7 % of the mean value.

Although internal carotid artery blood flow was not reduced significantly during the intravenous norepinephrine infusion in the 10 patients, the

C*			D*			E*				
						Blood flow		Blood pressure		
Blood flow Mean	Blood pressure Mean	PVR	Blood flow Mean	Blood pressure Mean	PVR	Max/min	Mean	Syst/diast	Mean	PVR
cm³/min	*mm Hg*	*cm³/min per mm Hg*	*cm³/min*	*mm Hg*	*cm³/min per mm Hg*	*cm³/sec*	*cm³/min*	*mm Hg*		*cm³/min per mm Hg*
70	101	1.443	65	101	1.554	8.2/−0.2	67	146/80	102	1.522
73	102	1.397	68	103	1.515	6.6/0.3	82	132/100	111	1.350
60	114	1.900	60	119	1.983	6.0/0	86	148/96	113	1.314
63	130	2.063	63	134	2.127	5.1/0	70	172/100	130	1.857
82	112	1.366	97	115	1.186	8.0/0.5	123	130/90	108	0.878
97	127	1.309	90	128	1.422	5.4/0	90	156/108	127	1.411
74	114	1.580	74	117	1.631	6.6/0.2	86	147/96	115	1.353
± 6	± 5	±0.14	± 7	± 6	±0.16		± 8		± 5	±0.08
47	113	2.404	47	116	2.468	6.4/−1.2	39	162/100	121	3.103
51	128	2.510	61	134	2.197	6.6/−0.6	57	168/96	132	2.316
124	121	0.976	101	112	1.109	5.4/−0.9	65	152/97	116	1.785
74	121	1.963	70	121	1.925	6.1/−0.9	54	161/98	123	2.401
± 25	± 4	±0.16	± 16	± 7	±0.42		± 8		± 5	±0.38
88	116	1.318	84	117	1.393	5.6/−0.3	91	142/96	116	1.275

increase in cerebral vascular resistance indicated that vasoconstriction of the cerebral circulation had taken place. These data are consistent with previously reported studies (1–4). In five patients in whom the arterial Pco_2 was obtained during norepinephrine infusion a slight reduction was noted, and in these patients the blood flow decreased slightly. Other investigators have not found a reduction in arterial Pco_2 during norepinephrine infusion. However, this discrepancy may be related to the use of pooled arterial samples for Pco_2 determinations thereby possibly missing transient changes. In the present study the values for blood flow were measured at the same time as the samples for Pco_2 were drawn. Although the fall in arterial Pco_2 was slight in these five patients this finding may have accounted partially for the reduction in blood flow noted during the norepinephrine administration.

The intravenous administration of angiotensin in eight subjects was also associated with a large increase in cerebral vascular resistance without significantly changing the internal carotid artery blood flow. The arterial Pco_2 was not altered during angiotensin infusion. Thus, hypocarbia cannot have played a role in the regulation of flow during angiotensin infusion.

At no time did we observe a rapid reduction in blood flow after the injection of norepinephrine into the internal carotid artery. At the beginning of the study very low doses of the drug were administered, but the final concentration (4.0–8.0 μg) is extremely large when one considers that it was given into a single arterial vessel having a flow of only approximately 200 ml/min. Since we did not find a reduction in blood flow in the internal carotid artery occurring during the first 20 sec after administration of norepinephrine, it is our contention that norepinephrine does not have a direct effect on these vessels.

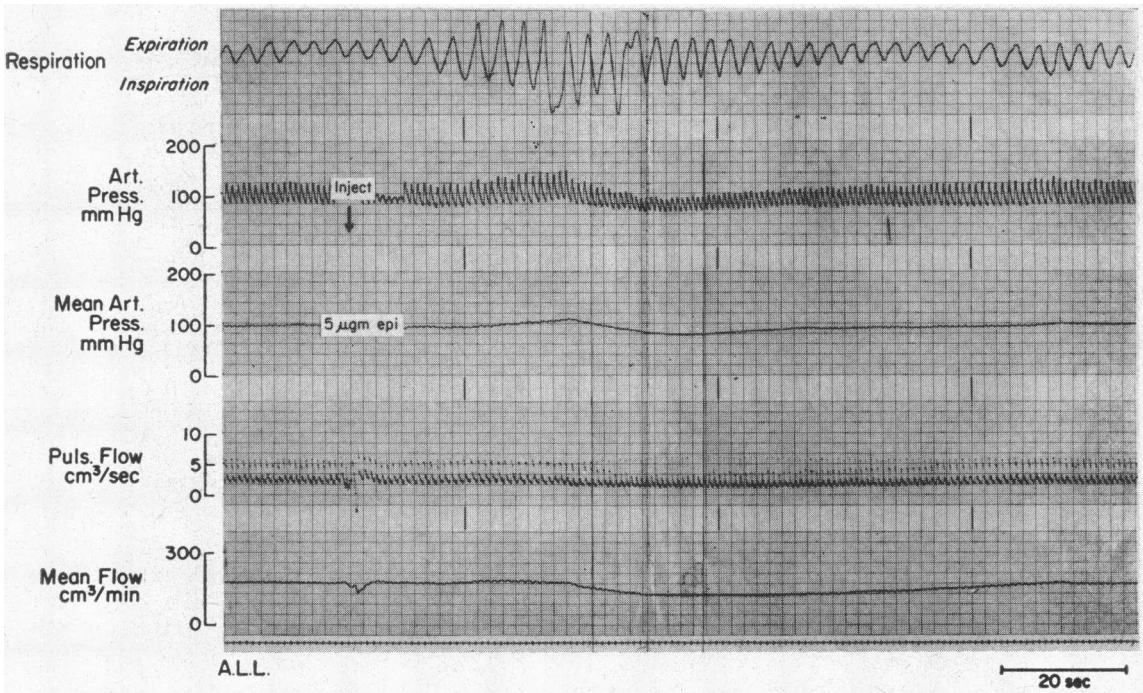

FIGURE 4 Recording of internal carotid artery pressure and flow after the intracarotid injection of 5.0 μg of epinephrine (*epi*). The artifact on the flow tracing is related to the administration of the drug. A pneumotachograph was used to record respiration on the upper channel. 10 sec after injection of the drug both the rate and depth of respiration begin to increase markedly. Note that both pressure and flow are unchanged for 22 sec, and at that time a slight increase in both pressure and flow occurs. Approximately 30 sec after injection both pressure and flow decrease.

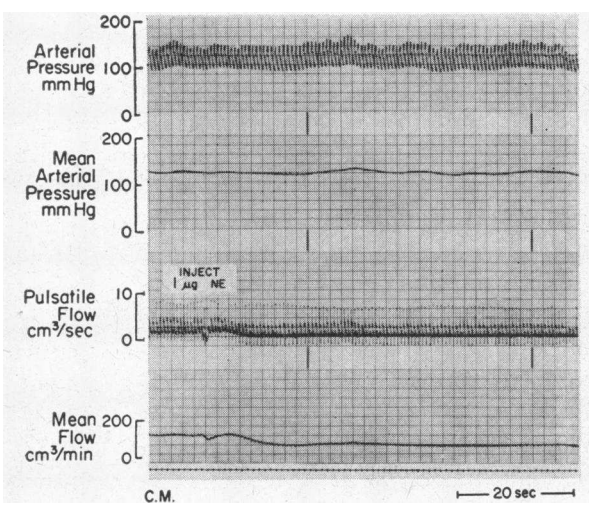

FIGURE 5 Recording of external carotid artery pressure and flow during administration of 1.0 μg of norepinephrine. The blood flow is markedly attenuated 10 sec after injection; however, little change in arterial pressure occurs. Note that the pulsatile flow drops below zero during the latter part of systole indicating that retrograde flow takes place at this time.

The selection of the time after drug administration for abstracting the data in Tables III, IV, and V is admittedly arbitrary, and each patient achieved a peak effect at slightly different times. However, the results among patients were consistent enough so that the selection of data at 10, 20, and 30 sec and 1 min after drug administration seemed reasonable and allowed comparison from patient to patient.

The fact that blood flow increased as the pressure rose after norepinephrine administration suggests that this effect was due to an increase in perfusion pressure. However, the cerebral vascular resistance calculated during this time (20 sec) was significantly increased. In a purely passive system one would expect that the calculated vascular resistance would decrease as perfusion pressure and flow increase (11). However, in order to obtain this finding in a vascular system which can autoregulate flow a very rapid increase in pressure (virtually a square wave) must be applied. Since the blood pressure rose over an 8–12 sec period,

we would not expect a decrease in cerebral vascular resistance. The findings in this study are consistent with the work of Green and Denison (12), who were unable to demonstrate in a canine preparation an effect on the cerebral circulation by either norepinephrine or epinephrine. The lack of response of the cerebral vessels to norepinephrine administration noted in this study would seem to be inconsistent with the recently reported findings of Krog (13) and Meyer, Joshida, and Sakamoto (14), who noted that stimulation of the cervical sympathetic ganglia both in man and in primates was followed by a reduction in internal carotid blood flow. From their studies, one might surmise that the cerebral vasculature would respond to circulating adrenergic drugs. We cannot explain these inconsistencies at the present time.

In seven patients a significant reduction in arterial P_{CO_2} occurred 30 sec after norepinephrine administration into the internal carotid artery. We have noted in these and in previous patients that hyperventilation will begin to reduce cerebral blood flow approximately 10–15 sec after it is initiated. Thus, part of the increase in cerebral vascular resistance noted after the intracarotid administration of norepinephrine clearly is related to the reduction in arterial P_{CO_2}. However, we feel that autoregulation also plays a major role in these results.

Epinephrine injections into the internal carotid artery also were not followed by any immediate changes in blood flow but were attended by marked hyperventilation within 8 sec as noted in Fig. 3. This finding clouds the issue concerning other mechanisms, which might explain the reduction in cerebral blood flow occurring 1 min after administration. However, the drug does not constrict directly the cerebral vasculature. The occurrence of hyperventilation in response to the intracarotid administration of epinephrine is inconsistent with the previously reported finding in four patients of Coles, Duff, Shepherd, and Whelan (15). Our results support the concept that these drugs, in the concentrations used in the present study, have a direct stimulatory effect on respiration.

Angiotensin also produced no immediate change in blood flow when injected directly into the internal carotid artery. The blood pressure rose more gradually than with the norepinephrine injection so that the flow did not appear to increase passively, but remained fairly constant. Again these data are consistent with the hypothesis that angiotensin does not directly constrict the cerebral vessels but that the increase in vascular resistance is due to autoregulation. Arterial P_{CO_2} samples were not obtained after intracarotid injection of angiotensin, but the intravenous administration of this drug was not attended by a change in arterial P_{CO_2}, and it is doubtful whether or not hypocarbia played a role in the increase in cerebral vascular resistance which occurred after the administration of angiotensin.

The almost immediate marked reduction (within 10 sec) in blood flow after injection of both norepinephrine and epinephrine into the external carotid artery clearly demonstrates a direct effect of these drugs on the vascular bed supplied by this vessel. The decrease in blood flow was not followed by a change in systemic arterial pressure. In the one patient studied angiotensin also reduced the external carotid artery flow almost immediately, but required somewhat longer than the other drugs to achieve its full effect.

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