THE EFFECTS OF *l*-EPINEPHRINE AND *l*-NOR-EPINEPHRINE UPON CEREBRAL CIRCULATION AND METABOLISM IN MAN [1]

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Studies comparing the effects of epinephrine and nor-epinephrine, the two sympathomimetic amines which occur naturally in the mammalian body, show that these two closely related substances differ in many of their pharmacodynamic properties. The metabolic rate in man has been shown to increase after epinephrine (1, 2), whereas there is no significant change produced by nor-epinephrine (2). Systemic administration of epinephrine to man has been shown to result in a decrease in total peripheral resistance (1, 3), indicating that vasodilatation has occurred in many portions of the body; in contrast, nor-epinephrine appears to be predominantly vasoconstrictor in its action, for total peripheral resistance is increased (3). These differences may be manifestations of the specific functions which these substances perform in the body; von Euler (4) believes that nor-epinephrine is the sympathetic mediator for general purposes, while epinephrine acts as an adjuvant for more special functions, especially in regard to metabolic actions.

In view of the importance of epinephrine and nor-epinephrine in physiological processes, their occurrence in pheochromocytomas, their use as therapeutic agents, and the possible relation of nor-epinephrine to essential hypertension (3), information regarding their effect on cerebral blood flow and cerebral metabolism is desirable. A preliminary report by Sensenbach, Madison, and Ochs (5) indicates that nor-epinephrine is a powerful cerebral vasoconstrictor. The animal studies upon epinephrine have yielded conflicting results (6–8). Qualitative measurements of cerebral blood flow in man by means of a thermoelectric flow recorder led Gibbs, Gibbs, and Lenox (9) to report an increase in cerebral blood flow following the intravenous injection of adrenalin, probably secondary to the increase in blood pressure.

The present study was undertaken to provide quantitative measurements of cerebral blood flow, vascular resistance and oxygen consumption in man during the intravenous infusion of synthetic *l*-epinephrine or *l*-nor-epinephrine.

METHODS

Subjects varied in age from 19 to 50 years. They were either volunteers or hospital patients with apparently normal cardiovascular systems. Two subjects (T. I. and T. C.) who received epinephrine served also as subjects for the nor-epinephrine study at a later date. Cerebral blood flow (CBF) was determined by the nitrous oxide method (10). Blood pressure and pulse rate were obtained by means of a Lilly capacitance electromanometer (11, 12) attached to the needle in the femoral artery, and recorded continuously by means of a Brush direct-inking oscillograph except when arterial blood samples were being drawn. Mean arterial blood pressure (MABP) was obtained by either a damped mercury manometer or by electrical integration of the pressure pulse curves from the Lilly manometer. Cerebral metabolic rate in terms of cerebral oxygen consumption (CMR_{O_2}) and cerebrovascular resistance (CVR) were calculated as previously described (10). Blood gas analyses were made by the manometric technique of Van Slyke and Neill (13). Measurements of blood pH were made anaerobically at room temperature by means of a glass electrode and a Cambridge potentiometer and corrected to 37° C. by the factors of Rosenthal (14). Values for blood carbon dioxide tension were calculated by means of the nomograms of Peters and Van Slyke (13). Total hemoglobin concentration of arterial blood was determined by a modification of the method of Evelyn and Malloy (15).

Before the control measurements, an intravenous infusion of physiological saline was begun. Subsequently the infusion was changed to one containing either synthetic

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l-epinephrine or *l*-nor-epinephrine,[2] 4 or 8 micrograms of drug per cc. of saline. The rate of drug infusion was adjusted until the desired pressor response was acquired and maintained or until undesired side effects occurred. When a steady state had been attained, a second set of blood flow determinations was made. The total quantity of drug and the rate at which it was administered are indicated for each subject in Table I.

RESULTS

The data are presented in Tables I, II, and III. Values for systolic and diastolic blood pressure and pulse rate were obtained for each blood flow determination by averaging measurements secured at five intervals on the continuous record. A maximum and minimum of blood pressure were selected at each of these intervals to take into account the effects of the respiratory cycle on blood pressure.

Effects of nor-epinephrine

Subjective sensations, except for a feeling that the heart was beating more forcefully, were notably absent during the infusions of nor-epinephrine. The skin and mucous membranes became pale. The pressor effect was more marked than with epinephrine and was produced with a much lower dose. Slowing of the pulse rate accompanied the rise in blood pressure in every case.

The hemoglobin concentration of arterial blood was increased significantly; this might be a result of fluid dislocation from the vascular bed or of emptying of red cell reservoirs. Arterial carbon dioxide tension was decreased, probably as a result of hyperventilation although this was not evident by inspection. These alterations in carbon

[2] *l*-Epinephrine as "Suprarenin" and *l*-nor-epinephrine as "Levophen" or "Levophed" were provided through the courtesy of Winthrop-Stearns.

TABLE I

Effects of l-nor-epinephrine and l-epinephrine on blood pressure and pulse rate

Subject	Age	Sex	Dose Total μg.	Dose Rate μg./min.	Syst. & Diast. Blood Pressure C+	Syst. & Diast. Blood Pressure E‡	Pulse Rate C	Pulse Rate E
				l-nor-epinephrine				
(1) H. A.	39	M	770	22	128/82	160/81	90	59
(2) E. H.	50	F	312	10	141/77	185/84	112	79
(3) A. H.	48	F	464	16	138/80	185/85	88	66
(4) L. W.	38	F	576	16	142/81	184/86	80	53
(5) M. S.	36	M	760	25	126/73	165/77	65	52
(6) T. C.	24	M	500	17	106/68	134/81	84	63
(7) T. I.	24	M	840	28	110/72	150/89	65	51
(8) L. H. I.	19	M	200	6	116/61	173/89	65	52
(9) N. Y.	22	M	300	9	125/78	172/97	74	61
Mean	33.3		524.7	16.6	126/75	168/85	80.3	59.6
Stand. error	±3.8						±5.2	±3.0
p*							<0.001	
				l-epinephrine				
(10) A. M.	34	F	1732	73	135/81	145/79	100	116
(11) T. I.	24	M	800	47	113/73	159/91	81	91
(12) T. C.	24	M	664	33	112/65	175/84	75	72
(13) J. F.	25	M	976	34	109/79	134/76	71	83
(14) L. H.	25	M	800	30	103/65	126/74	54	78
(15) A. Mc.	22	M	480	19	117/67	132/63	70	72
(16) D. F.	19	M	480	22	131/72	173/75	97	115
Mean	24.7		847.4	36.9	117/72	149/77	78.3	89.6
Stand. error	±1.7						±6.1	±7.1
p*							<0.02	

* Determined from the t value obtained by dividing the mean of the individual changes by its standard error.
\+ Control period - Saline infusion.
‡ Experimental period - Drug infusion.

TABLE II

Effect of l-nor-epinephrine and l-epinephrine on blood constituents

	Subject	Hemoglobin Concentration Gms. %		O_2 Content vol. %				CO_2 Content vol. %				Blood pH				CO_2 Tension mm. Hg			
				Arterial		Int. Jugular		Arterial		Int. Jugular		Arterial		Int. Jugular		Arterial		Int. Jugular	
		C+	E‡	C	E	C	E	C	E	C	E	C	E	C	E	C	E	C	E
l-Nor-Epinephrine	(1) H. A.	15.17	15.51	19.75	19.25	12.08	10.79	49.79	44.22	56.75	52.66	7.41	7.42	7.37	7.37	42	38	52	48
	(2) E. H.	10.48	10.39	13.89	13.80	8.47	8.91	53.08	51.04	56.97	56.02	7.43	7.42	7.38	7.37	40	40	48	48
	(3) A. H.	10.07	10.07	13.47	13.72	7.00	7.37	51.17	48.60	56.91	55.17	7.42	7.43	7.36	7.36	40	37	49	48
	(4) L. W.	10.72	10.56	14.37	14.61	7.89	7.48	56.23	51.92	61.75	59.05	7.41	7.43	7.37	7.37	44	40	53	50
	(5) M. S.	14.23	15.07	20.20	19.18	13.08	12.99	49.19	53.28	56.83	59.73	7.38	7.38	7.32	7.36	44	48	57	56
	(6) T. C.	13.56	13.94	16.23	16.66	12.53	12.39	48.87	45.34	52.68	49.83	7.38	7.38	7.37	7.36	43	40	48	46
	(7) T. I.	13.64	14.64	17.27	18.88	11.91	11.62	48.23	42.75	52.95	49.64	7.36	7.34	7.34	7.32	44	42	50	50
	(8) L. H. I.	16.16	16.73	19.88	20.96	13.37	13.44	48.37	45.35	54.29	52.07	7.35	7.38	7.30	7.30	46	42	57	55
	(9) N. Y.	17.16	17.64	21.86	22.51	15.75	16.53	47.53	42.93	53.31	49.19	7.39	7.41	7.35	7.37	43	38	52	46
	Mean	13.47	13.84	17.44	17.73	11.34	11.28	50.27	47.27	55.83	53.71	7.39	7.40	7.35	7.35	42.9	40.5	51.8	49.7
	Stand. error	±0.85	±0.95	±1.04	±1.06	±0.87	±1.00	±0.93	±1.34	±0.96	±1.33	±.01	±0.01	±0.01	±0.01	±0.7	±1.1	±1.2	±1.2
	p*	< 0.05		> 0.6		> 0.7		< 0.02		< 0.02		> 0.2		> 0.7		< 0.05		< 0.02	
l-Epinephrine	(10) A. M.	12.72	12.35	16.91	16.61	10.07	9.82	47.85	39.01	57.42	45.76	7.35	7.34	7.33	7.32	44	36	54	44
	(11) T. I.	13.10	13.86	18.92	20.51	13.32	14.25	48.12	44.75	53.27	50.88	7.44	7.45	7.33	7.34	38	34	52	49
	(12) T. C.	12.18	13.01	17.12	18.08	11.15	13.48	46.55	44.86	51.58	49.92	7.45	7.41	7.39	7.37	35	37	44	45
	(13) J. F.	13.48	13.86	19.38	20.12	11.93	11.90	51.23	44.55	58.02	52.40	7.39	7.47	7.37	7.33	44	33	53	51
	(14) L. H.	15.15	15.37	20.53	21.74	11.24	11.93	45.09	40.67	53.15	49.72	7.37	7.36	7.30	7.31	41	38	55	50
	(15) A. Mc.	16.90	16.90	21.16	22.45	15.80	16.37	43.42	41.57	48.92	47.27	7.33	7.33	7.28	7.24	43	42	57	57
	(16) D. F.	15.08	15.38	19.56	20.23	11.67	12.07	43.90	41.61	51.19	49.70	7.34	7.32	7.28	7.30	42	42	56	52
	Mean	14.09	14.39	19.08	19.97	12.17	12.83	46.59	42.43	53.36	49.38	7.38	7.38	7.33	7.32	41.0	37.4	53.0	49.7
	Stand. error	±0.63	±0.59	±0.60	±0.77	±0.71	±0.79	±1.04	±0.87	±1.25	±0.84	±0.02	±0.02	±0.02	±0.02	±1.3	±1.3	±1.6	±1.7
	p*	> 0.1		< 0.01		> 0.05		< 0.01		< 0.05		> 0.9		> 0.3		> 0.05		> 0.05	

* Determined from the t value obtained by dividing the mean of the individual changes by its standard error.

\+ Control period - Saline infusion.

‡ Experimental - Drug infusion.

TABLE III

Effects of l-nor-epinephrine and l-epinephrine on cerebral circulation and oxygen consumption

	Subject	MABP mm. Hg.		CBF cc/100gm/min.		CVR mm. Hg / cc/100gm/min.		(A-V)O_2 vol. %		CMR O_2 cc/100gm/min.		RQ (cerebral)	
		C+	E‡	C	E	C	E	C	E	C	E	C	E
l-Nor-Epinephrine	(1) H. A.	92	115	45	40	2.0	2.9	7.67	8.46	3.5	3.4	0.91	1.00
	(2) E. H.	100	123	61	49	1.6	2.5	5.42	4.89	3.3	2.4	0.72	1.02
	(3) A. H.	86	112	56	52	1.5	2.2	6.47	6.35	3.6	3.3	0.89	1.03
	(4) L. W.	100	130	60	56	1.7	2.3	6.48	7.13	3.9	4.0	0.85	1.01
	(5) M. S.	95	118	70	72	1.4	1.6	7.15	6.19	5.0	4.5	1.07	1.04
	(6) T. C.	84	102	80	80	1.1	1.3	3.70	4.27	3.0	3.4	1.03	1.05
	(7) T. I.	86	106	71	59	1.2	1.8	5.36	7.28	3.8	4.3	0.88	0.95
	(8) L. H. I.	83	124	69	52	1.2	2.4	6.51	7.52	4.5	3.9	0.91	0.90
	(9) N. Y.	93	123	41	40	2.3	3.1	6.11	6.01	2.5	2.4	0.95	1.04
	Mean	91.0	117.0	61.4	55.6	1.56	2.23	6.10	6.46	3.68	3.51	0.91	1.00
	Stand. error	±2.2	±3.0	±4.2	±4.5	±0.13	±0.20	±0.39	±0.44	±0.25	±0.25	±0.03	±0.02
	p*	<0.001		<0.05		<0.001		>0.2		>0.3		<0.05	
l-Epinephrine	(10) A. M.	103	109	47	49	2.2	2.2	6.84	6.79	3.2	3.3	1.00	0.99
	(11) T. I.	90	133	60	85	1.5	1.6	5.60	6.26	3.4	5.3	0.90	0.98
	(12) T. C.	88	128	49	68	1.8	1.9	5.97	4.60	2.9	3.1	0.84	1.10
	(13) J. F.	107	120	56	65	1.9	1.8	7.45	8.22	4.2	5.3	0.91	0.96
	(14) L. H.	78	90	35	44	2.2	2.0	9.29	9.81	3.2	4.0	0.97	0.92
	(15) A. Mc.	85	86	50	59	1.7	1.5	5.36	6.08	2.7	3.6	1.03	0.94
	(16) D. F.	85	95	54	55	1.6	1.7	7.89	8.16	4.3	4.5	0.92	0.98
	Mean	90.9	108.7	50.1	60.7	1.84	1.81	6.91	7.13	3.41	4.16	0.94	0.98
	Stand. error	±3.9	±7.1	±3.0	±5.2	±0.10	±0.09	±0.53	±0.65	±0.14	±0.34	±0.02	±0.02
	p*	<0.05		<0.02		>0.6		>0.4		<0.05		>0.3	

* Determined from the t value obtained by dividing the mean of the individual changes by its standard error.
\+ Control period - Saline infusion.
‡ Experimental period - Drug infusion.

dioxide tension were not of sufficient magnitude to have a significant effect on cerebrovascular dynamics (16).

Despite the marked rise in mean arterial blood pressure from 91 to 117 mm. Hg, cerebral blood flow decreased from 61 to 56 cc./100 gm./min. ($p < 0.05$), apparently because of an increase in cerebrovascular resistance from 1.6 to 2.2 resistance units ($p < 0.001$). An increase in resistance occurred in each of the individuals studied. There was no significant alteration in cerebral metabolism.

Effects of epinephrine

The administration of epinephrine was often accompanied by palpitation, tremor of the hands, or a sense of excitement or apprehension. Cutaneous and mucosal pallor was usually marked. The pulse rate, although significantly increased during the blood flow determinations, accelerated more at the beginning and immediately after the termination of the infusions when the blood pressure elevation was less prominent.

Mean arterial blood pressure increased from 91 to 109 mm. Hg, and cerebral blood flow rose from a mean of 50 to 61 cc./100 gm./min. ($p < 0.02$). This increase in cerebral blood flow is accounted for by the lack of significant change in cerebrovascular resistance during the period of hypertension. Of particular interest was the augmentation of cerebral oxygen consumption from 3.4 to 4.2 cc. O_2/100 gm./min. ($p < 0.05$).

DISCUSSION

These studies show that *l*-epinephrine and *l*-nor-epinephrine act differently with respect to both cerebral circulation and cerebral metabolism. The significant increase in cerebral oxygen consumption accompanying epinephrine infusions is of particular interest. Such observations indicate that the brain shares in the metabolic augmentation which is produced in the body as a whole by epinephrine. One subject (No. 11), in whom marked sensations of apprehension followed administration of the drug, had an increase in cerebral oxygen consumption from 3.4 to 5.3 cc. O_2/100 gm./min. The fact that a state of anxiety or apprehension may be associated with a greatly augmented cerebral oxygen consumption has been

pointed out by Kety (17), who reported a value of 5.0 cc. O_2/100 gm./min. under such circumstances when previous resting values were 3.4, 3.9, 3.2, and 4.2 cc. O_2/100 gm./min. These observations lead to speculation as to whether the increased cerebral oxygen consumption during apprehension is due to the liberation of endogenous epinephrine. Nor-epinephrine, which does not appear to produce such psychic effects, is not associated with such increases in cerebral oxygen consumption. These findings controvert the suggestion made by Scheinberg (18) that cerebral metabolism normally functions at nearly its maximal rate and that "no effective means of increasing cerebral metabolism in man have been found."

It should be pointed out that a rise in mean arterial blood pressure does not necessarily result in an increase in cerebral blood flow. Despite a marked rise in blood pressure caused by nor-epinephrine, there was a decrease in blood flow because of the simultaneous increase in cerebrovascular resistance. Since an important aspect of cerebral homeostasis consists in an adjustment of circulation to local metabolic needs (17), it is providential that epinephrine, which increases cerebral metabolism, does not simultaneously increase cerebrovascular resistance. It is possible that epinephrine might exert a vasoconstricting action on the cerebral vessels which is balanced by a vasodilator effect resulting from an accumulation of substances produced by the increased cerebral metabolism. However, the higher oxygen content and lower carbon dioxide tension existing in the internal jugular blood during the drug infusion indicate that cerebral blood flow is more than adequate, which prevents metabolic products from accumulating. The unchanged cerebrovascular resistance following the administration of epinephrine seems to indicate that if there were vasoconstriction from this drug, it was not sufficient to do more than overcome any passive dilatation resulting from increased systemic blood pressure.

Experiments upon anesthetized animals have indicated that epinephrine can cause cerebral vasoconstriction (6, 7). Our results may differ because of species difference, the state of consciousness, composition of the drug, or mode of administration. Both of the drugs used in this study were synthetic preparations, believed to be free from contamination by each other. On the other hand, chemical analysis of U.S.P. grade epinephrine has revealed that the nor-epinephrine content of epinephrine from animal sources may be as high as 18.5% (19); such contaminated epinephrine may have been used in earlier studies. Although the quantities of nor-epinephrine contained in natural epinephrine do not appear to alter significantly the hemodynamic actions of the latter drug (20), one cannot be assured such is the case in relation to cerebrovascular actions.

In this study the drug was given by continuous intravenous infusion. The concentration reaching the cerebral vessels under such circumstances is undoubtedly much lower than was attained in those animal experiments in which the drug was applied topically (7) or injected into the carotid artery (6) and in which cerebral vasconstriction was reported.

The question may be raised whether epinephrine could cause cerebral vasoconstriction if given in sufficient quantity to produce a pressor effect equivalent to that elicited by nor-epinephrine. Side effects such as arrhythmias, palpitation, or apprehension placed limitations on the amount of epinephrine which could be used in this study. However, in two individuals (Nos. 11 and 12) to whom sufficient epinephrine was given to produce pressor effects equal to or greater than those obtained in any of the subjects receiving nor-epinephrine, there was no significant rise in cerebrovascular resistance. We conclude that epinephrine, given systemically and within the limits of physiological tolerance, does not produce cerebral vasoconstriction in man.

Our data for nor-epinephrine are essentially in agreement with those of Sensenbach, Madison, and Ochs (5). The primary difference is a lack of a statistically significant decrease in cerebral blood flow in their series. This might be attributed to the variability of absorption of the drug from an intramuscular depot. In our series, a continuous intravenous infusion associated with continuous blood pressure recording allowed us to achieve a constant pressor effect.

Goldenberg and his co-workers (3) have suggested that a disturbed balance between nor-epinephrine and epinephrine might be an etiologic factor in essential hypertension. Evidence supporting this view is the fact that essential hypertension and infusions of nor-epinephrine are both

associated with increases in total peripheral resistance and blood pressure without any increase in cardiac output. Evidence against this view consists of the finding that nor-epinephrine decreases forearm blood flow and produces facial pallor and bradycardia, manifestations which are not characteristic of essential hypertension (21). Our data show another similarity between essential hypertension (22) and the state produced by infusions of nor-epinephrine, namely that both are associated with an increase in cerebrovascular resistance. Although cerebral blood flow was significantly decreased by nor-epinephrine, it still remained within normal limits, as is the case with essential hypertension (22).

Nor-epinephrine has been proposed as a useful and potent pressor drug (23), and is now available for clinical use. If the vascular beds of other vital organs such as the heart, liver, and kidneys respond with vasoconstriction as do the vessels of the brain, situations could occur where therapy with this and similarly acting drugs might be unsatisfactory or actually harmful. For example, if sympathetically induced vasoconstriction through most of the body was already maximal during an episode of hypotension, nor-epinephrine, which is unquestionably a cerebral vasoconstrictor, might increase cerebrovascular resistance out of proportion to the increase in perfusion pressure so that cerebral blood flow might actually decrease. For this reason, nor-epinephrine and related drugs should be evaluated not only by measurement of their pressor effects but also by measurement of blood flow through vital organs in normotensive and hypotensive states.

SUMMARY

1. The effects of continuous intravenous infusions of synthetic *l*-epinephrine and *l*-nor-epinephrine upon arterial blood pressure and pulse rate, arterial and internal jugular blood gases, and cerebral blood flow, oxygen consumption, and vascular resistance have been studied in man.

2. Epinephrine produced an increase in mean arterial blood pressure and cerebral blood flow without a significant change in cerebrovascular resistance. In addition there was a significant increase in cerebral oxygen consumption.

3. Nor-epinephrine, a more potent pressor drug, produced a marked increase in cerebrovascular resistance, and a decrease in cerebral blood flow despite a substantial increase in mean arterial blood pressure. Cerebral oxygen consumption was not significantly altered. The significance of these findings in relation to the clinical use of nor-epinephrine is discussed.

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