

Ill-Effects of Carotid Artery Ligation: Experimental Study on Influence of Age

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OBSTRUCTION of the internal or common carotid artery (hereinafter referred to as carotid) may have serious sequelae or a fatal outcome. Surgical ligation of the carotid artery has been performed on humans for treatment of cerebral aneurysms, hemorrhage, tumors and other pathologic states.¹⁸ Catlin⁶ and Lilienthal¹⁷ each reported a patient who survived bilateral carotid artery ligation. Another instance of simultaneous bilateral carotid artery occlusion, however, proved fatal.¹⁹ Slowly progressive occlusive disease of both carotid arteries is less deleterious and more common than sudden occlusion. Fields *et al.*,¹⁰ reported a series of 16 such patients, six of whom had no brain damage. On the other hand, unilateral occlusion often causes severe brain damage and death in some instances.²

The principal complication of carotid artery ligation or occlusion is ischemic brain damage. Such a complication is influenced by many factors, one of which is age.¹⁸ The statement has been made that bilateral carotid ligation could be harmless particularly in the younger age group.¹³ Dandy⁸ states that ligation in the aged is unsafe and cerebral complications increase with the patient's age. Reid²² concluded that hard sclerotic vessels in the aged would not collapse, therefore, the older the patients, the less likelihood of cerebral dis-

turbances. In Moore's¹⁸ study the ages of patients varied from 12 to 80. Moore and co-workers believe that there is a slightly but not significantly higher mortality and morbidity rate in the older group.

The subject also has been of interest to experimental investigators. Bunce⁵ working with dogs concluded that permanent interruption of the carotid and vertebral arterial supply is not incompatible with life and that collateral circulation to the head is adequate to maintain life for at least four months. Boyd and Connolly⁴ reported severe permanent brain damage or immediate death in dogs following transitory total cerebral ischemia. Chang and Liu⁷ reported 100% mortality in the first 24 hours after simultaneous bilateral common carotid ligations in rats. Krieger¹⁵ also stated that rats do not survive bilateral carotid ligations. On the other hand, Jilek¹⁴ reported 40% mortality in adult rats, while Levine and Klein¹⁶ reported from 8% to 56% survival in rats depending on the environmental conditions, especially temperature. The effects of cerebral ischemia in various strains of rats also has been studied²⁰ indicating zero to 100% mortality according to the strain. Such variability in experimental results might be due to differences in surgical technic, environmental conditions, diet, strain, sex, and finally, age of the animals. The present experiments were designed to study the mortality and morbidity of carotid artery liga-

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tion in rats as influenced by age. Results indicate that rats, during the neonatal period are relatively resistant to brain ischemia. When 10 days (20 Gm.) or older, however, the animals are extremely sensitive to obstruction of carotid artery blood flow. This sensitivity continues until the rats become sexually mature (50-60 days, or approximately 100 Gm.),¹ at which time, relative resistance to brain ischemia and its ill-effects is regained. The presence of arteriosclerosis in older rats did not influence the outcome of carotid artery ligation when compared with young, sexually mature animals.

Materials and Methods

First-pregnancy rats of three different strains, Sprague-Dawley (Holzman Farms), Wistar (Hemlock-Hollow) and Fisher 344 (Microbiological Associates) were purchased and maintained on Purina labora-

tory chow and tap water. The reason for selecting three different strains was to eliminate the effect of cerebral ischemia in various strains of rats.²⁰ The pregnant rats were received in our laboratory one week prior to delivery to insure environmental adjustment. Animals were housed in single plastic cages and allowed to construct nests of shredded newspaper. Adult female and retired breeders of the same strains and sources but of different weights (ages) were also included in the experiments as indicated in the tables. These animals were housed four or five together in suspended metal cages. The number of animals in various age groups are indicated in the tables. The initial body weight (IBW) signifies the weight of the animal on the day of carotid artery ligation. The animal quarters and operating room were air-conditioned and the temperature was kept at about 70° F. at all times. Ether was used

TABLE 1. *Influence of Age on Carotid Artery Ligation in Sprague-Dawley Rats*

Groups	IBW	Mortality*	Lesions		Mortality & Morbidity	
			Gross	Micro	No.	%
A	10-20	2/26	1/24	1/23	4/26	14
B	20-30	17/32	1/15	1/14	19/32	59
C	30-40	10/28	15/18	0/3	25/28	89
D	40-50	15/25	4/10	2/6	21/25	84
E	50-60	14/24	3/10	0/7	17/24	72
F	70-80	3/20	6/17	4/11	13/20	65
G	90-100	5/20	1/15	1/14	7/20	35
H	120-150	2/18	0/16	2/16	4/18	23
I	150-400	1/12	0/11	0/11	1/12	9

* The first 24 hours after carotid artery ligation.

TABLE 2. *Influence of Age on Carotid Artery Ligation in Wistar Rats*

Groups	IBW	Mortality*	Lesions		Mortality & Morbidity	
			Gross	Micro	No.	%
A	10-20	4/23	2/19	2/17	8/23	35
B	30-40	16/24	7/8	0/1	23/24	96
C	50-60	29/36	2/7	1/5	32/36	88
D	70-80	36/41	0/5	0/5	36/41	87
E	90-100	30/41	0/11	4/11	34/41	82
F	120/150	8/30	0/22	6/22	14/30	47

* First 24 hours after ligation.

TABLE 3. *Distribution and Intensity of the Ischemic Brain Lesions in Various Age Groups of Rats (Wistar and Sprague-Dawley) Following Bilateral Carotid Artery Ligation*

Groups	IBW	Number of Rats			Lesions*				Mor- tality	Mor- bidity among sur- vivors
		Total	Sur- viv- ors	With Lesion	Cortex	Cor- pus Stri- atum	Hip- po- cam- pus	Others		
A	10-20	49	43	6	12	15	—	—	12%	13%
B	20-100	291	116	54	149	68	18	—	59%	46%
C	120-400	60	49	8	5	2	2	1**	18%	16%

* Lesions were graded as minimal (1+), moderate (2+), and severe (3+).

** Corpus collosum.

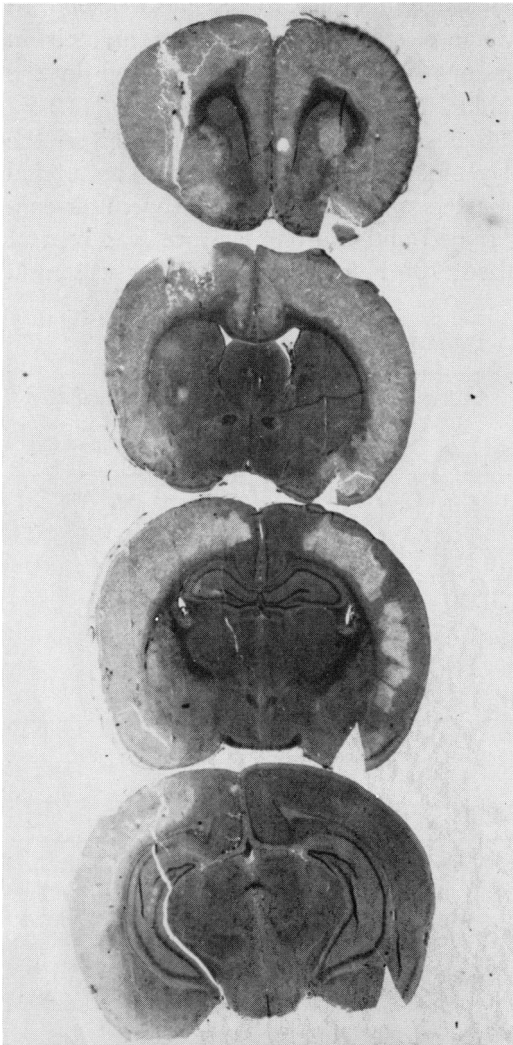
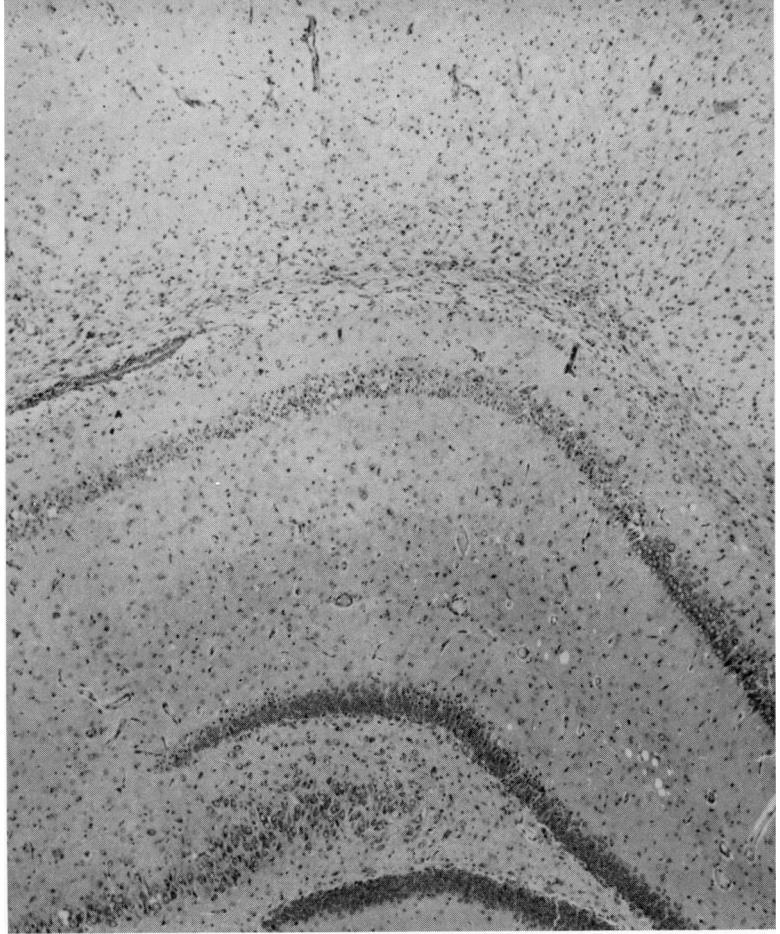


FIG. 1. Massive infarction of the brain involving both cerebral hemispheres. (Hematoxylin and Eosin $\times 10$.)

for anesthesia. A small central incision was made above the sternal notch, the carotid arteries were dissected and cut between two ligations. The left carotid was ligated first and the right carotid immediately thereafter. The skin was sutured with white silk and the wounds were washed with distilled water. Animals which died during or soon after operation most probably due to anesthesia were excluded from all experiments and analyses. The neonates and young animals were kept separate from their mothers for two hours to make sure that they were awake. All animals, following the operation, were observed for several hours. Convulsions occurred frequently among the young animals. These rats were marked, and it was noted that all died several to 24 hours after the operation. Except for very few animals which died two or three days after operation, early death occurred within the first 24 hours, as indicated in the tables. Survivors were sacrificed four to five days after bilateral carotid artery ligation. Calcification of the aorta and carotid arteries was noted at the time of autopsy in retired breeder rats.²³ Brains were fixed in Bouin's solution for 48 hours, cut in coronal slices and processed *in toto* for paraffin embedding. The sections were stained by hematoxylin-eosin and Luxal fast blue for examination of the general structures and myelin, respectively.

In histologic examination (Tables 1 and

FIG. 2. Complete destruction of the cortex is noted above with partial involvement of the hippocampus. (Hematoxyline and Eosin $\times 40$.)



2) the ischemic infarctions were divided into two groups, gross and microscopic lesions. The gross lesions were seen with unaided eye (Figs. 1, 2) in contrast to microscopic lesions which were noted only by the aid of a light microscope (Fig. 3). In preparation of Table 3, animals of the first two strains (Tables 1 and 2) were arbitrarily divided into three groups: neonates (10 to 20 Gm.), young (20 to 100 Gm.), and adults (120 Gm.+). The ischemic lesions of the various areas of the cerebral hemispheres were noted separately and graded arbitrarily as minimal (1+), moderate (2+), and severe (3+). Therefore, the sums noted in Table 3 represent the frequency as well as the intensity of the

brain lesions in surviving rats of each age group.

Results

The mortality rate following simultaneous bilateral carotid ligation is significantly higher in young rats varying in weight from 20 to 100 Gm. in both Sprague-Dawley and Wistar rats (Tables 1 and 2). Neonatal and adult rats including the arteriosclerotic retired breeders appear to be much more resistant to brain ischemia. Although the percentages vary slightly when the Wistar strain is compared with Sprague-Dawley group, the pattern of the change relative to age is almost the same in both strains. Animals of the Fisher 344

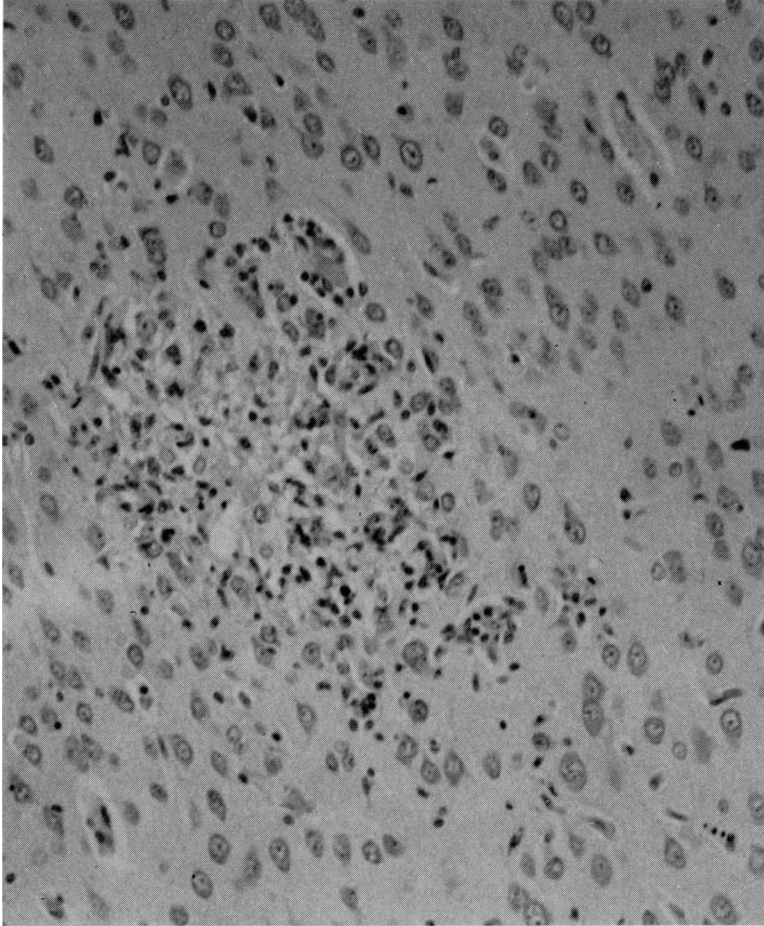


FIG. 3. A microscopic ischemic focus of the cortex is noted surrounded by normal tissue. (Hematoxyline and Eosin $\times 200$.)

strain of all ages died within the first 24 hours after bilateral carotid artery ligation. Such a response was expected.²⁰ Early death was caused by massive bilateral, acute cerebral infarction. Ischemic lesions in survivors varied from large areas of necrosis (Fig. 1) to minute focal infarcts (Fig. 2) or degeneration of a few neurons. The highest percentage of lesions, gross and microscopic, was found among *young* survivors (Table 3). Cortex was the most involved part of the brain, followed by corpus striatum. Other areas involved were, hippocampus in a few animals and corpus collosum in one (Table 3). The frequency and severity of the lesions were almost equal in both sides of the brain.

Discussion

These experiments demonstrate a significant difference in the incidence of cerebral ischemia following carotid artery ligation among various age groups in rats. During the neonatal period (1–10 days, or 8–20 Gm.) the animals are relatively resistant to ischemia. However, once 10 days (20 Gm.) or older, they become extremely sensitive to ischemia and remain so until they are sexually mature (about 100 Gm. or more).¹ The rate of morbidity and mortality is significantly higher during this period of *youth*. Adult animals including those which are old and have arteriosclerosis show more or less the same resistance as do neonates. These results are in agree-

ment with physiologic disturbances described by Jilek¹⁴ in young rats following carotid artery ligation.

The true incidence of carotid artery ligation and occlusion in children is difficult to determine. Very high mortality and morbidity rates, however, are obvious among reported cases.^{3, 9, 21} Wisoff²⁴ reported 10 deaths and 12 permanent neurological disturbances among 29 instances of unilateral carotid artery occlusion in children.

The most probable explanation for this hypersensitivity of the central nervous system to ischemia in children and young animals, is the brain blood flow. Gordon indicates that the average value for cerebral blood flow in young adults is 54 ml./100 Gm. brain weight per minute. This value, however, in children before sexual maturity is 105 ml./100 Gm./min.^{11, 12} Should we consider this greater blood flow "a physiologic necessity" in the brain of children and young animals, it immediately becomes apparent why grave effects of carotid artery ligation or obstruction should be significantly higher in young persons and animals before they are sexually mature.

For the purpose of statistical analysis, animals were classified as follows:

1. Neonates (10-20 Gm.).
2. Young animals (20-100 Gm.), before sexual maturity.
3. Adult (120 Gm.+), or sexually mature rats.

When groups one and three were compared with group two, the differences were highly significant ($p < 0.01$). Comparison of group one with group three, however, revealed no significant difference. Figures used in the statistical tests were mortality and morbidity for Sprague-Dawley strain (Table 1) and Wistar (Table 2). The same significant variance was found ($p < 0.01$) when animals of two strains were combined (Table 3) and compared in regard to ages (groups 1 and 3 to 2). Differences

between groups one and three as against two were compared in Sprague-Dawley strain versus Wistar. No significant variance was noted.

Summary

The ill-effects of carotid artery ligation or occlusion varies somewhat among humans. One of the factors influencing the result is age. Most investigators believe that the prognosis is always better in younger patients. The present experiments were designed to study the effect of carotid artery ligation on rats as influenced by age. The results indicate a significantly higher mortality and morbidity when the animals are young before sexual maturity, and a relative resistance during the neonatal life and adulthood. The most probable explanation for this extreme sensitivity of young animals is the blood flow of the brain which is almost twice as high prior to sexual maturity. The presence of arteriosclerosis in older rats did not influence the outcome of carotid artery ligation when compared with young, sexually mature animals.

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