There is a certain amount of evidence that both acute and chronic ischemia of the brain can cause hypertension in laboratory animals. It is worth reviewing this evidence, for it has bearing on the design of experiments to study the problem.

ACUTE ISCHEMIA AND HYPERTENSION

Hill records that both Poiseuille and Magendie observed acceleration of pulse and a rise of blood pressure in animals following ligation of both carotids, but gives no references. Nawalichin records that clamping the common carotids in anesthetized cats causes a rise in blood pressure; Hill in rabbits and Stewart et al. in dogs, among many subsequent workers, made the same observation. Hedon and Anrep and Starling showed by cross-circulation experiments that lowered perfusion pressure in the cranial circulation would raise blood pressure in the rest of the animal. All these workers interpreted their findings as demonstrating an autoregulatory system in the brain itself, but when Hering and his co-workers demonstrated the function of the carotid sinus, all these observations became explicable as due to carotid sinus reflexes.

There are, however, a few isolated observations showing a pressor effect of cerebral ischemia in which the carotid sinus is not implicated. Conty injected lycopodium spores into the carotid arteries of dogs, Bastgen did the same in the goat using oil, and Marchwald injected paraffin and olive oil into carotids and vertebrals in rabbits. All these workers noted acute rises in blood pressure shortly before death. M'Dowall observed an acute rise of blood pressure in cats after both vertebral arteries and one carotid had been clamped and the remaining internal carotid artery was clamped above the carotid sinus. Guyton, in dogs, first denervated the carotid sinus, and then ligated both carotids or vertebrals. When these animals had the remaining vertebral or carotid arteries clamped, an acute rise in blood pressure occurred, but in these animals the degree of ischemia was extreme, and in 60 per cent of the animals respiration ceased soon after the occlusion.

The only evidence then, that acute cerebral ischemia can cause hypertension without involving the carotid sinus reflex, concerns experiments with ischemia of almost lethal severity, and it is unlikely that this degree of ischemia could be maintained for long periods.

CHRONIC ISCHEMIA AND HYPERTENSION

Following the discovery of the significance of the carotid sinus, a number of observers have ligated carotid arteries in the course of excising or inactivating the carotid sinus. They reported chronic hypertension following this procedure, as have other workers following buffer nerve section alone, and attributed the hypertension to interference with buffer nerve mechanisms.

Other workers have investigated whether cerebral ischemia alone could cause chronic hypertension and have usually ligated or stenosed carotid arteries near the carotid sinus. An analysis of the methods used shows that nearly all workers actually or potentially interfered with buffer-nerve function. Fishback, Dutra, and MacCamy ligated common carotids in dogs, and Wakerlin et al. applied stenosing molds directly to the sinus area in dogs. Rosenfeld in many rabbits ligated the common carotids, and Roth-
FIGURE 1
Preparation of carotid system used throughout.

man apparently did the same. All workers reported the development of hypertension which was attributed not to interference with the carotid sinus mechanism, but directly to cerebral ischemia. Taylor and Page observed transient hypertension after severe multiple ligations of carotid and vertebral arteries in dogs but reported a more sustained hypertension after stimulation of the floor of the fourth ventricle in these animals.

There are only three incomplete reports which record the development of chronic hypertension in animals in which the carotid sinus might have remained undisturbed. Nowak and Walker reported hypertension in one dog after repeated carotid and vertebral operations, but they did not perform dummy operations on controls. Crandall et al. reported hypertension in three animals with stenosis of carotid arteries above the sinus, and Rosenfeld reported that some of his animals had above-sinus ligations and yet developed hypertension. Both these workers operated in the area of the carotid sinus and may have inadvertently damaged sinus nerves. It is noticeable in the report by Crandall et al. that, on their criteria for carotid sinus function (the effect on respiration of injected sodium cyanide), all three of the animals with above-sinus ligatures showed impaired function, and dummy operations were apparently not performed in control animals. Rosenfeld's work can also be criticized for the method of recording blood pressure which probably does not measure resting pressure, but only the blood pressure in conditions of stress.

The only report in which the carotid sinus definitely cannot be implicated is that of Wakerlin et al. who claimed that one out of six dogs with bilateral vertebral ligation developed hypertension.

Kezdi has repeated the work of Wakerlin et al., using above-sinus stenosis, and reports that in animals in which no damage to carotid sinuses has occurred, hypertension does not develop, but subsequently, when buffer nerves are sectioned, a rise in blood pressure does take place.

EFFECT OF RAISED CEREBROSPINAL FLUID PRESSURE

Naunyn and Schreiber first reported that an acute rise of cerebrospinal fluid (C.S.F.) pressure produces acute hypertension in dogs, an observation confirmed by Cushing and by M'Dowall in cats. Whether a chronic rise in C.S.F. pressure (for example by Kallin injection) can cause hypertension, is still disputed, successes and failures being almost equally frequent; the mechanism involved has never been elucidated, and it may well have little to do with cerebral ischemia.

Whether cerebral ischemia alone can cause chronic hypertension must, therefore, be viewed with some doubt, and it was decided to study this problem further. Choice of the dog as an experimental animal involves repeated laborious operations, for the dog will often survive bilateral ligature of carotid and vertebral arteries on the same day and develops collateral channels in the muscles of the neck with extreme rapidity. The rabbit was therefore selected, for reasons of size and availability. The main problem in the rabbit is the method of recording blood pressure. To produce lasting ischemia of the carotid area, both external and internal carotid arteries need to be ligated, since there is an anastomosis between the two in the orbit, but if the external carotid is tied blood pres-

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sure can no longer be measured in the central artery of the ear. After a number of preliminary experiments, this problem was largely solved.

To assess the efficacy of the ligations, it was decided to measure blood pressure in some part of the circulation distal to the carotid ligatures. Originally the left ear was used, but readings from this site were found to be insufficiently accurate; no pulsation was visible, and the precise end point was extremely difficult to judge. After some experiment, the retinal artery was found to be suitable.

**Methods**

Sixty-five rabbits, of both sexes, were studied, ranging in weight from 2.2 to 4.2 Kg. They were of mixed strains, predominantly Dutch and Flemish. Systolic blood pressure was recorded weekly by the method of Grant and Rothschild; 8 six consecutive resting readings within a scatter of 6 mm. Hg were accepted, and the mean was regarded as one blood pressure recording. Animals were anesthetized with intravenous Pentobarbitone (35 to 40 mg./Kg.) and open ether. No aseptic precautions were taken during operations, but benzathine penicillin (300,000 units) was given intramuscularly at the end of each operation, and no case of wound infection occurred. The diet given was Medical Research Council diet S.G. 1.

**CAROTID OPERATION**

Both carotid areas were explored by blunt dissection, taking extreme care to preserve the buffer nerves. On the right side, internal carotid, occipital, lingual, parotid, and internal maxillary arteries were doubly ligated and cut. On the left side internal and external carotid arteries were cut. This preparation leaves the superficial temporal artery intact for recording blood pressure in the right ear (fig. 1).

**VERTEBRAL OPERATION**

A longitudinal incision was made through pectoralis major and minor muscles. The subclavian artery was located and followed medially until the vertebral artery was found. It lies in close relation to the internal jugular and vertebral veins, thoracic duct, and esophagus, and care was needed in isolating it. The artery was cut between ligatures close to its origin from the subclavian artery.

**RETINAL ARTERY PRESSURE**

Anesthetized rabbits had their systolic retinal artery pressure measured by Bailliarts ophthalmodynamometer using the method which is applied to man. 38 These readings in grams measure the amount by which retinal artery pressure exceeds the resting intra-ocular pressure and were converted to true retinal artery pressure in mm. Hg by calibration curves from live rabbits, in which intra-ocular pressure was measured by a needle in the anterior chamber and pressure transducer, during ophthalmodynamometry (to be published).

**COLLATERAL CIRCULATION**

Rabbits were sacrificed by intravenous Pento-barbitone (240 mg.) to which 1,000 units of heparin had been added. The animal was immediately cut in half through the lower thorax and the descending aorta cannulated from below. Saline at room temperature was washed through the cannula, until the effluent from the vena
Effect on retinal artery pressure (R.A.P.) of applying a bulldog clip to carotid vessels on the same side. (A) Effect of clipping external carotid. (B) Effect of clipping internal carotid. (C) Further fall in pressure from levels in A when internal carotid is clipped after the external carotid. Each point represents the mean of duplicate readings in one animal.

cava was only slightly blood stained. Liquid Marco resorcin (Scott Bader Resin No. SB. 61C) was mixed in the following proportions: resin, 100 Gm.; monomer, 30 ml.; catalyst, 2 Gm.; red erystic dye, 4 ml.

The resin was pumped in at a pressure of 200 mm. Hg for eight minutes via a three-way junction piece which filled three rabbits simultaneously. After infusion, the rabbits were left for two hours until the resin was firm. The forelegs were cut off, and the remainder of the upper half was put into concentrated HCl for two days, which dissolves off all tissues.

COMBINED CAROTID AND VERTEBRAL LIGATIONS

The operative procedures were the same as for separate ligations with three exceptions: (1) the superficial temporal artery was cut distal to the origin of the auricular branch; (2) the ascending cervical artery was cut at the same time as the vertebral artery; (3) the right vertebral artery was stenosed by the application of a stainless steel clip made from a strip of metal 3 mm. wide by 12 mm. long, with a gap of 0.3 mm.

The carotid sinuses were denervated by stripping the right carotid bifurcation of all nervous connections and by excising the left sinus.

Results

Figure 2 shows the scatter of blood pressure readings in 130 normal rabbits observed for five to six weeks. The range accepted as normal is 55 to 95 mm. Hg, the limits of which are marked as dotted lines on subsequent charts. Blood pressure readings from the right ear following the right carotid operation differ by less than 1 mm. Hg (a) from preoperative readings in 34 rabbits, and (b) from readings in the normal left ear in 11 rabbits.

CAROTID LIGATIONS (TWENTY-SIX ANIMALS)

Two rabbits had bilateral ligation on the same day, five at a 10- to 12-day interval, three at 3 weeks, and the remainder at a 4-week interval; six died, one within minutes of the second ligation, the remaining five 2 to 4 days later with skin and mucous membrane necrosis in the external carotid distribution. Of the rabbits operated on at a 3- to 4-week interval, 16 remained healthy and active, 2 ceased to eat or drink and lost weight steadily with falling hair and a falling blood pressure before death 2 weeks post-operatively; one developed paralysis of all four limbs and was sacrificed.

Blood pressure in the 19 survivors is shown in figure 3. A few scattered readings above normal are seen after the second ligation, but by the end of 12 weeks, no rabbit shows persistent hypertension. Three rabbits showed transient hypertension.

VERTEBRAL LIGATIONS (FOURTEEN ANIMALS)

Of three rabbits with vertebral ligations on the same day, all died; one other animal died of unrelated causes soon after the second operation. The other animals with vertebral ligations at a two- to six-week interval
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remained healthy and showed no hypertension (fig. 4).

RETINAL ARTERY PRESSURE

Figure 5 shows the effect on the retinal artery pressure of clipping external and internal carotids in normal rabbits. Clipping the external produced a fall in all rabbits, whereas clipping the internal carotid often had no effect; the difference between the two is significant \((P<0.01)\). After the external carotid has been cut, clipping the internal carotid now produces a further fall in pressure in most animals tested (this is a selected series because in some rabbits retinal artery pressure is too low for accurate measurement after the external carotid has been cut).

These results show that the retinal artery comes from the external carotid, close to an anastomosis with the internal carotid. After internal and external carotids have been cut, there is no further fall in retinal artery pressure on clipping the common carotid. The superficial temporal artery in normal rabbits does not at any point anastomose with the internal carotid system, but it might possibly develop such anastomoses in the course of time.

In rabbits with the carotid preparation shown in figure 1, if the right temporal artery develops collaterals to supply the internal carotid, these should be detectable by noting the effect on retinal artery pressure of clipping the right common carotid. This test was carried out at various stages (fig. 6). At 0 and 4 weeks after the right carotid operation, there was no measurable effect, but at 8 weeks one out of seven and at 16 weeks six out of seven showed falls in retinal artery pressure on clipping the right common carotid, demonstrating that some anastomosis between temporal and internal carotid arteries does develop. This effect is almost negligible up to 8 weeks and probably unimportant even at 16 weeks (vide infra).

Figure 7 shows the rise in retinal artery pressure that occurs with time following carotid ligation; it is a composite chart, in which not all readings were taken under comparable conditions. The animals included are only those in which no contribution of the temporal artery to retinal artery pressure could be de-
14 weeks after bilateral vertebral ligation. Key as on figure 10.

Readings at 0 weeks represent postoperative readings in rabbits at the end of the right carotid operation, after the left common carotid as well had been temporarily occluded by a bulldog clip. Readings at 4 weeks are postoperative readings after the second carotid operation had been completed (4 weeks after the first). These same rabbits are subsequently anesthetized 5, 9, and 18 weeks after the right carotid operation, and retinal artery pressure is measured after blood pressure is recorded. The rabbits at 18 weeks had had the right external carotid cut to eliminate the temporal artery collateral flow, and blood pressure reading was no longer possible. Statistical analysis of retinal artery pressure is permissible only for readings at 5 and 18 weeks, and the difference between 5 and 18 is significant ($P<0.05$).

This increase in pressure might be expected to represent collateral flow from vertebral arteries, and this is confirmed by cutting one or stenosing two vertebral arteries in six rabbits, which produces a further fall of retinal artery pressure.

The dotted point in figure 7 is the point reached by the same seven animals shown at 18 weeks, before the temporal collateral flow had been eliminated, demonstrating that this collateral supply is small compared with the vertebral contribution.

**COLLATERAL CIRCULATION**

Figure 8 shows a normal control. One untouched specimen shows the normal distribution of external carotid and branches, and the other two have been extensively pruned to show internal carotid and circle of Willis. In normals, the internal carotid, vertebral, and basilar arteries are all of approximately equal size, and the external carotid is very much larger than any of these.

Rabbits 14 weeks after vertebral ligation are shown in figure 9. In all five animals perfused, the vertebrae filled entirely from above via enlarged posterior communicating arteries.

Fourteen weeks after the second carotid operation (fig. 10), the vertebral, basilar, posterior communicating, and ophthalmic arteries are very much enlarged; the external carotid area fills from the ophthalmic artery, and from anastomoses between the occipital artery and the vertebral. The collaterals from the temporal artery were visible on all animals tested, but were tortuous and much smaller than any of the numerous other collaterals.
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FIGURE 11
Intact specimens. (A) Normal. (B) One week after bilateral carotid ligation. (C) Eighteen weeks after bilateral carotid ligation. (Internal and external carotid cut.) a=auricular a.

Figure 11 gives the complete demonstration that the vertebral artery can take over supply of the whole carotid area. One week after bilateral carotid ligation, the vertebral and internal carotid area alone fill, and most of the external carotid area is apparently ischemic, although early collaterals can be seen forming from the anterior cerebral artery. The spared superficial temporal and auricular arteries can be seen, but these do not at this stage communicate with the cerebral circulation. Eighteen weeks after bilateral carotid ligation, the whole carotid area is filled almost as well as in normals but entirely from the vertebral arteries.

COMBINED CAROTID AND VERTEBRAL LIGATIONS (TWENTY-FIVE ANIMALS)

These rabbits had been subjected to the following procedures: (1) left carotid ligation and right vertebral stenosis; (2) right carotid ligation; (3) left vertebral, left ascending cervical, and right superficial temporal artery ligations; (4) removal of right vertebral clip and ligation of right vertebral and ascending cervical arteries; (5) denervation of both carotid sinuses. The timing of these procedures is shown in figure 12. Of the 25 animals, 12 survived until operation 4, 10 until operation 5, and 7 for the whole experiment.

Figure 13 shows a cast of the stenosis in a vertebral artery. For a period of four weeks, the blood supply to the brain and almost the whole carotid and vertebral areas of supply was maintained through this channel (shown by resin casts in four animals). After ligation of this artery, the collateral supply was maintained by muscular anastomoses in the neck.

The completeness of the original ligations was verified in 15 animals by resin casts. In 14 of these, it was confirmed that the original ligations were complete and no recanalization had occurred. In one animal, a duplicate internal maxillary artery had been overlooked.

Blood pressures in the whole series are shown in figure 12. No animal developed hypertension until the carotid sinuses were denervated, although a markedly lowered retinal artery pressure was maintained throughout the period of study (fig. 14). The hypertension shown after bilateral carotid sinus denervation seemed to have the labile
quality, so often observed in buffer-nerve hypertension; the animals tended to show wide fluctuations of pressure, with one or two normal readings in between a series of higher values.

Discussion

It is clear that neither carotid nor vertebral ligations by themselves produce any permanent ischemia in their area of supply, since the posterior communicating artery has a very great capacity for dilatation. It is, therefore, not surprising to find that persistent hypertension does not follow either of these procedures, provided that the carotid sinus is undisturbed. The results of Rosenfeld and Rothman are probably due to some other mechanism; whether to interference with the carotid sinus or to their method of blood pressure recording cannot now be decided. The results of multiple ligation of carotid and vertebral arteries demonstrate that even these procedures do not produce hypertension, although effective in markedly lowering perfusion pressure in the head. It remains a theoretical possibility that an even more drastic series of ligations might produce transient hypertension, but it is doubtful whether further research with these methods will be profitable.

Previous workers who have reported hypertension in rabbits after carotid ligation alone, have apparently been studying the effects of interference with the carotid sinus; this was probably the cause of transient hypertension observed in three rabbits in the present series.

Summary

A method is described of performing bilateral carotid ligation in the rabbit preserving the carotid sinus and the central artery of the ear. Of 26 animals prepared in this way, and 14 with bilateral vertebral ligation, none developed chronic hypertension. The development of a collateral circulation is shown by serial retinal artery pressure readings and by resin casts of cerebral vessels; neither carotid nor vertebral ligations produce any permanent ischemia in their area of supply. In 25 animals subjected to combined vertebral and carotid ligation, a marked lowering of arterial pressure in the head was obtained, but no animal developed hypertension until the carotid sinuses were subsequently denervated. It is concluded that previous workers who have reported chronic hypertension following ligation of cerebral arteries have been studying the effects of interference with buffer-nerve function.

References


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