Absence of Vasomotor Responses to Epinephrine and Arterenol in an Isolated Intracranial Circulation

By Harold D. Green, M.D. and Adam B. Denison, Jr., M.D.

With the assistance of the following senior medical students: Arthur T. Hill, Ronald C. Kelly, N. Maxwell Lewis, Bill R. McLain, William S. Myers, F. Byron Smitherman, Jr., Lester E. Watts and Arthur F. White

Four experimental procedures were tried with the dog before one was found which enabled us to record vasomotor changes in an intracranial vascular bed, uncomplicated by alteration in vasomotor tone in the extracranial beds. This required extensive dissection and cannulation techniques. In experiments in which this was accomplished by complete elimination, on one side, of the communications between the internal carotid artery and the various extracranial arteries, it was demonstrated that doses of epinephrine and arterenol, which have marked vasomotor activity on all other vascular beds, are without effect on the intracranial bed supplied by the internal carotid artery.

In 1907 Wiggers observed that epinephrine, injected intra-arterially in doses of 50 µg. to 12 mg. (1 ml of 1:20,000 to 3 ml of 1:250), constricted the cerebral blood vessels. Using the chilled thermocouple inserted into the brain substance, Schmidt noted that intra-arterial epinephrine caused a weak vasoconstriction in the hypothalamus, but not in the medulla or parietal cortex of the cat. More recently Sensebach, Madison, and Ochs measured cerebral blood flow in man using the nitrous oxide uptake method. They reported that 500 and 1400 µg. of norepinephrine in oil, injected intramuscularly, raised arterial pressure but increased cerebral vascular resistance sufficiently that blood flow was decreased. Epinephrine slightly lowered arterial pressure but had no effect on cerebral vascular resistance. In view of these varied results, we felt it desirable to re-investigate the problem by measuring arterial inflow directly by a technic similar to that used in our studies on other vascular beds.

In view of the reports of Wiggers, Jewell, and others that many collateral communications existed between intra- and extracerebral vessels, we attempted to devise a method for metering the blood flow to intracranial (cerebral) structures, without simultaneously metering blood which might be going to non-nervous tissues. These studies progressed through four distinct phases before we reached the present technic, which we believe finally allows us to study the true vasomotor reactivity of the intracranial arterioles. We shall describe briefly the steps involved and the results obtained in each phase, as we believe this will help to clarify the problem and may enable others to avoid the pitfalls we experienced.

GENERAL METHODS

Dogs weighing 19 to 22 Kg. were anesthetized with 30 mg./Kg. of sodium pentobarbital and, after completion of all dissections and just before cannulation, were given mepesulfate, 125 mg./Kg., intravenously (femoral vein) as an anticoagulant. An additional 250 mg. was given every hour thereafter.

The technic for flow measurement was similar to that used in previous experiments from this laboratory. Blood, obtained at pulsatile aortic pressure by way of a cannula inserted in the proximal

From the Department of Physiology and Pharmacology, The Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N.C.

This work was supported by a grant from the Life Insurance Medical Research Fund.

Preliminary reports of this work were presented at various meetings of the American Physiological Society and the Society for Pharmacology and Experimental Therapeutics.

Received for publication April 10, 1956.
stump of the severed right common carotid artery, was passed through a "loop" containing an electromagnetic flowmeter and a Statham P23A strain gage and then entered the distal stump of the artery that was to be perfused (fig. 1). The tubing was principally polyethylene plastic except for a section of rubber tubing downstream from the flowmeter for insertion of hypodermic needles for making drug injections. In the last three phases of the experiment, two separate loops and flowmeters were used.

The length and diameter of the tubing system from the point of injection back to the bifurcation of the flow stream was sufficiently great and the volume and rate of injection were such that drugs injected in one arm would not be carried back to the other arm even if a fairly large component of backflow were present with each heart cycle. This possibility was further minimized in later experiments by insertion of an air expansion chamber to damp partially the arterial pulsations.

RESULTS

Phase 1

In a first set of experiments, all branches of the common carotid artery except the internal carotid artery were ligated on the right side and the common carotid artery was cannulated proximally and distally. Flows obtained in the internal carotid artery averaged 12 ml./min. Intra-arterial injections of epinephrine and arterenol caused constriction, and injections of isopropylarterenol caused dilation of a magnitude similar to those obtained in skeletal muscle. In view of these responses, we felt that we were perfusing a considerable mass of extracranial blood vessels.

Phase 2

Both the right external and internal carotid arteries were cannulated and perfused simultaneously in the hope of minimizing or preventing interchange of blood between intracranial and extracranial beds. Flows obtained in the right external carotid artery averaged 12 ml./min. and 5.9 ml./min. in the right internal carotid artery. Occlusion of the left common carotid artery decreased resistance to 74 per cent of control in the right external carotid artery and to 53 per cent of control in the right internal carotid artery. Occlusion of the right external carotid artery decreased resistance in the right internal carotid artery to 63 per cent of control, but occluding the internal carotid artery had no apparent effect on the external carotid artery resistance. Injection of epinephrine into either artery caused simultaneous increases in resistance in both arteries. These studies suggested that there was still a considerable interchange of flow between the internal carotid, the opposite common carotid, and the ipsilateral external carotid arteries.

Phase 3

Plastic Injection Studies. The common carotid arteries of several dogs were flushed with saline and acetone and then injected with Ward's vinyl acetate plastic. All the anastomoses previously described by Jewell were identified, with the exception of the one between the internal carotid and ascending pharyngeal arteries (fig. 1).

Saline Perfusion Studies. Saline was injected into the right internal carotid in several dogs and the various vessels were observed for backflow. None was seen in the lingual, external maxillary, posterior auricular, superficial temporal, deep temporal, or inferior alveolar arteries. Backflow was noted in the middle meningeal, anastomotic, ophthalmic, and external ethmoidal arteries which are branches of the internal maxillary artery. Simultaneous perfusion of the internal maxillary and internal carotid arteries produced no backflow in the common carotid stump when the occipital artery was occluded. It was concluded, therefore, that the ascending pharyngeal-internal carotid anastomosis was of little or no functional importance.

Dissection. The skin was incised in the midline from the mental symphysis to the sternum. All branches of the right common carotid artery between the sternum and carotid bulb were ligated and divided. The sympathetic plexus about the carotid bulb was usually divided. The intervertebral artery is formed by the junction of the occipital and vertebral arteries. It was not found possible to ligate this communication where it enters the vertebral canal; therefore, the occipital artery was prepared for cannulation and separate perfusion. The pharyngeal, lingual, and inferior alveolar arteries were ligated. Another skin incision was then made.
Fig. 1. Diagram of the intra- and extracranial arteries and of the communications between them in the head of the dog, and of the flowmeters, pressure gages, cannulae, and connections used in phases 3 and 4. The letters and numbers have the following significance. Arteries: A = anastomotic, AP = ascending pharyngeal, B = basilar, CB = carotid bulb, CC = common carotid, EC = external carotid, EE = external ethmoidal, EO = external ophthalmic, IC = internal carotid, IM = internal maxillary, IO = internal ophthalmic, IV = intervertebral, MM = middle meningeal, O = occipital, V = vertebral. Canal: ASC = alisphenoid canal. Cannulae: C-CC = in common carotid, C-EC = in external carotid, C-IC = supplying the internal carotid, C-IM = in internal maxillary, C-O = in occipital. Ligatures: 1 = on the continuation of the internal maxillary artery within the orbit (phase 3), 2, 3, 4 = on the external and internal ophthalmic and external ethmoid arteries within the orbit (phase 3), 5, 6, 7 = on pharyngeal, lingual, and inferior alveolar arteries, 8 = clamp on anastomotic artery (phase 4), 9 = clamp on portion of the internal maxillary artery—distal to end of long catheter (phase 4). Apparatus: EXC = expansion chamber, FM, G = flowmeter and Statham pressure gage arranged to record flow in either the external carotid artery (clamps I and III open, clamps II and IV closed) or in the internal maxillary artery (clamps II and IV open, clamps I and III closed), FM2, G = flowmeter and pressure gage for measuring flow in the internal carotid artery, R, R1 = segments of rubber tubing for making drug injections.

from the outer canthus of the eye, over the angle of the mandible, to the previous incision. The zygomatic arch was resected, the mental symphysis divided in the mid-line, and the right half of the mandible resected by dividing the tendinous insertions of the muscles of mastication, being particularly cautious at the articulation because of the proximity of the external carotid artery to the joint capsule. This exposed the internal maxillary artery.

The orbital structures were then resected after placing ligatures around the optic nerve and surrounding structures.

The communications between the internal maxillary and internal carotid arteries are the middle meningeal and anastomotic arteries. These arise from the internal maxillary artery within and just distal to the alisphenoid canal. Both communicate with the internal carotid artery within the cranium. It appeared impos-
sible to ligate these arteries at their points of entrance into the skull. They were, therefore, perfused by way of a cannula inserted a short distance into the internal maxillary artery just proximal to the alisphenoid canal and the distal portion of the internal maxillary was ligated in the orbit.

The communications between the extracranial and intracranial vascular beds in the orbit. These include the internal and external ophthalmic and the external ethmoid arteries, and were ligated within the orbit.

The ascending pharyngeal artery. This was ligated at its origin from the external carotid artery. The left common carotid artery was exposed and untied ligatures were placed about it.

Cannulation. Mepesulfate was given intravenously at least 15 minutes before cannulation was started. A cannula was inserted in the proximal stump of the right common carotid artery and blood was shunted through separate flowmeters and pressure gages to a cannula in the right internal maxillary artery (proximal to alisphenoid canal) and to a cannula in the right internal carotid artery by way of the right common carotid artery (distal stump) (fig. 1). Separate nonmetered cannulae were placed in the right external carotid and right occipital arteries.

X-ray Studies. After the animals expired, the metered arteries were flushed with 20–40 ml saline and then injected with a mixture of BaCl₂ (40 per cent) and gelatin (10 per cent) suspended in water at 40 C., at a pressure of 150–170 mm. Hg. The left common carotid artery was injected simultaneously with a radiolucent material (35 per cent corn starch in water at 40 C.) at a similar pressure. Dorso-ventral and lateral x-ray films were then made.

Results. Mean control flow was 2.3 ml./min. in the internal carotid artery and 8.5 ml./min. in the internal maxillary artery. Occlusions of flow in the internal carotid artery did not appreciably affect the resistance in the internal maxillary artery, but occlusion of the internal maxillary flow decreased resistance in the internal carotid artery to 81 per cent of control (table 1A). All doses of either epinephrine or artenol, when injected into either the internal maxillary or the internal carotid artery, increased resistance to flow in both. However, the response was usually greater in the internal maxillary, especially when the injections were into the former (table 1A). In many of these experiments, the x-ray studies revealed barium in the extracranial sites on the right side, particularly in the orbital region.

It appeared from the above that the extensive dissection in this phase had eliminated all communications between the right intracranial and right extracranial structures, except those existing between the internal carotid and the internal maxillary arteries. In this phase constrictor responses were present in the internal carotid artery but consistently were less than those in phase 2. One possible explanation for this observation was that the meningeal vessels, which are supplied by the internal maxillary artery, responded differently from those in brain substance supplied by the internal carotid artery. In view of the x-ray findings, a more likely explanation is that a goodly portion of the internal maxillary flow was going to extracranial structures and that some of the internal carotid blood also reached these extracranial structures by way of the anastomoses between the internal carotid and internal maxillary arteries.

Phase 4

Methods. The catheter in the internal maxillary artery was passed further, to such a distance that it bypassed and occluded the orifice of the middle meningeal artery (fig. 1). The cannula could not consistently be passed to a point where it would also occlude the orifices of the anastomotic and external ophthalmic arteries; therefore, dissection of the optic foramen was extended to the point where the anastomotic artery could be clamped. The internal maxillary artery was also clamped at this point.

Frequently, after such dissection, no measurable blood flow could be obtained in the internal maxillary artery. To obtain a reactive vascular bed as a control for the drug responses, as well as a control against possible intracranial-extracranial exchange of blood flow, a shunt was arranged so that blood flow could
<table>
<thead>
<tr>
<th>Procedure</th>
<th>Dose</th>
<th>Vessel</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>With anastomosis</td>
<td>Without anastomosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Right internal carotid</td>
<td>Right internal maxillary</td>
<td>No. of observations</td>
</tr>
<tr>
<td>LCC</td>
<td>75</td>
<td>(60-101)</td>
<td>50</td>
<td>(45-76)</td>
</tr>
<tr>
<td>RIC</td>
<td>100</td>
<td>(92-108)</td>
<td>87</td>
<td>(53-102)</td>
</tr>
<tr>
<td>RIM</td>
<td>81</td>
<td>(63-129)</td>
<td>98</td>
<td>(93-100)</td>
</tr>
<tr>
<td>REC</td>
<td></td>
<td></td>
<td>90</td>
<td>(89-91)</td>
</tr>
</tbody>
</table>

**Occlusions**

A—average results in 6 experiments (phase 3) in which we believe there were residual communications between intracranial and extracranial vascular beds.

B—average results in 6 experiments (phase 4) in which we believe we successfully occluded all communications between the intracranial and extracranial vascular beds on the right side of the head.

RIC = right internal carotid artery (intracranial), RIM = right internal maxillary artery (extracranial), REC = right external carotid artery (extracranial), LCC = left common carotid artery.

Procedure indicates the artery that was occluded or the amount of the drug and the artery into which it was injected.

Figures = the average and range (in parentheses) of the per cent of control resistance (experimental resistance(control resistance × 100). Resistance was measured in PRU = mm. Hg perfusion pressure ÷ ml./min. of flow.
be metered in either the external carotid or the internal maxillary artery while the other was perfused at aortic pressure (fig. 1).

Results. Mean control flows were 5.3 ml./min. in the internal carotid artery, 15.4 ml./min. in the internal maxillary artery, and 21.1 ml./min. in the external carotid artery. Occlusion of the left common carotid artery decreased resistance in the right internal carotid artery to 59 per cent of control but had little effect in the right external carotid or internal maxillary artery resistances. Occlusion of the right internal carotid artery had no significant effect on either the internal maxillary or the external carotid resistances. Occlusion of the internal maxillary artery had no significant effect on

![Image](https://example.com/image.png)

**Fig. 2. Intracranial vs. Extracranial Blood Flow.** Typical simultaneous flow and pressure records from a phase 4 experiment. **RIMP, RIMF** = right internal maxillary artery pressure and flow, **RICP** = right internal carotid artery pressure and flow, **RECP, RECF** = right external carotid artery pressure and flow. Figures adjacent to the pressure curves are the mean arterial perfusion pressures in mm. Hg referred to zero at the level of the carotid artery; figures adjacent to the flow curves are the mean rates of flow in ml./min.; figures in () adjacent to the flow curves are the per cent of control resistance induced by each procedure; dashed lines ending in 0 = position of the recording line at zero flow or zero pressure.

**Upper set of four records:** **OCC R.I.M.** = occlusion of (interruption of flow in) the right internal maxillary artery, indicated by the drop in the internal maxillary flow line to zero (0), **OCC R.I.C.** = similar occlusion of the right internal carotid artery, **OCC R.E.C.** = occlusion of the right external carotid artery, indicated by horizontal bar adjacent to **RICF**, **OCC L.C.C.** = occlusion of the left common carotid artery, indicated by period of increased flow in **RICF**, **EPI 10 µg. R.I.C.** = injection of 10 µg. of epinephrine into the right internal carotid artery during the period of time indicated by the horizontal bar adjacent to **RICF**.

**Lower set of four records:** **EPI 0.3 µg. R.I.M.** = injection of 0.3 µg. of epinephrine into right internal maxillary artery during the interval indicated by the horizontal bar adjacent to **RIMP**, **EPI 10 µg. R.I.C.** = injection of 10 µg. of epinephrine into right internal carotid artery during the interval indicated by the horizontal bar adjacent to **RICF**, **OCC R.I.M.** = occlusion of right internal maxillary artery, indicated by horizontal bar adjacent to **RICF**, **EPI 1 µg. R.E.C.** = injection of 1 µg. of epinephrine into the right external carotid artery, indicated by horizontal bar adjacent to **RECF**.

Time, 12 vertical arcs = 1 min.; experiment DD16.
the internal carotid resistance, but occlusion
of the external carotid artery occasionally de-
creased resistance in the internal carotid ar-
tery, on the average, to 90 per cent of control
(fig. 2 and table 1B). The last might be due to
anastomotic connections between the poste-
rior auricular and/or superficial temporal ar-
terries, since these were the only arteries left
intact in the course of the external carotid
artery (fig. 1). However, such connection was
not demonstrated in the x-ray studies (see
below).

Injections of 0.3, 1.0, and 10 μg. of either
epinephrine or arterenol into the right internal
carotid artery, produced no response in any of
the beds. Similar doses of these drugs, injected
into either the internal maxillary or external
carotid artery, increased resistance, on the
average, to 296 to 709 per cent of control in
these arteries but had no demonstrable effect
on the internal carotid bed (fig. 2 and table
1B).

After death barium was injected into the
internal maxillary artery and x-ray films made.
Barium was then injected into the external
carotid artery and a second set of films taken.
A third set of films was made after injection
of the internal carotid artery. These studies
demonstrated absence of barium from the in-
tracranial vasculature after both the first and
second injections but filling of the intracranial
bed after injection of the barium into the in-
ternal carotid artery.

**Discussion**

In the first two phases of this study, occlu-
sion of, or injection of drugs into, either the
internal carotid artery or branches of the ex-
ternal carotid artery influenced flow in both
beds. This observation suggests that inter-
mixture of blood occurred, so that both arterial
systems supplied both intra- and extracranial
beds. In phase 3, this intermixture was reduced
but not abolished; accompanying this modifi-
cation there was a reduction in, but not aboli-
tion of, the constrictor responses to injection
of the adrenergic drugs into the internal ca-
rotid artery. This suggested but did not prove
that the intracranial vessels might have little,
or in fact no, responsiveness to the adrenergic
substances.

In phase 4, occlusion of, or injection of drugs
into, branches of the external carotid artery
had no significant effect on flow in the internal
carotid artery. Conversely, occlusion of, or in-
jection of drugs into, the internal carotid ar-
tery had no significant effect on flow in the
residual branches of the external carotid ar-
tery. A slight increase in flow in the right
internal carotid was noted when the right ex-
ternal carotid was occluded and occasionally
when epinephrine was injected into it; but
these were probably due to the rise in per-
fusion pressure in the internal carotid artery
arm caused by the reduction of flow in the
external carotid arm of the perfused schema.

In view of the observations reported in this
paper, it would appear that the vasoconstric-
tion reported by Wiggers* was due to the use
of unphysiologically large doses. The con-
strictor response to arterenol noted by Sensen-
bach, Madison and Ochs8 may mean that man
acts differently from the dog. However, we
believe it is possible that the nitrous oxide
technic measures both intracranial and extra-
cranial flow. If this is the case, the prominent constriction of extracranial vessels, demonstrated by us, could account for the vasoconstriction noted by them.

SUMMARY

In phase 4 of these experiments, all communications between the right internal carotid artery and the extracranial arteries on the right side of the heads of dogs were successfully eliminated by inserting a catheter into the right internal maxillary artery where it enters the alisphenoid canal and then passing the catheter into the artery until it reaches the exit of the canal in the orbit. This occludes the origin of the middle meningeal, which occurs within the canal. The distal portion of the right internal maxillary artery and the orifices of the anastomotic, the external ophthalmic, the internal ophthalmic, and the external ethmoidal arteries were all ligated in the orbit.

The right occipital artery was perfused at aortic pressure. The internal carotid and either the external carotid or internal maxillary artery (above catheter) were perfused at aortic pressure and the blood flows measured simultaneously with two electromagnetic flowmeters. Perfusion pressures were recorded with strain gages.

Using this technic, it was noted that occlusion of, or injection of drugs into, one of the right extracranial arteries had no significant effect on the resistance and flow in the right internal carotid artery bed and, conversely, injection of drugs into, or occlusion of, the internal carotid artery had no effect on the resistance in either of the extracranial arterial beds. Occlusion of the left common carotid artery still caused a reduction of resistance as measured in the right internal carotid artery.

Under the conditions of these experiments, 0.3 to 10 μg. of either epinephrine or arterenol injected intra-arterially caused marked vasoconstriction in the beds supplied by the internal maxillary and external carotid arteries but was without effect on the bed supplied by the internal carotid artery.

It is concluded that there are no significant adrenergic constrictor receptors in the intracranial arterioles supplied by the internal carotid artery of the dog.

ACKNOWLEDGMENTS

The mepesulfate was obtained in powder form from Hoffmann-LaRoche, Inc., Nutley, N. J. The epinephrine (adrenaline) was supplied in 1 ml. ampules of 1:1000 solution without preservative by Parke, Davis and Company, Detroit, Mich. Doses are expressed in terms of the chloride salt. Levarterenol (arterenol, norepinephrine, Levophed Bitartrate) was supplied in 4 ml. ampules containing 0.1 per cent of the base (0.2 per cent of the salt) by Winthrop Laboratories, Inc., Department of Medical Research, Baltimore, Md. Doses are expressed in terms of the base.

SUMMARIO IN INTERLINGUA

In phase 4 de iste experimentos, omne communication inter le dextere arteria carotide interne e le arterias extracranial al latere dextere del capite de canes esseva eliminate per le insertion de un catheter in le dextere arteria maxillari interne ubi illo entra in le canal alisphenoide, sequite per le avantiamento de ille catheter usque al puncto ubi le canal exi a in le orbita. Iste intervention occlude le origine del arteria meningeal medie que se trova intrin le canal. Le portion distal del dextere arteria maxillari interne e le orificios del arterias anastomotic, ophthalmic externe e interne, e ethmoide externe esseva omnes ligate in le orbita.

Le dextere arteria occipital esseva perfundite a pression aortic. Le arteria carotide interne e le arteria carotide externe o le arteria maxillari interne (supra le catheter) esseva perfundite a pression aortic, e le fluxos sanguine esseva mesurate simultaneamente per medio de duo electromagnetic fluxometros.

Per medio de iste technica il esseva constatale que le occlusion de un del arterias extracranial o le injection de drogas in illos habeva null significative effecto supe le resistentia e le fluxo in le dextere arteria carotide interne e inversehenmente que le injection de drogas in le arteria carotide interne o su occlusion habeva null effecto supe le resistentia in le un o le altore del arterias extracranial. Le occlusion del sinistre arteria carotide commun causava ancora un reduction del resistentia, mesurate in le dextere arteria carotide interne.
Sub le conditiones de iste experimentos, inter 0,3 e 10 mg. de epinephrina o de arterenol injicite intra-arterialmente causava marcate grados de vasoconstriction in le vasculatura alimentate per le arterias maxillari interne e carotide externe sed remaineva sin effecto super le vasculatura alimentate per le arteria carotide interne.

Nos conclude que il ha nulle significative receptores constrictori adrenergic in le arteriolas intracranial alimentate per le interne arteria carotide del can.

REFERENCES
4 WIGGERS, C. J.: The innervation of the cerebral vessels as indicated by the actions of drugs. Am. J. Physiol. 20: 206, 1907-08.
Absence of Vasomotor Responses to Epinephrine and Arterenol in an Isolated Intracranial Circulation


Circ Res. 1956;4:565-573
doi: 10.1161/01.RES.4.5.565

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1956 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/4/5/565

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org/subscriptions/