JCI The Journal of Clinical Investigation

PLETHSYMOGRAPHIC STUDIES OF THE CEREBRAL CIRCULATION: EVIDENCE FOR CRANIAL NERVE VASOMOTOR ACTIVITY

Thomas J. Bridges, … , Kemp Clark, Melvin D. Yahr

J Clin Invest. 1958;37(5):763-772. https://doi.org/10.1172/JCI103662.

Research Article

PLETHSYMOGRAPHIC STUDIES OF THE CEREBRAL CIRCULATION: EVIDENCE FOR CRANIAL NERVE VASOMOTOR ACTIVITY [1, 2]

By THOMAS J. BRIDGES, KEMP CLARK,[3] AND MELVIN D. YAHR

(From the Departments of Neurological Surgery and Neurology, College of Physicians and Surgeons, Columbia University, The Neurological Institute, Presbyterian Hospital, and the Francis Delafield Hospital, New York, N. Y.)

(Submitted for publication December 6, 1956; accepted January 23, 1958)

Cerebral vasodilatation and vasoconstriction may be recorded by the electronically-amplifying pneumoplethysmograph. This method represents an adaptation of the plethysmographic method of recording digital vasomotor changes. The brain is enclosed in a largely nondistensible dural envelope (1), which, in effect, is a naturally-occurring plethysmograph chamber. The dura, backed by the skull, is a substitute for the rigid plastic cup used for digital plethysmography (2).

Cerebral plethysmographic responses to a number of vasomotor stimuli and to cervical sympathetic nerve stimulation and nerve block are reported.

Early efforts (1881 to 1929) to relate change in cerebral circulation to differences in amplitude of pulsation over human cranial defects, as recorded by the kymograph, are summarized by Shepard (3) and Stevenson, Christensen, and Wortis (4). These observations could be obtained from subjects with large cranial defects capable of transmitting a volume-pressure change sufficient to activate a mechanical recording system. Electronic amplification permits volume pulse recordings to be obtained through a small cranial trephination.

Cerebral vasodilator and vasoconstrictor agents have been identified by a method of pial vessel photography and measurement (5, 6), and by calculation from dye-dilution (7) and nitrous oxide (8) blood flow methods. Vasomotor stimuli of predictable action may be utilized in the evaluation of a cerebral plethysmographic method.

METHOD AND MATERIAL

One of two electronically-amplifying, direct recording plethysmographs is connected to the human subdural space in an air-and-water-tight fashion. A small trephination is made in the temporal region of the skull under local anesthesia. The dura is opened widely. Effort is made to preserve the integrity of the arachnoid. A chambered, cast vitallium, trephine button is inserted into the trephination opening in the skull. A short length of plastic tubing is threaded onto the stem of the trephine button and led out through a separate stab wound in the scalp. The button is then connected to the recording plethysmograph by means of 10 to 15 feet of plastic tubing. Recordings may be obtained for periods up to 23 days. After this time, the dura will be reformed, and pulsations will be considerably damped. At the conclusion of the recording period, the plastic tubing is gently pulled away from the cast vitallium trephine button and removed from the stab wound, allowing this wound to heal. The trephine button may be left *in situ* indefinitely, avoiding the need to perform further surgery to remove the button.

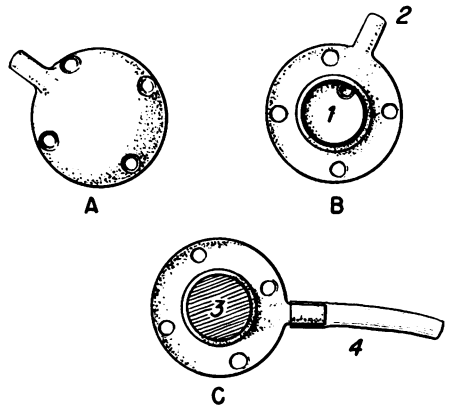

FIG. 1. DIAGRAM OF CAST VITALLIUM TREPHINE BUTTON

A. External surface of volume recording button.

B. and C. Internal surface of recording button.

1) Volume transmitting air chamber; 2) volume transmitting stem; 3) lax rubber diaphragm separating cerebrospinal fluid and air; 4) Portex tubing for connection to plethysmograph.

[1] This study was aided in part by a research grant from the Veteran's Administration VAM-23238, V-1001-M4078.

[2] A preliminary report of this project was presented before the Harvey Cushing Society, May 18, 1955.

[3] Present address: Southwestern Medical School, University of Texas, Dallas, Texas.

MATERIAL

The cerebral plethysmographic observations to be reported were obtained from 18 patients, 10 women and 8 men, undergoing "injection-type" lobotomy, cervicothoracic sympathectomy, or "head-and-neck dissection" operations. The age range was 26 to 48 years, with an average age for the group of 33.3 years. None of these patients had cerebrovascular, cardiovascular, or central nervous system disease. Observations of cerebral plethysmographic changes have been made in a few patients with cerebrovascular disease or brain tumor, but these observations have been purposely excluded, and will be reported when a sufficiently large number of observations will have been made.

The trephine button (*Figure 1*). The cast vitallium trephine button was designed to fit snugly into a 14 mm. trephination. The chamber of the button is open to a side tube (stem) to which No. 6 hard-walled Portex tubing attaches firmly. The inner aspect of the chamber may be left open over the arachnoid, or may be covered with a lax, thin rubber membrane to prevent infection of the subarachnoic space, or a leak of cerebrospinal fluid into the plastic tubing.

The plethysmograph. The two plethysmographs used for this study were designed and constructed to reflect changes in digital volume (9, 10). The rubber membrane of the tambour rises or falls slightly with change of volume of a digit enclosed in a rigid plastic cup or of the intradural contents. Movements of the tambour in turn stretch or relax slightly a strain gauge wire, thereby changing electrical resistance. The strain gauge forms part of a sensitive alternating current wheatstone bridge. Changes in bridge resistance are amplified and transmitted to a phase detector whose output actuates the pen of the ink recorder to produce traces.

Plethysmograms. Traces are made by the ink-writer on moving chart paper graduated with vertical curved lines, 1.0 cm. apart, and horizontal straight lines 1.0 mm. apart. Chart speed is 1.0 cm. per 10 seconds. Calibration marks (cal) indicate direction of increasing volume. The amplitude of the pulse volume chart excursion may be increased or decreased by electronic amplification (gain). A base-line pulse amplitude of 2 or 3 mm. is convenient for most observations. An increase or decrease of 0.5 mm. of pulse amplitude may be significant, but larger amplitude changes will be more easily de-

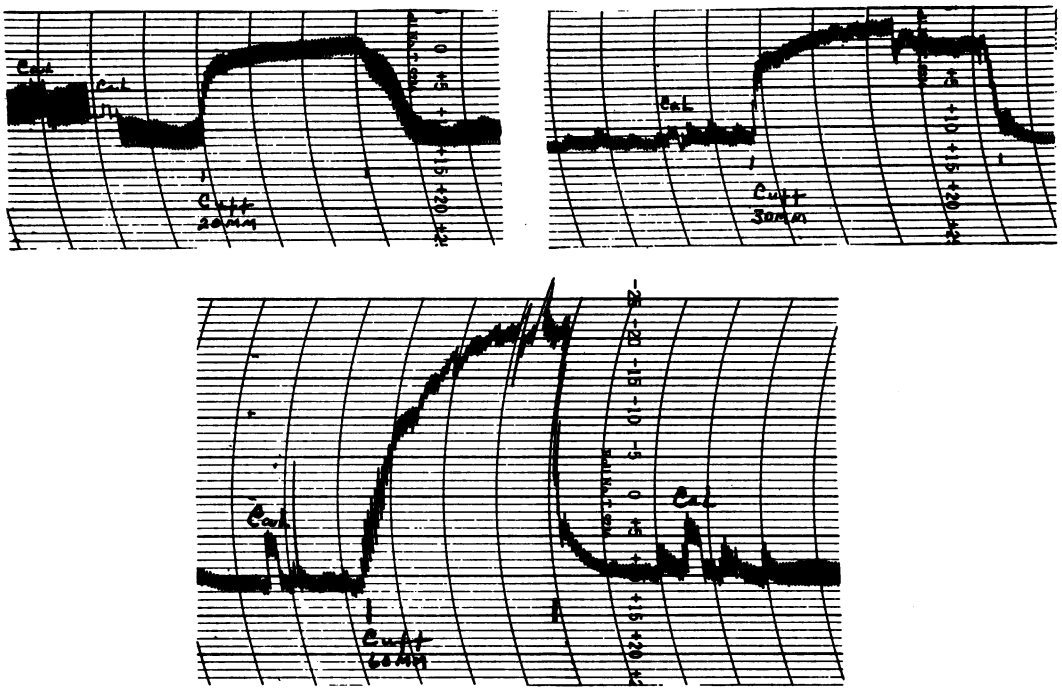

FIG. 2. EFFECT OF JUGULAR VEIN OCCLUSION ON INTRADURAL VOLUME AND PRESSURE

Jugular vein occlusion causes an increase of intradural volume and pressure, but has little effect upon pulse volume amplitude.

Manometric cuff pressure about neck	Spinal fluid pressure I.P.	Max. P.
20 mm.	90	160
30 mm.	100	180
60 mm.	100	260

tected. No quantitative significance can be attached to these arbitrary chart distance readings or changes.

Three types of volume displacement may be noted in cerebral plethysmogram traces:

1) Arterial pulse volume. Though many factors may influence pulse volume amplitude, the pulse volume excursion may be considered to be the resultant of intravascular pressure and volume forces tending to distend the pulsatile vascular field during systole as opposed by resistance of the walls of pulsating vessels to stretch. Vascular resistance to stretch will depend upon the anatomy of the vessel wall, its luminal size, and the ability of the vessels to constrict or relax. Change of pulse volume amplitude is the most sensitive plethysmographic response to cerebral vasomotor change.

2) Total, or intradural, volume deflection may represent change of brain, blood, or cerebrospinal fluid volume. Fortunately, intradural volume (and also arterial pulse amplitude) may remain constant over several hours of observation. Intradural volume is changed most rapidly and frequently by a change of volume of blood within or about the dural sac. Vasoconstriction is usually, though not always, accompanied by reduced total volume, and vasodilatation may cause an increase of intradural volume. The effect of increased or decreased cerebrospinal venous pressure is frequently seen, as the valveless veins of the cerebrospinal axis readily transmit pressure changes from the chest or abdomen in a retrograde fashion, or become engorged when the patient is placed in a head-down position. When position of the patient is little changed, intradural volume remains quite constant; hence, if changes of cerebrospinal fluid volume are occurring with any frequency, they are compensated by other volume changes, probably by the degree of venous engorgement.

3) Respiratory waves may or may not appear. Propagated along the cerebrospinal veins, their amplitude is affected by venous engorgement and by respiratory effort, in order of influence. By selection of patient position for optimum venous engorgement, these waves may be caused to disappear. The arterial pulse volume is little affected by cerebrospinal pressure changes or by degree of venous engorgement, within normal limits of cerebrospinal fluid pressure (Figure 2). Greater than normal levels of cerebrospinal fluid pressure might be expected to have an effect upon pulse volume amplitude.

Damping. Initially, "undamped" recordings of changes in intracranial volume were obtained in the operating room. To permit long-term observations, the vitallium button was fitted with a thin rubber diaphragm to minimize the chance of intracranial infection and to prevent escape of cerebrospinal fluid into the conducting tubing to the plethysmograph.

In practice, the damping effect of the rubber diaphragm has been of unexpected value. Pulse volume changes of the pulsating human brain are of much greater magnitude than are those originating from the invisibly pulsating digit. Without "damping" the amplitude of cerebral

TABLE I

Cerebral vasomotor, pulse and blood pressure responses to various stimuli

	No. patients	No. obs.	Pulse rate From	Pulse rate To	Blood pressure From	Blood pressure To	Intradural vol. change mm. +	Intradural vol. change mm. −	Pulse vol. change mm. C	Pulse vol. change mm. E
Cerebral vasodilatation										
CO_2 5%–O_2 95% inhalation	6	36	82	96	120/80	135/95	10		2	25
Voluntary apnea	10	14	72	84	120/80	125/85	2		1	10
Sleep	4	20	Variable				5–7		2	5
Alcohol, 250 ml. of 10% sol., I.V.	2	3	88	84	124/78	124/78	2		2	3
Priscoline®, 50 mg., I.V.	2	2					0	0	2	3
Papaverine, 100 mg., I.V.	2	2					5		1.5	2
Facial nerve activity	2	12	84	84	115/80	115/80	5		2	4
Sup. cerv. gang. block	2	4	82	90	115/75	115/75	4		2	3
Cerebral vasoconstriction										
Hyperventilation	10	14	94	94	115/80	125/85		5	3	2
Carotid occlusion	3	14	82	82	118/80	118/80		5	3	2
Cold constrictor test	3	10	76	86	120/80	135/85	3		3	1
Abdominal pain	2	8	84	88	110/70	115/80		3	2.5	2
Cutaneous pain	4	10	76	86	120/80	135/85		5	3	2
Apprehension	3	6					4		3	1
Anesthesia	4	5	Variable		120/80	120/80			5	2
Stim. of sup. cerv. gang.	4	15	84	100	120/80	130/85		5	2.5	1
Stim. of mid. cerv. gang.	4	15	84	100	120/80	130/85		5	3	2.5
Block of stellate gang.	6	8	76	84	115/70	115/70	0	0	2.5	2
No cerebral vasomotor change										
Nicotinic acid, 200 mg., I.V.	4	6					0	0	2	2
Mental test	1	5	72	80	115/75	120/75	0	0	2	2
Stim. of stellate gang.	4	15	84	100	120/85	130/85	0	0	3	3

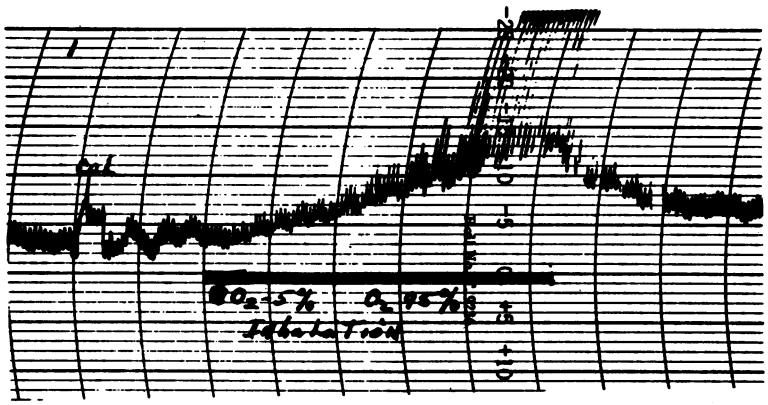

FIG. 3. EFFECT OF CARBON DIOXIDE INHALATION ON PLETHYSMOGRAPH RESPONSE

Pronounced cerebral vasodilator plethysmographic response occurs during inhalation of carbon dioxide 5 per cent-oxygen 95 per cent. There is a precipitous onset and cessation of pulse volume change during and at the termination of inhalation of the gas mixture.

pulse volume, an excursion on the chart of 3 to 6 cm. is obtained. Such a large amplitude is inconvenient for study of pulse volume change and precludes an increase of trace amplitude without being off the chart. A much less sensitive plethysmograph might be substituted for the ones used in these studies. However, it would seem preferable to use a highly sensitive plethysmograph with appropriate damping to permit detection of onset of volume change.

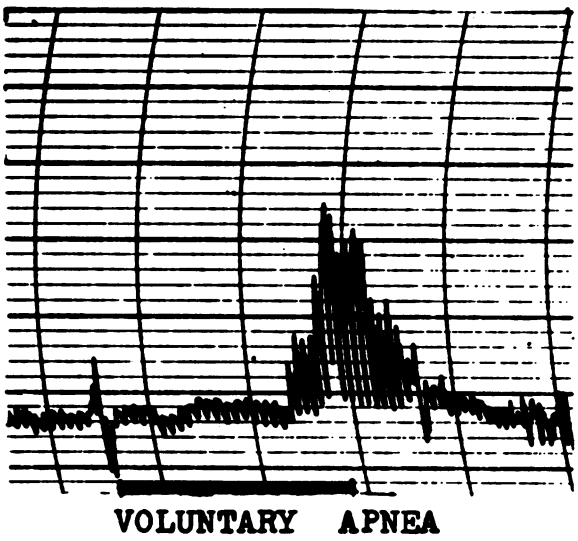

FIG. 4. EFFECT OF VOLUNTARY APNEA

Voluntary apnea (breath holding) for 22 seconds causes cerebral vasodilatation. There are no respiratory pulsations in this tracing (compare with Figure 2). Again sudden onset and cessation of vasodilatation is pronounced.

RESULTS

Cerebral vasomotor changes which occur in response to various stimuli or changing physiological states are summarized in Table I.

The number of patients studied and the number of observations (traces) for each test situation are listed. Brachial artery blood pressure, as obtained by ausculation, and pulse rate changes are recorded, and are the average of measurements taken during the total number of observations. The lowest pulse rate in any patient at any time was 64; the highest, 110. Blood pressure was within the range 90/60 to 140/100 mm. of mercury, including all test situations. Resting blood pressure was not greater than 120/80 in any patient.

The average deflection of the traces, indicating an increase or decrease of intradural (total) volume is tabulated as excursion, above (positive), or below (negative) the base line, in millimeters of chart distance.

An increase or decrease of amplitude of pulse volume is shown in the last column of Table I by comparison of the amplitude obtained during the experiment with the preceding and following control periods.

The degree of plethysmographic response varied from patient to patient and from test to test in the same patient, but the direction or type of response was consistent in this group of relatively young adults for the stimuli listed in Table I. Elderly persons, or the use of stimuli such as

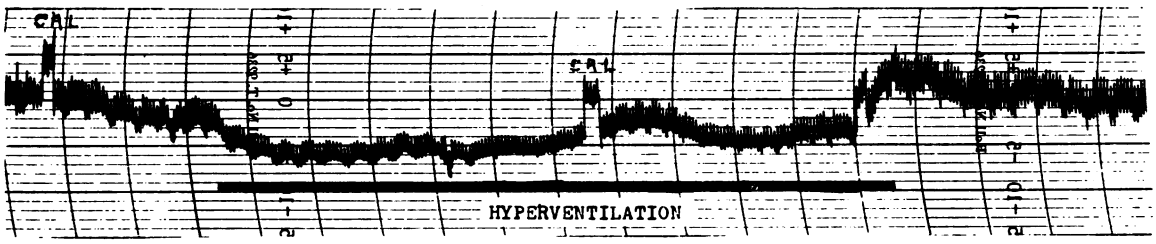

FIG. 5. EFFECT OF HYPERVENTILATION ON CEREBRAL PLETHYSMOGRAPHIC RESPONSE

Cerebral vasoconstriction occurs during hyperventilation, as indicated by reduced cerebral pulse and intradural volumes. Onset and termination of vasoconstriction are abrupt.

caffeine sodium benzoate, may show variability of response with respect to direction as well as degree.

Cerebral vasodilatation accompanies carbon dioxide 5 per cent-oxygen 95 per cent inhalation (Figure 3), voluntary apnea (Figure 4), sleep, sedative effect of intravenous alcohol, and intravenous administration of undiluted tolazoline hydrochloride (Priscoline®), 50 mg., and papaverine, 100 mg.

Cerebral vasoconstriction occurs with active hyperventilation (Figure 5), carotid occlusion, cold immersion or constrictor test, exacerbations of abdominal pain due to cancer, cutaneous painful stimulation, apprehension, and anesthesia.

Carotid artery occlusion causes reduced cerebral pulse volume and intradural volume as a "passive" vasoconstriction response to reduced blood flow and pressure.

Apprehension (fright) was produced by threatening the patient with immersion of the leg in ice water. The cold pressor test itself was carried out with reassurance and verbal support to gain maximum patient cooperation.

No cerebral vasomotor response was detected after intravenous administration of nicotinic acid, 0.2 Gm., or during performance of arithmetical or reading tests.

The cold pressor test causes reduced cerebral pulse volume, increase of pulse rate, and increased blood pressure. This pattern is consistent with cerebral vasoconstriction. Total, or intradural, volume usually increases, which might be considered vasodilatation. However, total volume increase in this instance is associated with rise of cerebrospinal venous and fluid pressure due to increased intra-abdominal and possibly intrathoracic pressure caused by obvious anxiety and muscular tension during the cold constrictor test.

Cerebral vasomotor activity following nerve stimulation. Cerebral vasodilatation accompanies facial nerve activity in the form of repetitive movement of the facial muscles (Figure 6). The patient carries out a series of "grimacing" movements, consisting of opening and closing the eyes, accompanied by alternately smiling and puckering lip movements. This obviates any apprehension which might be associated with electrical stimulation of the facial nerve. The dilator response is prompt and pronounced. Repetitive movements of the jaw muscles (fifth nerve), pharynx (ninth

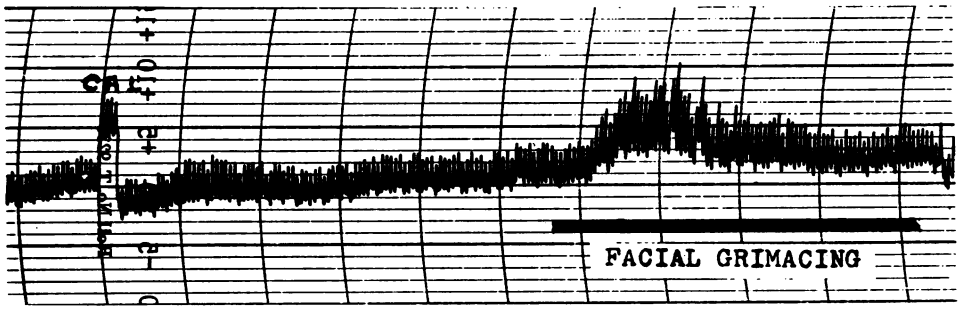

FIG. 6. CEREBRAL VASODILATATION IN RESPONSE TO VOLUNTARY REPETITIVE MOVEMENTS OF FACIAL MUSCLES

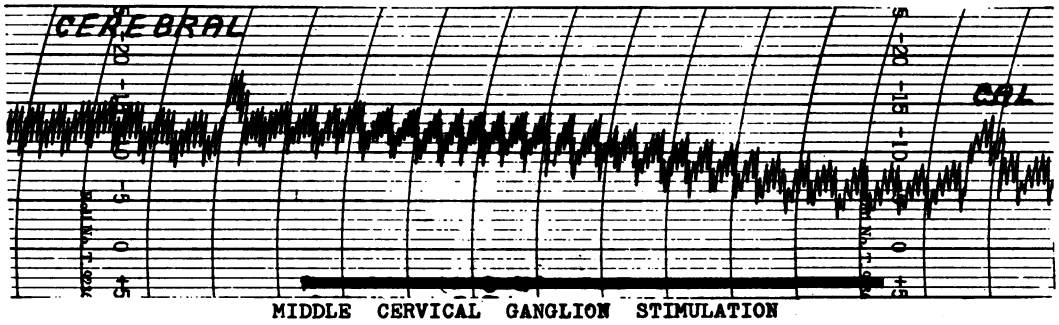

FIG. 7. EFFECT OF MIDDLE CERVICAL GANGLION STIMULATION ON CERVICAL PLETHYSMOGRAPHIC RESPONSE

Middle cervical ganglion stimulation results in cerebral vasoconstriction. Note that pulse volume decreases less strikingly than in Figure 8, but that intradural volume is decreased, and amplitude of respiratory wave increases, as with superior cervical ganglion stimulation.

and tenth nerves), or tongue (twelfth nerve) produce no change in the cerebral plethysmogram.

Cerebral vasoconstriction follows electrical stimulation of the middle or superior cervical sympathetic ganglion in anesthetized man (Figures 7 and 8). The response is more easily elicited from the superior cervical ganglion. Electrical stimulation of the stellate ganglion fails to alter the cerebral plethysmogram (Figure 9), though digital vasoconstriction is easily recorded.

Cerebral vasodilatation, indicated by increased cerebral pulse amplitude and intradural volume, accompanies procaine block of the superior cervical ganglion in the conscious subject (Figure 10). Stellate ganglion block causes a slight reduction in cerebral pulse volume without change of intradural volume (Figure 11). This is "passive vasoconstriction," as blood is shunted from the brain to the vasodilated arm. Elevation of the arm or placing the patient in a head-downward position partially restores the cerebral pulse volume toward the prestellate block amplitude.

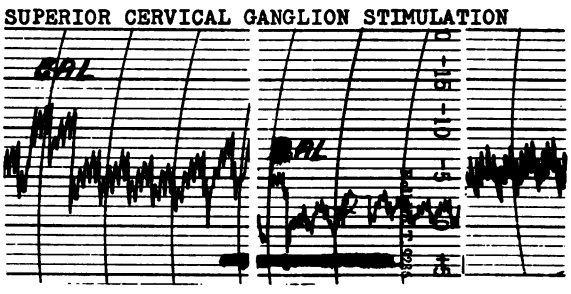

FIG. 8. EFFECT OF SUPERIOR CERVICAL GANGLION STIMULATION ON CEREBRAL PLETHYSMOGRAPHIC RESPONSE

Superior cervical ganglion stimulation causes cerebral vasoconstriction. Pulse volume is reduced from 2.5 mm. to 1 mm. One hundred and thirty second section of stimulation phase and 60 second section of recovery phase deleted to facilitate reproduction.

DISCUSSION

The plethysmographic method of recording regional vasomotor change has been adapted for the study of cerebral circulation. The plethysmographic responses may be compared with cerebral vasomotor changes which have been computed by investigators using the nitrous oxide technique for the determination of cerebral blood flow.[4] Cerebral vasodilatation has been indicated by both the cerebral plethysmographic technique and the nitrous oxide method to accompany inhalation of carbon dioxide 5 per cent-oxygen 95 per cent (11), sleep (12, 13), and administration of alcohol (14) or papavarine (15). Intravenous Priscoline® causes vasodilatation by plethysmography, but results in slightly reduced cerebral blood flow by the nitrous oxide method (16). Voluntary apnea has not been studied by the nitrous oxide technique. Undiluted Priscoline® intravenously and voluntary apnea (breath holding) have short pe-

[4] Though cerebral vasomotor activity may be indicated by the nitrous oxide method and by cerebral plethysmography, cerebral pulse volume change need have no relation to cerebral blood flow. For example, stellate ganglion stimulation increases pulse rate with unchanged pulse amplitude, a response which might be construed as indicating increased cerebral minute blood flow in the absence of cerebral vasomotor change.

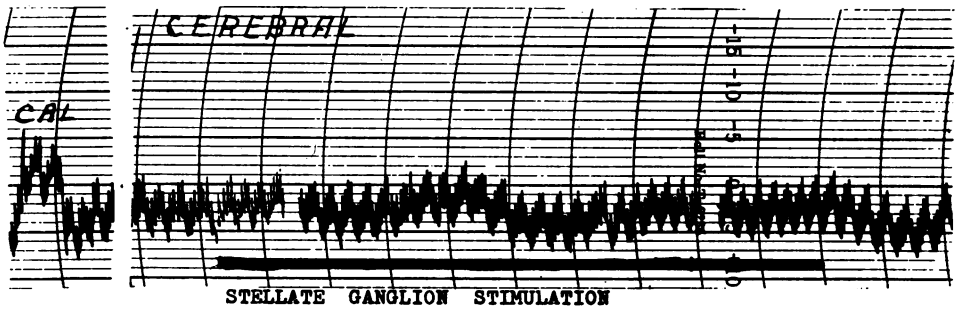

FIG. 9. EFFECT OF STELLATE GANGLION STIMULATION ON CEREBRAL PLETHYSMOGRAPHIC RESPONSE

Stellate ganglion stimulation does not change pulse or intradural volume, though increase in pulse rate may be noted.

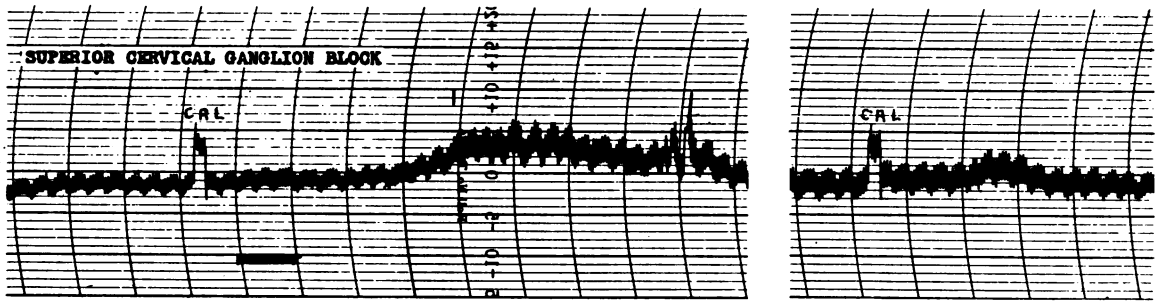

FIG. 10. PROCAINE BLOCK OF SUPERIOR CERVICAL GANGLION CAUSES CEREBRAL VASODILATATION

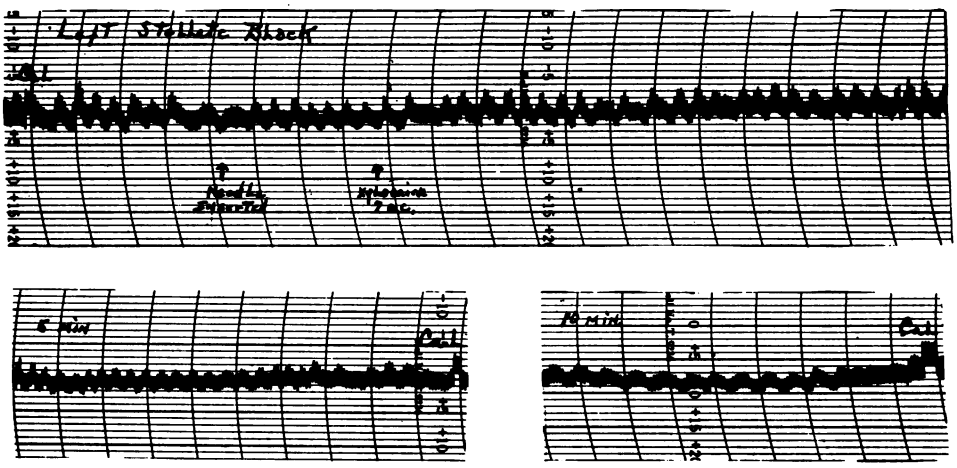

FIG. 11. EFFECT OF STELLATE GANGLION BLOCK ON CEREBRAL PLETHYSMOGRAPHIC RESPONSE

Stellate ganglion block consistently results in the reduced cerebral pulse volume of "passive" cerebral vasoconstriction, secondary to shunting of blood into vasodilated arm and face.

riods of activity, which would render their reaction more appropriate for plethysmographic study than for evaluation by the nitrous oxide method which required 5 or 10 minute periods of equilibration.

Cerebral vasoconstriction is indicated by plethysmographic and nitrous oxide methods to accompany active hyperventilation (17) and carotid artery occlusion (18). The short, though pronounced, constrictor response to the cold pressor

test, pain, or apprehension (fright), lends itself to plethysmographic recording, but is too brief for the nitrous oxide method to be conveniently applied.

Surgical anesthesia causes cerebral and digital vasoconstriction type of plethysmographic responses, whereas thiopental sodium (Pentothal®) anesthesia is accompanied by an increased cerebral blood flow (vasodilatation) as measured by the nitrous oxide technique (19). This discrepancy may be due to the complicated anesthesia mixture [thiopental sodium, nitrous oxide, oxygen, meperidine (Demerol®), and carbon dioxide absorption] administered to our subjects. Natural sleep and barbiturate- or alcohol-induced sleep are accompanied by cerebral vasodilation. Whatever the explanation may be, cerebral pulse volume amplitude is reduced by the anesthesia prior to cervical sympathetic nerve stimulation; hence further pulse volume reduction is more striking.

Mental activity and intravenous nicotinic acid have no effect upon the cerebral plethysmogram. Neither stimulus has been reported to alter cerebral blood flow (15, 20).

The neurogenic mechanisms which may influence cerebral circulation have been of particular interest to us. Activity of the facial nerve is associated with cerebral vasodilatation in the conscious human. The presence of a cerebral vasodilator mechanism involving the facial nerve was reported by Chorobski and Penfield from S. Cobb's laboratory, and the pathway of vasodilator fibers from the facial nerve to the carotid artery plexus was described (21). In the laboratory animal, pial vessel dilatation occurred during stimulation of the distal segment of the divided facial nerve. These investigators could detect no vasomotor response to electrical stimulation of the trigeminal, glossopharyngeal, or hypoglossal nerve, and we found no plethysmographic change during chewing, talking, or repetitive tongue movements.

Stimulation of the superior and middle cervical ganglia cause cerebral vasoconstriction and stellate ganglion stimulation is not accompanied by cerebral vasomotor activity in the anesthetized human. This result is similar to the observations of the effect of sympathetic stimulation upon pial vessel diameter in cat, dog and monkey, reported by Forbes, Wolff, and Cobb (5, 22–24). Cerebral vasodilatation in response to superior cervical ganglion block and slight reduction of cerebral pulse volume after stellate ganglion block occur as might be anticipated from the results of stimulation. Quantitative methods show no change or slight reduction of cerebral blood flow after stellate ganglion block (25).

From these observations, it is apparent that the concept that the outflow of all vasoconstrictor nerves is limited to the thoracic and lumbar anterior roots deserves reevaluation. Cerebral vasoconstrictor fibers are present in the cervical sympathetic nerves of animal and man, but do not traverse or involve the stellate ganglion.

Cerebral vasoconstrictor fibers pass to the superior cervical ganglia and adjacent cervical sympathetic chain from the vagus, as is found by stimulation of a segment of vagus nerve isolated at the base of the skull and in the lower part of the neck by double, procaine (4 per cent) block. Other possible routes of preganglionic fibers to the superior cervical ganglion are the ninth, eleventh and twelfth cranial and upper cervical nerves (26) and we are attempting to determine the presence or absence of vasoconstrictor fibers in these nerves. The sympathetic, vasoconstrictor system is composed of two divisions: *1*) cranial-cervical, and *2*) thoracolumbar.

Cerebral plethysmograms were obtained with surprising consistency and with little difficulty. It is our feeling that cerebral plethysmography is a useful technique for "scanning" a wide range of conditions which might produce a cerebrovascular reaction, and to permit recording of cerebral vasomotor changes of short duration.

SUMMARY

Cerebral vasomotor change has been recorded by an adaptation of the plethysmographic technique.

Increase in amplitude of cerebral pulse volume, accompanied by an increase of intradural volume, occurs in response to inhalation of a mixture of carbon dioxide 5 per cent-oxygen 95 per cent, voluntary apnea, sleep, voluntary facial nerve activity, superior cervical ganglion block, and the intravenous administration of alcohol and papaverine. We consider this to be cerebral vasodilatation.

Decrease of pulse volume amplitude with reduced intradural volume (cerebral vasoconstriction) is the plethysmographic response to hyperventilation, abdominal and cutaneous pain, and stimulation of the middle or superior cervical ganglion. The cold pressor test and apprehension cause reduced pulse amplitude and increased total volume. This is interpreted as cerebral vasoconstriction in the presence of increased cerebrospinal venous pressure due to muscular tension.

Administration of nicotinic acid, performance of mental tests, and electrical stimulation of the stellate ganglion do not affect cerebral vasomotor activity.

A craniocervical sympatheic system whose fibers appear to accompany the vagus nerve to the superior cervical ganglion has been shown to subserve cerebrovascular activity. This system is separate from the thoracolumbar sympathetic outflow.

ACKNOWLEDGMENTS

The authors wish to express their deep appreciation for the helpful and critical suggestions of Professor Harry Grundfest, designer of the plethysmograph used for this study.

The Austenal Laboratories, Inc., 224 East 39th Street, New York, New York, provided generous assistance in designing and casting of the vitallium trephine button.

REFERENCES

1. Flexner, L. B., Clark, J. H., and Weed, L. H. The elasticity of the dural sac and its contents. Amer. J. Physiol. 1932, **101**, 292.
2. Bridges, T. J., and Yahr, M. D. Digital vasomotor responses following nerve root stimulation. Arch. Neurol. Psychiat. (Chicago) 1955, **74**, 534.
3. Shepard, J. F. The Circulation and Sleep. New York, Macmillan Co., 1914.
4. Stevenson, L., Christensen, B. E., and Wortis, S. B. Some experiments in intracranial pressure in man during sleep and under certain other conditions. Amer. J. med. Sci. 1929, **178**, 663.
5. Forbes, H. S. Cerebral circulation. I. Observation and measurement of pial vessels. Arch. Neurol. Psychiat. (Chicago) 1928, **19**, 751.
6. Wolff, H. G., and Lennox, W. G. Cerebral circulation. XII. The effect on pial vessels of variations in the oxygen and carbon dioxide content of the blood. Arch. Neurol. Psychiat. (Chicago) 1930, **23**, 1097.
7. Gibbs, F. A., Maxwell, H., and Gibbs, E. L. Volume flow of blood through the human brain. Arch. Neurol. Psychiat. (Chicago) 1947, **57**, 137.
8. Kety, S. S., and Schmidt, C. F. The nitrous oxide method for the quantitative determination of cerebral blood flow in man: Theory, procedure and normal values. J. clin. Invest. 1948, **27**, 476.
9. Grundfest, H., Hay, J. J., and Feitelberg, S. Strain gage recorder for physiological volume, pressure and deformation measurements. Science 1945, **101**, 255.
10. Fiasconaro, J. E., Sherman, H., and Grundfest, H. Determination of clinical dental local anaesthesia by electrical stimulation and digital plethysmography. J. Amer. dent. Ass. 1957, **54**, 33.
11. Kety, S. S., and Schmidt, C. F. The effects of altered arterial tensions of carbon dioxide and oxygen on cerebral blood flow and cerebral oxygen consumption of normal young men. J. clin. Invest. 1948, **27**, 484.
12. Kety, S. S. Cerebral circulation *in* Symposium on Circulation and Homeostasis, United States Army, Medical Service Graduate School. Washington, D. C., U. S. Gov. Printing Office, 1953, pp. 191–194.
13. Mangold, R., Sokoloff, L., Therman, P. O., Conner, E. H., Kleinerman, J. I., and Kety, S. S. Cerebral blood flow and oxygen consumption during natural sleep. Fed. Proc. 1951, **10**, 89.
14. Battey, L. L., Heyman, A., and Patterson, J. L., Jr. Effects of ethyl alcohol on cerebral blood flow and metabolism. J. Amer. med. Ass. 1953, **152**, 6.
15. Shenkin, H. A. Effects of various drugs upon cerebral circulation and metabolism of man. J. appl. Physiol. 1951, **3**, 465.
16. Scheinberg, P., Blackburn, I., and Rich, M. The effects of intravenous priscoline on cerebral circulation and metabolism. J. clin. Invest. 1953, **32**, 125.
17. Kety, S. S., and Schmidt, C. F. The effects of active and passive hyperventilation on cerebral blood flow, cerebral oxygen consumption, cardiac output and blood pressure of normal men. J. clin. Invest. 1946, **25**, 107.
18. Shenkin, H. A., Cabieses, F., van den Noordt, G., Sayers, P., and Copperman, R. The hemodynamic effect of unilateral carotid ligation on the cerebral circulation of man. J. Neurosurg. 1951, **8**, 38.
19. Schmidt, C. F. The Cerebral Circulation in Health and Disease. Springfield, C. C Thomas, 1950.
20. Sokoloff, L. Relation of cerebral circulation and metabolism to mental activity *in* Neurochemistry, S. R. Korey and J. I. Nurnberger, Eds. New York, P. B. Hoeber, 1956, pp. 216–229.
21. Chorobski, J., and Penfield, W. Cerebral vasodilator nerves and their pathway from the medulla ob-

longata, with observations on pial and intracerebral vascular plexus. Arch. Neurol. Psychiat. (Chicago) 1932, **28**, 1257.

22. Forbes, H. S., and Wolff, H. G. Cerebral circulation. III. The vasomotor control of cerebral vessels. Arch. Neurol. Psychiat. (Chicago) 1928, **19**, 1057.
23. Cobb, S. The cerebral circulation. IX. The relationship of the cervical sympathetic nerves to cerebral blood supply. Amer. J. med. Sci. 1929, **178**, 528.
24. Forbes, H. S., and Cobb, S. S. Vasomotor control of cerebral vessels. Brain 1938, **61**, 221.
25. Harmel, M. H., Hafkenschiel, J. H., Austin, G. M., Crumpton, C. W., and Kety, S. S. The effect of bilateral stellate ganglion block on the cerebral circulation in normotensive and hypertensive patients. J. clin. Invest. 1949, **28**, 415.
26. Billingsley, P. R., and Ranson, S. W. Branches of the ganglion cervicale superius. J. comp. Neurol. 1918, **29**, 367.