Hemodynamic Effects of Cerebral Arteriovenous Aneurysms

By John M. Wallace, M.D., Blaine S. Nashold, Jr., M.D.,
and Anthony P. Slewka, M.D.

Peripheral arteriovenous aneurysms cause chronic increases in cardiac work load and heart failure may result. These phenomena have been widely observed in patients\(^1\)\(^–\)\(^5\) and in experimental animals.\(^6\)\(^–\)\(^7\) However, there still appears to be doubt concerning the cardiovascular effects of such aneurysms when they are located above the heart.\(^8\)\(^–\)\(^12\)

Hemodynamic measurements in eight patients with cerebral arteriovenous aneurysms have convinced us that such lesions can produce circulatory changes qualitatively similar in all respects to those caused by extracranial arteriovenous aneurysms. This report presents our observations.

Methods

The patients were men with an average age of 36 years. All underwent catheterization of the right heart. Blood samples for oxygen analysis were obtained from both jugular bulbs, the pulmonary artery, and the brachial artery. Cardiac output was calculated from the oxygen consumption and central arteriovenous oxygen difference and from dye-dilution curves with indocyanine green. Observations were made on patients in the supine position at rest and during the administration of isopropylnorepinephrine (isoproterenol), which was given at a rate of 2 ml./minute (1 \(\mu\)g/ml.) for 10 minutes before cardiac output was measured. Pressures in the brachial and pulmonary arteries were recorded continuously throughout the study. All patients underwent complete neurologic examinations and had electrocardiograms, chest and skull x-rays, and bilateral carotid arteriograms.

Results

Cardiovascular Data

Results in the group with cerebral arteriovenous aneurysms were compared with those obtained in eight hospitalized male patients who were similarly studied over the same period of time but were without cardiovascular disease. The mean age of this control group was 34 years.

Clinical Findings

Mean blood pressures in the control and aneurysm groups were 83.6 ± 8.4 mm. Hg and 83.9 ± 9.3 mm. Hg, respectively, the pulse pressures having been 53 and 54 mm. Hg. The resting pulse rate was 72 in the control group and 83 in the patients with aneurysm, this difference being of borderline significance (\(p = 0.05\)). Cardiothoracic ratios as determined from the chest x-rays were 0.44 ± 0.02 in the control and 0.43 ± 0.05 in the aneurysm patients. Electrocardiograms were normal in all except one control patient with right bundle-branch block. There was no evidence of cardiac enlargement by x-ray, electrocardiogram, or physical examination. The mean hemoglobin value was 14.5 ± 1.5 Gm. per cent in the control and 12.1 ± 1.7 Gm. per cent in the patients with cerebral arteriovenous aneurysm. This difference is significant (\(p = 0.01\)) and accounts for the greater oxygen content of brachial arterial blood found in the control subjects, which is shown in table 1. The anemia of the cerebral arteriovenous aneurysm group is not sufficient to account for the increased cardiac output\(^13\)\(^,\)\(^14\) but might possibly account for a portion of the high aneurysm blood flow\(^15\) reported below. The mean body surface area

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Table 1

Summary of Data in Eight Patients with Cerebral Arteriovenous Aneurysms and Eight Control Patients. Mean Values with Standard Deviations are given

<table>
<thead>
<tr>
<th></th>
<th>Resting</th>
<th>Control patients</th>
<th>Isoproterenol</th>
<th>Cerebral arteriovenous aneurysm patients</th>
<th>Isoproterenol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body surface area, M²</td>
<td>1.93 ± 0.33</td>
<td>1.77 ± 0.13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin, Gm. per cent</td>
<td>14.5 ± 1.5</td>
<td>12.1 ± 1.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean brachial artery pressure, mm. Hg</td>
<td>83.6 ± 8.4</td>
<td>85.6 ± 11.2</td>
<td>83.9 ± 9.3</td>
<td>86.1 ± 9.8</td>
<td></td>
</tr>
<tr>
<td>Mean pulmonary artery pressure, mm. Hg</td>
<td>14.5 ± 2.6</td>
<td>14.1 ± 2.9</td>
<td>11.4 ± 1.5</td>
<td>11.8 ± 2.3</td>
<td>109.0 ± 5.7</td>
</tr>
<tr>
<td>Pulse rates, beats/min.</td>
<td>72.0 ± 16.1</td>
<td>91.0 ± 11.4</td>
<td>83.0 ± 6.4</td>
<td>6.10 ± 0.77</td>
<td></td>
</tr>
<tr>
<td>Cardiac index, L/min./M²</td>
<td>2.82 ± 0.43</td>
<td>4.26 ± 0.98</td>
<td>4.40 ± 0.33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke volume, ml./stroke</td>
<td>75.5 ± 27.2</td>
<td>90.5 ± 11.7</td>
<td>94.0 ± 19.7</td>
<td>99.1 ± 7.3</td>
<td></td>
</tr>
<tr>
<td>Systemic vascular resistance, dyne sec. cm⁻⁵</td>
<td>1254 ± 57.5</td>
<td>857 ± 154.1</td>
<td>888 ± 107.2</td>
<td>653 ± 91.4</td>
<td></td>
</tr>
<tr>
<td>Pulmonary vascular resistance, dyne sec. cm⁻⁵</td>
<td>221 ± 60.5</td>
<td>144 ± 34.3</td>
<td>126 ± 11.5</td>
<td>87 ± 7.6</td>
<td></td>
</tr>
<tr>
<td>Oxygen consumption, ml./min./M²</td>
<td>127.2 ± 13.4</td>
<td>133.9 ± 19.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brachial artery O₂, vols. per cent</td>
<td>18.0 ± 2.12</td>
<td>16.1 ± 1.99</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary artery, O₂, vols. per cent</td>
<td>13.4 ± 1.96</td>
<td>13.1 ± 2.15</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mean circulation time, sec.</td>
<td>13.9 ± 1.0</td>
<td>10.8 ± 0.8</td>
<td>13.3 ± 2.4</td>
<td>10.8 ± 1.5</td>
<td></td>
</tr>
<tr>
<td>“Central” blood volume, ml./M²</td>
<td>609.5 ± 67.5</td>
<td>695.9 ± 137.4</td>
<td>941.0 ± 88.0</td>
<td>1064.0 ± 125.8</td>
<td></td>
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</table>
was also significantly greater in the control
(1.93 M.2) than in the aneurysm group
(1.77 M.2), p = 0.02. We interpret the smaller
body size and lower hemoglobin values of
the aneurysm patients to be a reflection of
the adverse effects of the intracranial
lesions on the general well-being. These
effects were striking, as is apparent from the
results of the neurologic examinations given
below. Oxygen data are given in table 2.
In seven of the eight patients the arterial-
jugular venous oxygen difference was de-
cesured on both sides regardless of the
location of the aneurysm. Patient C.T. with a
right-sided lesion had a normal left jugular
arteriovenous oxygen difference.

Hemodynamic Findings

These are summarized in table 1. Each
control patient was studied once, but five of
the eight patients with cerebral arteriove-
nous aneurysm were studied on two separate
occasions (three patients), three occasions
(one patient), or four occasions (one pa-
tient). The findings were similar in each
study in these cases, amply confirming the
abnormalities found. In all patients dye-dilu-
tion curves were obtained with indocyanine
green, injecting into the pulmonary artery and
sampling from the brachial artery. Curves
from the patients with cerebral arteriovenous
aneurysm had significantly shorter disap-
ppearance times, appearance to recirculation
times, and peak-to-peak times than curves
from the normal subjects, p values < 0.01
(table 3). The appearance times were not
significantly different, however, having been
8.5 seconds in the control and 8.3 seconds in
the cerebral aneurysm subjects (p = 0.60).
The above measurements were all made ac-

Table 2
Cerebral Arteriovenous Oxygen Differences in Patients with Cerebral Arteriovenous
Aneurysms

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>C.R.</td>
<td>Right</td>
<td>17.0</td>
<td>14.8</td>
<td>2.2</td>
</tr>
<tr>
<td>B.G.</td>
<td>Midline</td>
<td>17.6</td>
<td>16.5</td>
<td>1.1</td>
</tr>
<tr>
<td>R.A.</td>
<td>Right</td>
<td>16.8</td>
<td>16.6</td>
<td>0.2</td>
</tr>
<tr>
<td>E.A.</td>
<td>Midline</td>
<td>15.9</td>
<td>13.0</td>
<td>2.9</td>
</tr>
<tr>
<td>B.N.</td>
<td>Left</td>
<td>16.9</td>
<td>14.8</td>
<td>3.1</td>
</tr>
<tr>
<td>R.G.</td>
<td>Left</td>
<td>16.3</td>
<td>12.8</td>
<td>2.1</td>
</tr>
<tr>
<td>J.W.</td>
<td>Bilateral</td>
<td>16.3</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>C.T.</td>
<td>Right</td>
<td>17.1</td>
<td>15.5</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Table 3
Measurements in Seconds of Various Components of Indicator-Dilution Curves. Control
and Cerebral Arteriovenous Aneurysm (CAVA) Curves Differ More at Rest than during
Administration of Isoproterenol

<table>
<thead>
<tr>
<th>Patients at rest</th>
<th>Receiving isoproterenol</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>Appearance time</td>
<td>8.5</td>
</tr>
<tr>
<td>Disappearance time*</td>
<td>14.5</td>
</tr>
<tr>
<td>Appearance to recirculation time†</td>
<td>12.3</td>
</tr>
<tr>
<td>Peak-to-peak time‡</td>
<td>19.5</td>
</tr>
</tbody>
</table>

*Measured on semilog plot of original curve; peak of curve to baseline intercept of 
descending slope.
†Measured on original curve; first appearance to first apparent recirculation of dye.
‡Measured on original curve; peak of first circulation to peak of recirculation.
CEREBRAL ARTERIOVENOUS ANEURYSMS

According to the description of Schreiner et al., \(^{16}\) and the curves from our cerebral aneurysm patients resemble those found by him in patients with peripheral arteriovenous aneurysm. The highest resting cardiac index in the control group was 3.3 L./min./M.\(^2\) while the lowest in the aneurysm group was 4.1 L./min./M.\(^2\).

In six of the patients aneurysm blood flow at rest was estimated by comparing data between the two groups of subjects. This was done in two ways: (1) with data obtained from dye curves. The average cardiac index of the aneurysm subjects was 4.4 L./min./M.\(^2\) and that of the control group was 64 per cent of this figure or 2.8 L./min./M.\(^2\). The average cardiac output of the aneurysm patients was 7,788 ml./min. (body surface area times cardiac index) and 64 per cent, or 4,984 ml./min., would have been present without the aneurysms. Aneurysm flow = 7,788 ml. - 4,984 ml., or 2,804 ml. (2) with oxygen consumptions and brachial-pulmonary arterial venous oxygen differences. The difference in the control group was 4.6 vol. per cent and that in the aneurysm group was 3.0 vol. per cent. The decrease in arteriovenous oxygen difference caused by the aneurysms was 35 per cent. The over-all oxygen consumption in this group was 238 ml./min. which, divided by 3.0 vol. per cent, gives a cardiac output of 7,930 ml./min. Aneurysm flow = 35 per cent of 7,930, or 2,780 ml.

Isoproterenol was given to all control subjects and to five of the eight patients with cerebral aneurysm. Aneurysm flow was estimated to be 3,260 ml./min. or 30 per cent of the total cardiac output at that time rather than the 36 per cent found at rest. Conversely, the proportion of the total output perfusing the body tissues was 70 per cent with isoproterenol rather than 64 per cent as at rest. These changes suggest that the aneurysms received relatively less blood when resistance in the general circulation was lowered by isoproterenol to compete more favorably for the available output. Further support for this view is provided by the dye curves in the two groups, which were more nearly alike with isoproterenol than they were at rest (table 3). This would not be expected if aneurysm flow had been increased in the same proportion as systemic flow. In the control patients the resting cardiac index of 2.82 L./min./M.\(^2\) was increased to 4.26 L./min./M.\(^2\) by the isoproterenol, a figure not far different from the resting value of 4.40 L./min./M.\(^2\) in the aneurysm group. In the cerebral aneurysm patients, the index rose from 4.40 to 6.10 L./min./M.\(^2\).

Mean circulation times and "central" blood volumes were calculated as detailed by Doyle and co-workers.\(^{17}\) The values for mean circulation time (table 1) and appearance time (table 3) were similar in the two groups at rest and with isoproterenol. In three control and three aneurysm patients the general blood volume was estimated with use of the blue dye T-1824 (table 4). It was increased in the cerebral aneurysm cases, as was the

Table 4

<table>
<thead>
<tr>
<th>General Blood Volume (GBV) and &quot;Central&quot; Blood Volume (CBV) in Three Patients with Aneurysms and Three Control Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Control patients</td>
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<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Mean</td>
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<tr>
<td>CAVA patients</td>
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<tr>
<td></td>
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<td></td>
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<tr>
<td>Mean</td>
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ratio of "central" blood volumes to general blood volumes.

**Neurologic Findings**

All patients with cerebral arteriovenous aneurysms complained of severe headaches, the site of the headache and the location of the lesion coinciding in three of them. One patient had retro-orbital headaches on the side opposite the lesion. Another, with an aneurysm involving the posterior parietal and cerebellar areas, had tic-like pain over the distribution of the trigeminal nerve. All eight patients had convulsive seizures, which were focal in three and generalized in five. Slowly progressive mental deterioration was noted in four patients who had large intracranial aneurysms coupled with dilatation and pulsation of arteries over the scalp. Focal neurologic signs were present in every case, six having hemiparesis and two monoparesis. Visual-field defects were noted in two cases and severe cerebellar signs in one. Intracranial bruits were heard in five patients, a carotid bruit in one. Manual compression of the carotid bulb diminished the bruits and in one case relieved the headache.

Subarachnoid hemorrhage was an initial symptom in four cases and was often recurrent. One patient had multiple "minor" episodes of subarachnoid bleeding over a single 10-day period. The only accompanying signs were slight fluctuations in mental awareness and nuchal rigidity. The intermittent nature of the bleeding was confirmed by repeated lumbar punctures. This suggested that these lesions may produce small and relatively silent hemorrhages which are difficult to detect but which result in progressive pathologic changes.

Repeated cerebral arteriograms were performed. Two of the patients had other vascular anomalies in addition to the main lesions. A saccular aneurysm was present in one case and an unusual pattern of the anterior cerebral artery in the other. The larger lesions were invariably fed by multiple vessels which frequently originated on both sides of the intracranial circulation. In two instances there was also extensive involvement of the extracranial arteries and veins. Evidence of bilateral venous drainage of the aneurysm could usually be seen on the arteriograms as well as in the elevated oxygen content of jugular venous blood (table 2). Electroencephalograms showed generalized abnormalities in the six cases in which they were obtained.

Despite the usual severity of the neurologic disease we have seen an additional case which demonstrates that an immense cerebral arteriovenous aneurysm may be present for at least 10 years without causing neurologic or cardiac symptoms, neurologic signs or electroencephalographic abnormalities. The patient, S.J.F., is a 17-year-old boy who was first taken to a doctor at the age of 7 years because of a "passing-out spell." He never again had such an episode or any other symptoms but was found then to have a heart murmur. He has seen doctors periodically ever since, purely to have the murmur followed. Repeated chest x-rays and electrocardiograms during the past 7 years were reported to be "suggestive" of cardiac enlargement and left ventricular hypertrophy. The present examination revealed evidence of a hyperdynamic heart with bruits over the right side of the head and neck and a systolic murmur over the precordium. The cardiac output was 12.77 L./min., cardiac index 6.65 L./min./M.², stroke volume 177 ml., stroke index 92 ml./stroke/M.², heart rate 72, and body surface area 1.92 M.². Assuming that his cardiac index would be 3.0 L./min./M.² without the aneurysm, the excess cardiac index of 3.65 L./min./M.² multiplied by the body surface area of 1.92 M.² would give an estimated flow of about 7 L./min. through the aneurysm. The right jugular arteriovenous oxygen difference was 0.67 vol. per cent. An electroencephalogram and a complete neurologic examination were entirely normal. The current chest x-ray, as well as the earliest one available to us, taken when the patient was 10 years old, showed definite cardiac enlargement. Carotid arteriograms are shown in figure 1.

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Discussion

Large cerebral arteriovenous aneurysms produce hemodynamic abnormalities qualitatively similar to other arteriovenous aneurysms. This was evidenced in our cases by increases in cardiac index, stroke volume and pulse rate, narrowed central arteriovenous oxygen differences, diminished systemic and pulmonary vascular resistances and, in the three subjects tested, increased general blood volumes. The absence of significant hemodynamic abnormalities in other reported cases is probably due to the relatively small size of the lesions encountered.

Despite the rather impressive findings in our patients, none of them had congestive heart failure, a complication that appears to be rather infrequent with cerebral arteriovenous aneurysm. This may be due in part to the location of the lesions above the heart, which might favor a lower shunt flow in the upright posture. Freeman et al. showed with experimental femoral arteriovenous fistulas in dogs that fistula flow was less when the animals were tilted to place the lesions above the heart. The drop in femoral artery pressure was greater than that in distal inferior caval pressure, thus reducing the pressure gradient and lowering flow. If similar changes occurred on standing in patients with cerebral aneurysm, fistula flow and cardiac effects during the waking hours would be less than those expected from recumbent studies.

Other factors might also lessen the cardiac effects of cerebral compared with peripheral arteriovenous aneurysms. The isoproterenol data suggest that elevations in cardiac output per se increase the flow through cerebral aneurysms less than would be expected on the basis of the output itself. This might not be true of peripheral aneurysms especially if the lesions involve arteries supplying exercising muscle, provided the exercise itself does not occlude the aneurysm. Exercise may in this way contribute more to the continuing enlargement of peripheral than cerebral arteriovenous aneurysm. It also appears possible that the intracranial location might retard enlargement of the aneurysms and growth of collateral channels, both of which may be factors in the progressive cardiac effects of other arteriovenous aneurysms. The study of Hook and Johanson might be interpreted to support this view. They followed 13 cerebral arteriovenous aneurysms in 12 patients for periods of 20 months to 21 years. During the various periods of observation only three of the aneurysms increased appreciably in size, five others showed relatively small increases, and no changes were
noted in the remaining five. Finally, most of our patients had been forced by their severe neurologic symptoms to lead sedentary lives. This may have retarded the development of cardiac failure.

Nevertheless, cardiomegaly and heart failure have been reported in some cases. This complication may develop more readily in newborns and infants, possibly due to accentuation of aneurysm flow and cardiac effects by a head-down fetal attitude in utero.

In the patients with cerebral arteriovenous aneurysm the mean circulation time to the brachial artery was normal (table 1) as was the appearance time (table 3). Similarly, in a recent study of peripheral arteriovenous aneurysm the published dye curves indicate that appearance times in vessels not feeding the aneurysm were nearly normal. Elevated "central" blood volumes will be calculated in patients with elevated cardiac output if a normal mean circulation time is used, as in our cases. However, if the mean circulation time to the aneurysm, which was undoubtedly short, had been used in the calculation, a different and smaller volume would have been determined. Such volumes should not be called the "central" blood volume. These cases are analogous to experiments in which high velocities of flow are produced locally and cardiac output is elevated by reactive hyperemia or exercise of one area of the body. If mean circulation time is determined in an artery elsewhere with relatively slowly moving blood, high "central" blood volumes are calculated. If the mean circulation time of the rapidly moving stream itself is used, low "central" blood volumes result. In contrast, when the over-all velocity of flow is increased along with the cardiac output, as in our subjects receiving isoproterenol, significant changes in the calculated volume do not occur. This suggests that when cardiac output changes, if changes in flow velocities are uniform throughout the aortic distribution the estimated "central" volume will be little affected. In recent years discussions of central blood volume have

Figure 2
Arteriovenous aneurysm of left frontoparietal area in patient C. R. Partial resection of this lesion relieved his intractable headaches.

shifted away from the patient with heart failure, a large heart and a (presumably) generalized decrease in circulatory velocity to the subject whose heart is normal but who has a circulatory bed with an abnormally low resistance somewhere in the body. The more classic concept of the central blood volume may not be entirely invalid in the former case.

The progressive mental and neurologic deterioration in our cases might be explained both by a diminished blood flow to brain tissue and by the repeated occurrence of small subarachnoid hemorrhages. Although at the present time it seems generally agreed that curative surgery is too hazardous to attempt with large cerebral arteriovenous aneurysms, palliative procedures are sometimes successful. Figure 2 illustrates the lesion in one of our patients, which was partially removed because of severe and intractable headache. The symptom was ameliorated. More definitive surgery may soon become possible through development of the technics of temporary cardiac arrest and deep hypothermia.

Summary
The hemodynamic alterations produced by large cerebral arteriovenous aneurysms are qualitatively similar to those caused by ar-
Cerebral arteriovenous aneurysms elsewhere in the body. Congestive heart failure was not observed in our eight patients; it appears to be unusual in adult cases.

By comparing cardiac outputs with a control group the mean aneurysm blood flow in six patients was estimated to be 2,804 ml per minute at rest. Isoproterenol increased cardiac output relatively more than the estimated aneurysm flow.

Implications of the present data with respect to the concept of “central” blood volume are discussed.

Progressive mental and neurologic deterioration is the rule with large cerebral arteriovenous aneurysms. Repeated bleeding episodes, which may not be obvious clinically, appear to be partially responsible.

References
Residuary Problems

The theory of deficiency disease introduced to pathology a principle as wholly new as did the microbe. Like that it involved an immense change of scale and the demonstration that what might be called the naked-eye view of the constituents of the living body was inadequate. But the new principle was of a different kind from that necessary to found bacteriology. No pursuit of the old climatic and sanitary theories of disease with whatever thoroughness could have led to the doctrine of microbic pathology without the revolutionary inquiries of Pasteur which disclosed an unsuspected mode of existence. On the other hand dietetics failed to disclose the vitamins because inquiries had not been exact and exhaustive enough. The problem of the vitamins was in fact a residuary problem. The dietetic field had been harvested and even gleaned except for what seemed a few inconspicuous remnants that for a long time it was agreed to ignore. Yet it was these very residues that were to yield the richest harvest of all. This peculiarity makes the solution of the vitamin problem of special interest to the student of scientific method. . . .

The economic value of working-over rejected residues has often been proved by the mining engineer and the metallurgist. . . .

These lessons may usefully serve as metaphorical injunctions in the prosecution of scientific research itself. Time after time it has been shown in the latter activity that the humblest residual phenomena have concealed great secrets.—The Collected Papers of Wilfred Trotter, F.R.S. London, Oxford University Press, 1946, p. 130.
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