Influence of Anatomic Origin on Intracranial Distribution of Micro-Emboli in the Baboon


SUMMARY The purpose of this study was to investigate whether the anatomic origin of micro-emboli influences their intracranial distribution. In twenty-two baboons, we examined the distribution of 99-Tc-radioulminated aggregates (5 to 40 microns in size) after injection into the circulation at the left atrium (LA), carotid trifurcation (CA), and anterior and posterior common carotid artery (CC1). In a further subgroup, the emboli were introduced at the carotid trifurcation with the contralateral carotid artery ligated (CA + L). The results of this study demonstrated that aggregates introduced at the carotid artery lodged preferentially in the ophthalmic (p = 0.032) and middle cerebral artery territories (p = 0.016). If the contralateral common carotid artery was ligated, however, more aggregates were found in the ipsi- and contralateral anterior cerebral artery territories (p = 0.01, p = 0.003). Aggregates introduced into the cardiac circulation were equally distributed throughout the brain. This experimental model determined patterns of flow that may be analogous to the human situation where unilateral or bilateral carotid stenosis or stenosis with contralateral occlusion has occurred or embolus from cardiac source has occurred. The results do not imply that the 40 micron microaggregates do cause TIA. These experimental findings support clinical observations that cardiac lesions may cause transient ischemic attacks (TIA) anywhere in the brain. In contrast, those of carotid artery origin cause predominantly middle cerebral or ophthalmic artery territory TIAs unless the contralateral carotid artery is severely stenosed or occluded.

There is good evidence that transient ischemic attacks (TIA) in the internal carotid, vertebrobasilar and ophthalmic artery territories may be caused by micro-emboli arising from the extracranial circulation.\(^1\) Although it has been recognized for some time that the carotid arteries\(^2\) or heart\(^3\)^{4} may be the source of origin of such emboli,\(^5\) relatively little has been documented about the intracerebral distribution of emboli arising selectively from either of these two anatomic sites.\(^5\) We are unaware of good experimental data explaining why TIAs of carotid artery origin occur predominantly in the ophthalmic and middle cerebral artery territories of the carotid territory blood supply and, in particular, in Broca's speech area. This observation is contrary to the expected distribution of such events in both the anterior cerebral and middle cerebral artery territories on anatomic grounds. This predilection for the middle cerebral and ophthalmic artery territories may be due to: 1. Anatomical arrangement of cerebral arteries. 2. A greater blood supply or streaming of blood to the middle cerebral artery territory. 3. A larger number of apparently silent TIAs in areas supplied by arteries other than the ophthalmic or middle cerebral arteries. If a purely anatomic explanation for this phenomenon exists, then it could be surmised that TIAs caused by aggregates arising from the left atrium would result in TIAs throughout the brain; whereas, those arising in the carotid would be expected to be distributed equally in the ophthalmic, anterior and middle cerebral artery territories.

We are unaware of experimental studies that have investigated the relationship of the anatomic origin of aggregates to their subsequent distribution within the intracranial circulation.

A method of embolizing the middle cerebral artery was described by Millikan in 1955.\(^6\) Since then, many methods of embolisation, including the use of microspheres, have been reported.\(^7\)^{12} We have previously demonstrated that either macro or micro-emboli (blood clot, air, collagen, arachidonic acid or adenosine-di-phosphate (ADP)) all produce focal cerebral ischemia resulting in detectable changes both on electroencephalogram (EEG) and post mortem pathological studies.\(^1\)^{4}

The aim of this study was to determine the influence of the anatomic origin of micro-emboli on the resultant pattern of flow to the brain. A further objective was to establish whether micro-emboli, originating from different sites in the carotid artery, would still lodge selectively in the middle cerebral artery territory if the contralateral carotid artery was occluded. The clinical value of such results might help to differentiate patients with cardiac disease from those with carotid artery disease and determine how contralateral carotid artery occlusion influences the distribution of micro-emboli.

Materials and Methods

We chose the Chacma baboon (Papio Ursinus) as our experimental species to study this problem. Pri-
mates have an extra- and intra-cranial blood supply similar to man. The branching pattern of the cervical carotid artery is almost identical to that of man with the exception that two major branches of the external carotid artery arise close to the internal carotid artery origin. Similarly, the branching pattern of the internal carotid artery is identical to man with the sole exception that both anterior cerebral arteries unite to form a single pericallosal artery which enters the interhemispheric fissure, from where it gives off cortical branches to both hemispheres. In dogs and cats the intracranial vascular anatomy differs significantly from man in that an extensive system of anastomoses exists between the carotid artery and the maxillary and anterior cerebral arteries. In addition, the posterior cerebral artery is the major continuation of the internal carotid artery. For these reasons, any conclusions drawn on the basis of experimental work in these species should be viewed with caution when extrapolating results with reference to man. We deemed the baboon an appropriate animal for the study of the pattern of flow of microemboli (5 to 40 microns in size), injected into the left atrium or common carotid, with or without occlusion of the ipsilateral external carotid artery and contralateral carotid artery. This model merely aimed to determine patterns of flow that might be analogous to the human situation. The data does not imply that 40 micron microaggregates cause TIAs.

Twenty-two adult baboons of both sexes and weight 15.6 to 24 kg, were immobilized with ketamine (2-3 mg/kg) and anesthesia was maintained with intermittent pentobarbitone sodium (Sagatal, Maybaker) by intravenous infusion. Four groups of animals were studied. All animals were sacrificed at the completion of the experiments.

**Group One**

The left atrial group (LA) consisted of six animals. In each of these animals a thoracotomy was performed and a 21G Jelco cannula was inserted into the left atrium. One thousand microcuries of 99-Technetium labelled human albumin aggregates (5-40 microns in size) were introduced into the cardiac circulation over a 10 second interval by injection through the left atrial cannula.

**Group Two**

The second group of seven animals constituted the carotid artery injection group (CA). In each animal the carotid artery trifurcation was surgically exposed. The lingual branch of the external carotid artery was cannulated with a 21G Jelco cannula and the cannula ligated in place with the tip of the cannula flush with the carotid bulb of the carotid artery. The third branch of the trifurcation, the maxillary artery, was then ligated. Figure 1 demonstrates the method used to prepare the cannula in the external carotid artery. Five hundred microcuries of the same labelled aggregates were then injected into the carotid bulb circulation via the cannula over a period of 10 seconds.

**Group Three**

In the third group of baboons the same procedure was adopted as in group 2 but, in addition, the contralateral common carotid artery was ligated prior to the injection of the aggregates (CA + L, N = 4).

**Group Four**

In the fourth group of animals, the aggregates were injected into the common carotid artery through a size 23G needle (CCI; N = 5). The procedure used was the same as in group 2 with the exception that the external carotid artery was not cannulated. Instead, after ligation of all the branches of the external carotid artery (in the same way as the group 2 animals), the aggregates were then injected into the anterior aspect of the common carotid either 2 cm below the external carotid artery (N = 3) or into the posterior aspect of the common carotid 5 cm below the origin of the external carotid artery (N = 2).

In one animal the branches of the common carotid artery, with the exception of the ICA, were ligated and the aggregates injected via the left atrium as described.

In each of the four groups, 10 minutes after the injection, the respective animals were killed with a 400 mg bolus of pentobarbitone sodium (Euthana, Centaur Lab). The brains and eyes were then removed from the skull by removal of the calvarium. The brain was divided through the corpus callosum and brain stem into two equal halves and each hemisphere was then sectioned in a sagittal plane into two further equally thick portions. The four longitudinal brain sections and eyes were then scanned under a gamma scintillation camera and photographs taken of the distribution of the emission. Thereafter, one specimen of 0.5 g
to 1 g wet weight was taken from each of the following territories on the same side of the injection; the anterior frontal lobe, anterior temporal lobe, medial motor, sensory and parietal cortex, posterior occipital cortex, lateral hemispheric cortex (Broca's speech area), cerebellum, brain stem, thalamus, putamen, insula, operculum, and posterior hemisphere of the eye. Specimens were also taken from the contralateral frontal, temporal, lateral, and occipital cortex, as well as from the cerebellum and brain stem. Each specimen was then weighed and inserted into a capped, polyethylene tube and the emission count was obtained for each specimen in a gamma scintillation counter and expressed as counts per minute/g of tissue. After subtraction of the background counts of each specimen, the count per minute per gram of tissue for each specimen was calculated as a relative percentage of the total count for all the specimens of that animal.

Statistical analyses were performed on the data obtained from the emission counts using the nonparametric Wilcoxon two tailed test for paired comparisons and the Mann-Whitney U test for independent groups. The qualitative data obtained from the scintillation camera photographs was not statistically analyzed but a representative photograph is illustrated in the results.

Results

In group 1, the LA group (fig. 2), the aggregates were equally distributed to all brain specimens studied (range 4.4 to 8.5%, p not significant).

In group 2, the CA group (fig. 3), areas supplied by the MCA alone had uniformly high counts (lateral cortex 11.2%, operculum 9.6%, insula 11% and putamen 12.8%). The watershed areas between the middle cerebral and anterior cerebral artery territory (motor cortex 3.6%, sensory cortex 2.8%), as well as the watershed area between anterior, middle and posterior cerebral artery territory (parietal cortex 3.8%) all had intermediate counts. Posterior cerebral and vertebral artery supplied territories (occipital cortex 0.2%, cerebellum 0.8% and brain stem 0.7%) had low counts, as did the territory purely supplied by the anterior cerebral artery (anterior frontal cortex 2.9%). The posterior eye, supplied by the ophthalmic artery, had a particularly high mean count (23.2%).

When the data obtained in group 2 (CA) were subjected to statistical analyses the following results were found (fig. 4). The middle cerebral artery territory tissue yielded significantly higher counts when compared to the posterior cerebral artery territory tissue (lateral cortex compared to occiput p = 0.016) or the anterior cerebral artery territory (lateral cortex compared to anterior frontal lobe p = 0.016). Ophthalmic artery territory tissue counts were greater than the anterior cerebral artery territory tissue (eye compared to frontal lobe p = 0.032). There was no significant difference between middle cerebral artery and ophthalmic artery territories (lateral cortex compared to posterior eye p = 0.16).

In a comparison between the results obtained in groups 1 and 2 (LA and CA), certain statistical differences were noted. The CA group had a significantly higher count than LA in the middle cerebral artery territory (p = 0.008), significantly lower count in the vertebral artery (p = 0.008) and posterior cerebral artery (p = 0.003) areas and no difference in the ophthalmic artery (p = 0.18) artery territory. Figure 5 shows a gamma-camera photograph of brain slices of groups LA and CA.

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![Figure 2](image-url)  
*Figure 2. Distribution of aggregates injected into the left atrium.*

![Figure 3](image-url)  
*Figure 3. Distribution of aggregates injected into the carotid artery.*

![Figure 4](image-url)  
*Figure 4. Comparison of territories supplied by various arteries. ACA = anterior cerebral artery, MCA = middle cerebral artery, PCA = posterior cerebral artery.*
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scans are of the Left Atrial Group; Lower two of Carotid Artery
gates in the area of the middle cerebral artery in the CA group.

FIOURE 5. Gamma-camera scan photographs. Upper two
scans are of the Left Atrial Group; Lower two of Carotid Artery
Group. A = Anterior, P = Posterior, left column scans are of
the lateral hemisphere cortex, right column are of the medial
hemisphere portion with the cerebellum and brain stem inferior-
ly. Note the denser emission of the radioactive albumin aggre-
gates in the area of the middle cerebral artery in the CA group.
between the middle cerebral and anterior cerebral ar-
tery territory counts was abolished (p = 0.43). Fur-
thermore, the number of aggregates in group 3 in the
frontal cortex was significantly greater than in the CA
(group 2) (p = 0.01). The number of aggregates
that had crossed over to the contralateral frontal cortex
was also greater as compared to the CA group (p = 0.003).
The number of counts in the eye, however,
remained significantly greater (p = 0.034) than the
anterior cerebral artery territory as observed in group 2
(CA).
The results obtained in group 4, the CCI group,
were essentially no different from those of the CA
group. In the five animals studied, there was no sig-
nificant difference from results obtained in the CA
group (group 2) irrespective of whether the aggregates
were injected into the anterior or posterior common
carotid artery. As in the CA group, the counts in the
middle cerebral territory were significantly higher than
those in the anterior cerebral artery territory (p = 0.02).
The number of aggregates was also greater in
the eye compared with the anterior cerebral artery terri-
(ty (p = 0.022).

Discussion

This study in the baboon supports the hypothesis that
microaggregates of cardiac origin are distributed
equally throughout the brain. Secondly, microaggre-
gates originating from the common carotid or bifurca-
tion of the carotid artery have been noted to lodge
selectively in the territory of the middle cerebral and
ophthalmic arteries. However, if the contralateral ca-
rotid artery is occluded, although the number of emboli
occurring to the eye will remain high, the difference
between the middle cerebral artery and anterior cere-
bral artery territories tends to be lost. Under such cir-
cumstances, a greater number of emboli will lodge in
the contralateral frontal cortex.
The finding that aggregates of cardiac origin are
distributed evenly in the brain can be expected on

anatomical grounds. Radioactive microspheres inject-
ed into the left atrium, which then cross two cardiac
valves, are well mixed with the ejected blood from the
heart, and thus, selective streaming of aggregates to
the vertebralbasilar or carotid artery systems is unlikely
to occur.
De Bono and Warlow5 showed that in patients with
TIA or amaurosis fugax 32% had cardiac abnormalities,
32% had arrhythmias and only 37% of patients
with carotid territory events had significant carotid
arterial lesions. Furthermore, structural cardiac lesions
causd a greater proportion of non-carotid artery terri-
tory TIA/amaurosis fugax than carotid territory lesions
(p < 0.05). These observations are in agreement with
the results of the present study.
The equal distribution of aggregates of carotid ori-
within the opthalmic artery territory and middle
cerebral artery territory compares well with the fre-
cently observed clinical association of TIA and
amaurosis fugax in patients with carotid artery sternotic
lesions. The results of this study are similarly in keep-
ing with the clinically observed occurrences of TIAs in
patients with carotid artery stenosis. The exact hemo-
dynamic reason for this observation has yet to be eluci-
dated.
The frequently tendered explanation is that of
streaming of particulate material in the carotid circula-
tion. However, in this experimental model, as well as
in man, due to the presence of the anterior communi-
cating artery, a possible explanation is that competitive
blood flow from the contralateral internal carotid ar-
tery mixing with the ipsilateral anterior cerebral artery
blood supply dilutes the number of aggregates in the
blood supplied to the anterior cerebral artery territory.
This concept of blood from the contralateral anterior
cerebral artery diluting the number of emboli is sup-
ported by the finding that when an atheromatous lesion
occudes the anterior cerebral artery proximal to the
anterior communicating artery (if the anterior commu-
nicating cerebral artery is patent), continued flow is
 maintained by crossover from the contralateral anterior
cerebral artery. Similarly, if there is a pressure dis-
crepancy at the level of the carotid siphon between the
two internal carotid artery systems because of a proximal
carotid artery stenosis or occlusion, this cross-
over flowfrom the opposite carotid would occur. The
finding of a greater number of aggregates in group 3
(CA + L) in the ipsi- and contralateral anterior cere-
bral artery territories when the contralateral carotid
artery was ligated, may therefore be due to the exis-
tence of crossover flow from the ipsilateral anterior
cerebral artery, resulting in the absence of dilution of
the blood carrying the aggregates. This finding cor-
rborates the clinical observation by Gacs et al17 in
patients with anterior cerebral artery and contralateral
internal carotid artery occlusion who were presumed to
have embolized their anterior cerebral arteries because
of an increased flow via the anterior communicating
ttery to the opposite hemisphere. A possible explana-
tion for the rarity of symptomatic anterior cerebral
artery occlusion and infarction is that brain tissue in
this area may derive collateral blood flow from the opposite internal carotid circulation.

In patients with carotid artery disease, TIAs do not usually occur in the vertebrobasilar territory. Similarly, in this experiment, a minimal number of aggregates were noted in the vertebrobasilar territory after carotid artery injection. The explanation for these observations is on a simple anatomic basis.

We chose direct exposure of the heart as the means of injecting the cardiac emboli as this ensures complete mixing with the blood which would not be achieved with retrograde catheterization and obviates the possibility of the injection catheter interfering with transvalvular blood flow and subsequent blood streaming. The possibility does exist that ligation of the branches of the external carotid artery may have influenced the hemodynamics of carotid artery blood flow and hence disturbed carotid artery streaming. This was examined in one animal in which ligation of the external carotid artery branches had no influence on the distribution of aggregates injected into the left atrium.

The aggregates of 5 to 40 microns in size were chosen because we had previously shown that microemboli, containing the constituents of platelets, cause EEG detectable changes. These are probably smaller than atherothrombotic material, but of the same size as platelet aggregates. The number and size of the aggregates may have influenced the final flow pattern and thus these results may only be applicable to platelet aggregates and not to the distribution pattern of atherothrombotic material in human beings. However, these results do not imply that 5 to 40 micron microaggregates cause TIAs. We speculate that larger embolic clots originating from the heart or bifurcation of the common carotid artery might travel in a similar manner.

Although the embolic theory of etiology of TIA was initially opposed because TIA occurred at the same point in the arterial tree each time, this argument failed to take into account the phenomenon of streaming. Gacs et al. have shown in human beings that balloon catheters will preferentially follow the same pathway as emboli that have caused spontaneous vascular occlusion. This could account for recurrent, stereotype, repetitive TIAs. Furthermore, as Pickering suggested, we have previously shown that emboli cause EEG changes which then go on to histologically detectable cerebral lesions commensurate with stroke. In the present study we found aggregates of carotid artery origin selectively lodged in the middle cerebral artery territory (lateral cortex, putamen, operculum and insula). Selective streaming of aggregates of carotid artery origin to the middle cerebral artery territory, and particularly to the lateral hemisphere cortex and putamen, appears to be the reason for the greater frequency of middle cerebral artery territory motor, sensory and speech dysfunction with TIA of carotid origin. A similar explanation appears to be operative in the case of amaurosis fugax occurring as a result of micro-emboli to the ophthalmic artery territory in carotid artery disease.

In conclusion, our results support the theory that emboli arising from carotid artery lesions, either ulcers or stenosis, tend to cause selective middle cerebral artery territory TIA, particularly in Broca's speech area and lateral hemisphere cortex and/or amaurosis fugax. However, if the contralateral carotid artery is stenosed or occluded, a greater number of emboli can be expected in the ipsi- or contralateral cerebral territory although these may be asymptomatic. Emboli arising from carotid lesions may cause TIA anywhere in the brain.

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