Septic Cerebral Embolism

BY GAETANO F. MOLINARI, M.D.*

Abstract:
Septic Cerebral Embolism

In order to study the effects of septic embolism on neurovascular structures, cerebral infarction was produced in a series of dogs by injecting silicone rubber cylinders through an internal carotid artery cannula. Each embolic particle was first incubated with one of four known bacterial pathogens. Death occurred in three animals on the second postoperative day, at which time ten other moribund dogs were sacrificed. Eleven animals made apparently uneventful recoveries from early hemiplegia and appeared well when sacrificed electively one to five weeks after embolism. Autopsies revealed subarachnoid and acute subdural hemorrhages in the early group with gross and microscopic evidence of mycotic aneurysm in each instance. Chronically surviving animals showed histological lesions in the putamen or temporal pole consistent with brain abscess. In this series, mycotic aneurysm with hemorrhage was an extremely dramatic complication of emboli infected with the virulent pathogens, Staphylococcus aureus and Escherichia coli, while brain abscess developed insidiously in ischemic areas, after embolism with the opportunistic pathogens, Streptococcus viridans and Enterococcus.

ADDITIONAL KEY WORDS: brain abscess, subarachnoid hemorrhage, Escherichia coli, acute subdural hemorrhage, Staphylococcus aureus, Streptococcus viridans, Enterococcus.

Introduction

Although mycotic aneurysm and brain abscess are well-recognized complications of bacterial endocarditis,1 3 the precise mechanisms responsible for their development are obscure. Retrospective studies suggest septic embolism as a primary event in pathogenesis,4 5 but this can rarely be proved at autopsy. The purpose of this paper is to report the clinical and pathological effects of septic cerebral embolism in experimental animals.

Methods

In a previous report, we have described a method for producing segmental cerebral arterial occlusions in dogs, using elastic silicone rubber emboli.6 Cylindrical emboli of presellected diameter, introduced through an internal carotid artery cannula, lodge in the proximal middle cerebral segment, obstructing lenticulostriate arteries at their origins. This technique produces unilateral bland infarction in the basal ganglia and internal capsule on the side injected.7

In order to study septic embolism, this basic method was slightly modified. Embolic cylinders measuring 1.6 x 6 mm were placed on blood agar plates containing pure growths of known pathogenic bacteria. Using sterile technique, the material was gently rotated to obtain a uniform distribution of organisms on the surface of the embolus.

Twenty-four dogs were given septic emboli prepared in this way.

The organisms used were Staphylococcus aureus (9), Escherichia coli (3), Streptococcus fecalis (2), and Streptococcus viridans (10).

Animals were observed clinically for signs of complications for up to five weeks after embolism. Euthanasia was performed promptly on acutely ill...
Scattergram summarizing results. Three animals in the Staph. aureus group were sacrificed electively on the first day after embolism, to obtain specimens of unruptured aneurysms. Closed squares indicate animals which died spontaneously or were sacrificed in a moribund state after subarachnoid hemorrhage had occurred.

Animals were anesthetized by intravenous barbiturate injection. The others were sacrificed electively at varying time intervals after septic embolism.

At postmortem examination, swab cultures were obtained from cerebral fluid, subdural and subarachnoid blood, and brain surface at the site of the arterial lesion. Cultures were also made of needle aspirates taken from areas of encephalomalacia, deep to surface emboli.

After fixation, brain specimens were studied and blocked for representative sections of neural and vascular pathology. Histological sections were prepared with hematoxylin and eosin, van Gieson elastic and trichrome stains.

**Results**

Figure 1 is a scattergram which summarizes the clinical and pathological results. The closed squares represent spontaneous deaths or animals killed in a moribund state. Open squares signify animals with hemiplegia or minor residual signs of infarction when sacrificed electively.

On the first day after embolism, all twenty-four animals in this series were alert and responsive but hemiplegic on the side opposite the injection. These were the characteristic features of middle cerebral artery occlusion in previous studies of bland infarction.

Three hemiplegic animals with staphylococcal emboli were sacrificed 24 hours after embolism. All three showed unruptured aneurysms at the site of vascular occlusion.

Another six animals given emboli infected with *Staph. aureus* and the three given *E. coli* died abruptly or showed catastrophic deterioration on the second or third day after embolism. All nine had subarachnoid hemorrhages at autopsy; many were associated with acute subdural hematomas on the side of the embolism.

In contrast to this group, 11 of 12 dogs given streptococcal emboli survived the acute phase and showed continuous improvement and adaptation to their hemiplegia, as they progressed into the chronic postoperation course. Many had no apparent deficit at all when sacrificed several weeks after embolism. Only one dog in the streptococcal group developed mycotic aneurysm and died in the acute phase from subarachnoid hemorrhage. Despite the clinical improvement, all of the others had brain abscess at autopsy.

Therefore, both clinical course and brain pathology were closely related to the type of organism used.

![Subarachnoid hemorrhage in the dog. Brain specimen, in situ, after removal of the calvarium and reflection of the dura. Blood fills the sulci of the subarachnoid space on the side of the aneurysm. The arrow marks the extravascular embolic material in the subdural clot adjacent to the reflected dura mater.](image-url)
Mycotic aneurysm. Upper. Ventral surface of dog brain with a mycotic aneurysm on the right middle cerebral artery. Lower. Magnification of the aneurysm outlined above. The right optic nerve is at the top of the picture. The saccular aneurysm contains small perforation filled by clotted blood. The proximal end of the embolus is seen in the upper right quadrant of the aneurysm, while the remainder of the embolic material is contained within the sac.
**Bacteriological Correlations**

Pure cultures of *Staph. aureus* or *E. coli* were recovered from intracranial blood, cerebral fluid, and brain surface in all cases of aneurysm with hemorrhage. Staphylococci were also grown from the arterial lesion on the brain surface in the three animals killed before hemorrhage occurred.

In addition, the organism was recovered from the one case of streptococcal aneurysm, but streptococci were grown from brain abscess specimens only if obtained during the first week after embolism. Even in abscesses less than a week old, swabs taken from the brain surface, occluded arterial segment, or cerebral fluid grew the injected streptococcal organism, but aspirates of the deep lesion yielded mixed flora or no growth. Recovery of the injected organism from any source was rare in mature abscesses more than a week old.

**Pathology**

On gross inspection, two types of hemorrhage were seen in specimens of ruptured mycotic aneurysm. Through the intact dura, bright red blood was seen throughout the subarachnoid space bilaterally. There was also a large, dark subdural clot on the side of the aneurysm. Upon reflecting the dura, the embolus was always found in the subdural clot. Unclotted subarachnoid blood could be seen in the sulci of both hemispheres, but was more abundant on the side of the aneurysm. Figure 2 shows the typical appearance of subarachnoid hemorrhage as found at autopsy.

The brilliant yellow embolus was easily identified and recovered. In specimens of ruptured aneurysms, the embolus was extravascular, having escaped the artery through the ruptured aneurysm.

Figure 3A shows the ventral surface of a dog's brain. Note the component arteries of the circle of Willis and the course and position of the unaffected middle cerebral artery, sweeping anterior to the left temporal pole. The outline marks the right middle cerebral artery containing an aneurysm overlying an intravascular embolus.

Figure 3B is a tenfold magnification of the outlined area showing a portion of the embolus in the artery just proximal to a saccular aneurysm, containing a minute perforation.

On microscopic study, aneurysmal segments showed fusiform or saccular dilatation compared to control contralateral segments. Aneurysmal segments, in both longitudinal and cross section, showed an intense inflammatory cell response on the adventitial surface and irregular penetration of the muscularis layer with polymorphonuclear infiltrate. Only the intima and internal elastic membrane remained intact in unruptured aneurysms. Within the media, at the periphery of zones of inflammation and frank necrosis, the vasa vasorum were congested with polymorphonuclear inflammatory cells. Sections through ruptured segments demonstrated coiling and retraction of the intima and elastica on either side of the rent at the site of rupture.

Gross brain specimens from the animals with chronic lesions each showed an embolus within a surface artery. Small accumulations of pus surrounded the occluded segment, but aneurysmal dilatation was not observed. Locally, flattening of gyri and sulci indicated focal brain swelling. Larger lesions produced easily recognized asymmetries, occasionally involving most of the affected hemisphere.

The most common site for abscess formation was in the distribution of the penetrating arteries of the lateral striate group, involving the deep brain substance.

In section, older abscesses were consistently larger than those found in specimens taken within the first week after embolism, despite similarity in size and site of segmental artery occlusions.

Brain sections from the animals given streptococcal embolism revealed typical brain abscesses in gross and microscopic preparations. Lesions were usually lateral to the internal capsule, involving the basal ganglia and temporal pole. White matter was rarely involved directly but in the older lesions, which were larger, some displacement and distortion did occur. This factor plus the slow growth of these lesions probably accounts for the apparent benignity of the clinical course in the brain abscess group.

Abscess lesions had sharply defined borders, were greenish in color, and were always found in relation to an intravascular embolus in a surface artery. Cavities were found only as artifacts produced by needle aspiration; otherwise, the necrotic centers contained homogeneous gelatinous pus.

Figure 4 is a hematoxylin stain through a brain abscess. The capsule is clearly seen,
SEPTIC CEREBRAL EMBOLISM

Brain abscess. Magnification of a horizontal section through right anterior quadrant of canine brain. Note the sharp line of demarcation and intense cellular response of the capsule. The cavity and tract to the surface were produced by needle aspiration at autopsy. Hematoxylin and eosin stain.

composed of densely packed, deeply staining polymorphonuclear leukocytes. Cellular reaction of this type at five weeks, the age of this lesion, is distinctive of abscess and is in marked contrast to bland infarction.

Microscopically, abscess walls showed three layers. Each had an inner necrotic layer, a thick middle band of acute inflammatory cells, and an outer zone of gliosis, fibrosis, and prolific vascularization. Within the outer zone, more central blood vessels were frequently surrounded by inflammatory cells, while in the peripheral, transitional regions, there was bland proliferation of endothelial cells around patent lumina.

Discussion
This series of experiments demonstrates the pathogenesis of mycotic aneurysm and brain abscess from a single mechanism. The controlled variable was the organism used to produce each type of lesion.

Stroke, Vol. 3, March-April 1972
The experimental models presented parallel most of the clinical and pathological features of the naturally occurring prototypes. This method offers the additional advantage of an embolism that is easily traced and recovered at autopsy.

This study shows that in canine brain the interval from septic embolism to aneurysm formation is remarkably short. The entire process including embolism, local arteritis, aneurysm formation and hemorrhage usually occurred within two days.

Despite delivery of bacteria to the intimal surface of occluded arteries by septic emboli, the inflammatory response in mycotic aneurysm proceeded from the adventitial surface toward the media. The internal elastic membrane and intima were last affected. This supports the hypothesis of other investigators that infection of the arterial wall is mediated through stasis and sepsis in the vasa vasorum.

While there have been several previous models of brain abscess, all have in common a primary brain injury, usually surgical introduction of a foreign body, allowing invasion by bacteria. Our method demonstrates that both ischemic injury and infection may be caused simultaneously by a single event, septic embolism.

Virulence of the organism was the determinant of morbidity and mortality in this series. The more virulent pathogens, *Staph. aureus* and *E. coli*, caused immediate and dramatic infections of the arterial wall, with aneurysm and hemorrhage. In contrast, the so-called “opportunistic” streptococci usually caused progressive lesions, beginning in areas of infarction or ischemia.

**Summary and Conclusions**

Septic cerebral embolism may cause either mycotic aneurysm or brain abscess. In this series, the virulence of the organism determined the pathology and clinical course of the cerebral lesions. The experimental models presented are representative of the clinical, pathological and histological features of naturally occurring disease states, and therefore offer opportunity for further research in medical and surgical treatment.

**References**

The experimental models presented parallel most of the clinical and pathological features of the naturally occurring prototypes. This method offers the additional advantage of an embolism that is easily traced and recovered at autopsy.

This study shows that in canine brain the interval from septic embolism to aneurysm formation is remarkably short. The entire process including embolism, local arteritis, aneurysm formation and hemorrhage usually occurred within two days.

Despite delivery of bacteria to the intimal surface of occluded arteries by septic emboli, the inflammatory response in mycotic aneurysm proceeded from the adventitial surface toward the media. The internal elastic membrane and intima were last affected. This supports the hypothesis of other investigators that infection of the arterial wall is mediated through stasis and sepsis in the vasa vasorum.4,8

While there have been several previous models of brain abscess,6-11 all have in common a primary brain injury, usually surgical introduction of a foreign body, allowing invasion by bacteria. Our method demonstrates that both ischemic injury and infection may be caused simultaneously by a single event, septic embolism.

Virulence of the organism was the determinant of morbidity and mortality in this series. The more virulent pathogens, Staph. aureus and E. coli, caused immediate and dramatic infections of the arterial wall, with aneurysm and hemorrhage. In contrast, the so-called "opportunistic" streptococci usually caused progressive lesions, beginning in areas of infarction or ischemia.

Summary and Conclusions

Septic cerebral embolism may cause either mycotic aneurysm or brain abscess. In this series, the virulence of the organism determined the pathology and clinical course of the cerebral lesions. The experimental models presented are representative of the clinical, pathological and histological features of naturally occurring disease states, and therefore offer opportunity for further research in medical and surgical treatment.

References

4. Bell WE, Butler C: Cerebral mycotic aneurysm in children—two case reports. Neurology (Minneapolis) 18: 81-86 (Jan) 1968

Molinari

Stroke, Vol. 3, March-April 1972
Septic Cerebral Embolism
GAETANO F. MOLINARI

Stroke. 1972;3:117-122
doi: 10.1161/01.STR.3.2.117

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/3/2/117

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke 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 Stroke is online at:
http://stroke.ahajournals.org/subscriptions/