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## Pathology of Cervico-Cranial Artery Occlusion

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### INTRODUCTION

Brain ischemia is caused by a heterogeneous array of different vascular disorders. The general categories of vascular disorders most often used are embolism, “thrombosis” (referring to a local *in situ* process that narrows and often occludes an artery or vein), and systemic hypoperfusion. Systemic disorders that lead to brain ischemia include cardiac disorders (cardiac arrest, arrhythmias, low cardiac output), conditions that cause hypovolemia and lack of adequate oxygen-carrying blood (blood loss, severe anemia, shock, carbon monoxide poisoning, hypotension), and acute pulmonary conditions (i.e., pulmonary embolism). Because patients with systemic disorders are not candidates for thrombolysis and there are usually no associated intracranial vascular occlusions, this large category is not discussed here. This chapter, therefore, focuses entirely on embolic and thrombotic disorders.

### BRAIN EMBOLISM

Embolism has been variously defined and categorized. Although some use this category to include only cardiac-origin embolism, the author urges a more general approach. An embolus refers to a particle that originates in one place and moves to another site; a traveling particle rather than one that stays at the place

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it originated (thrombus). Embolism is the process of particle migration within the vascular bed.

There are three main descriptors of embolism: (a) the *donor site* that is the source of the embolus, (b) the *material* that makes up the embolus, and (c) the *recipient site* where the embolus rests or remains. All are important determinants when considering treatment (1–3).

### *Donor Sources*

The donor sites for embolic material are the heart, aorta, and extracranial and intracranial arteries. Emboli originating from the heart are usually called cardio-genic, whereas emboli originating within the aorta or proximal arteries are called intra-arterial or artery-to-artery emboli but are sometimes referred to as local emboli.

Some emboli arise in the venous system and simply pass through the heart to reach the brain and other systemic arteries. These emboli traverse communications between the right heart-pulmonary system and the left heart-systemic circulation. The most common such communications are intra-atrial septal defects and patent foramen ovals. Occasionally incriminated are ventricular septal defects and pulmonary arteriovenous malformations. These emboli are often referred to as *paradoxical emboli*. Studies have shown that paradoxical embolism is much more common than previously thought.

A variety of different cardiac disorders can provide the source for embolism. The most common categories are listed in Table 1. In all published series, arrhythmias—especially atrial fibrillation and coronary artery disease-related conditions—are the most common sources, followed in frequency by valve disorders. Table 2 enumerates the most frequent cardiac sources in the Stroke Data Bank (1,4,5) and designates the Stroke Data Bank's categorization of high- and medium-risk heart conditions with respect to their importance in serving as sources of emboli. Table 3 lists the most frequent potential cardiac sources of embolism in the Lausanne Stroke Registry (1,6,7).

The aorta is now also recognized as a very important source of emboli to the brain, especially during and after cardiac surgery (8–10). Clamping an atheromatous aortic arch often leads to release of particles into the brain and systemic arteries. Atherosclerosis is often severe in the aorta and the plaques are often located in the ascending aorta and the arch proximal to the origins of the carotid and brachiocephalic arteries (11). Particles released can consist of cholesterol crystals, calcified plaque debris, white clots, and red thrombi. Protuberant mobile large plaques are most often associated with brain embolism.

Arterial sources of embolism are also quite varied. Emboli arise from a variety of different disorders and from a variety of different sites. Although atherosclerosis is by far the most common condition that leads to intra-arterial embolism, other vascular diseases also can serve as donor sources. Trauma and dissections

Table 1  
Most Frequent Cardiac Disorders Associated With Brain Embolism

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Arrhythmias

Atrial fibrillation

Sick-sinus syndrome (brady-tachy syndrome)

Valve diseases

Rheumatic mitral and aortic valve disease

Calcific aortic and mitral valve disease

Prosthetic valves

Bacterial endocarditis

Nonbacterial thrombotic endocarditis (marantic endocarditis)

(most common causes: lupus erythematosus, cancer, antiphospholipid antibody syndrome)

myxomatous valve degeneration (mitral valve prolapse)

mitral annulus calcification

? valve strands

Myocardial disorders

Myocardial infarction

Hypokinetic regions

Myocardial aneurysms

Myocarditis

Myocardopathies

Septal lesions

Patent foramen ovale

Atrial septal defects

Ventricular septal defects

Atrial septal aneurysms

Cardiac chamber lesions

Cardiac tumors (myxomas, rhabdomyomas, fibroelastomas)

Ball thrombi

“Spontaneous echo contrast”

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of arteries leads to local thrombus formation and embolism. Occasionally inflammatory diseases of the brachiocephalic branches of the aortic arch, such as temporal arteritis and Takayasu's disease, are sources of intra-arterial embolism. Thrombi sometimes form within arterial aneurysms, saccular, dissecting, and fusiform dolicocephalic aneurysms, and can then break off and embolize to distal branch arteries. Fibromuscular dysplasia (FMD) is an important but relatively uncommon vascular disease that affects the pharyngeal and occasionally the intracranial portions of the carotid and vertebral arteries; stenosis resulting from FMD can occasionally serve as a source of distal intra-arterial embolism.

Table 2  
Patients in the Stroke Data Bank With Selected  
Cardiac Characteristics in High and Medium Cardiac-Risk Groups

<i>Cardiac-risk categories</i>	<i>High-risk (n = 250)</i>	<i>Medium-risk (n = 166)</i>
<b>High-risk categories</b>		
Valve surgery	15	
A-fib, A-flutter, sick sinus with valve disease	28	
A-fib, A-flutter, sick sinus but no valve disease	162	
Ventricular aneurysm*	5	
Mural thrombus*	12	
Cardiomyopathy or left ventricle hypokinesis*	7	
Akinetic region*	52	
<b>Medium-risk categories</b>		
Myocardial infarct within 6 mo	25	18
Valve disease without A-fib, A-flutter, sick sinus	31	19
Congestive heart failure	92	95
Decreased left ventricle function*	0	3
Hypokinetic segment*	0	12
Mitral valve prolapse (by history or echocardiogram)	5	13
Mitral annulus calcification*	14	46

\* Determined by echocardiography. Some patients had more than one characteristic. (Modified from ref. 5 with permission.)

Table 3  
Potential Cardiac Sources of Embolism in the Lausanne Stroke Registry

<i>Cardiac abnormalities</i>	<i>n patients (%)</i>
<b>Isolated myocardial abnormalities</b>	84 (27.5%)
Focal left ventricle akinesia without thrombus	61 (20%)
Focal left ventricle akinesia with thrombus	7 (2.3%)
Global ventricular hypokinesia	7 (2.3%)
Patent foramen ovale	6 (2%)
Left atrial myxoma	2 (0.7%)
Left ventricle thrombus	1 (0.3%)
<b>Isolated valve abnormalities</b>	71 (23.3%)
Mitral valve prolapse	51 (16.7%)
Mitral stenosis or insufficiency	10 (3.3%)
Prosthetic mitral or aortic valve	10 (3.3%)
<b>Isolated arrhythmia</b>	127 (41.6%)
Atrial fibrillation	118 (38.7%)
Sick-sinus syndrome	9 (2.9%)

(continued)

Table 3 (*Continued*)  
Potential Cardiac Sources of Embolism in the Lausanne Stroke Registry

<i>Cardiac abnormalities</i>	<i>n patients (%)</i>
<b>Arrhythmias plus myocardial abnormalities</b>	12 (3.9%)
Atrial fibrillation plus focal left ventricular akinesia without thrombus	6 (2%)
Atrial fibrillation plus focal left ventricular akinesia with thrombus	1 (0.3%)
Atrial fibrillation plus global hypokinesia	3 (1%)
Atrial fibrillation plus left ventricular thrombus	2 (0.7%)
<b>Arrhythmias plus valve abnormalities</b>	11 (3.6%)
Atrial fibrillation plus mitral valve prolapse	6 (2%)
plus mitral stenosis	2 (0.7%)
plus prosthetic valve	3 (1%)

Modified from ref. 7 with permission.

Table 4  
Embolic Materials

<i>Cardiac origin</i>	<i>Arterial origin</i>
Red erythrocyte-fibrin clots	Red erythrocyte-fibrin clots
White platelet-fibrin clots	White platelet-fibrin clots
Calcific particles	Calcific particles
Bacteria	Cholesterol crystals
Fibrous strands	Parts of plaques
Myxomatous tumors	
Prosthetic valve parts	

Thrombi can, on occasion, form within large arteries in the absence of important arterial disease in patients with cancer and other causes of hypercoagulability (12). These luminal thrombi then embolize to intracranial arteries causing strokes.

These conditions are discussed further in the section, Disorders—“*In Situ* Arterial Thrombosis.”

*Embolic Material*

The actual “stuff” that embolizes is of great importance (1–3). As far as is known, thrombolytic drugs lyse so-called “red” erythrocyte-rich thrombi. The mechanism relates to breaking or relaxing the fibrin bridges and bonds that hold the thrombus together. Fresh, soft, red thromboemboli are more easily lysed than old, organized, fibrotic thromboemboli. There are a variety of different particles that can embolize from cardiac and arterial sources. These are listed in Table 4.

### ***Recipient Sites and Resultant Infarct Patterns***

About 80% of emboli that arise from the heart go into the anterior (carotid artery) circulation, equally divided between the left and right sides. The remaining 20% of emboli go into the posterior (vertebrobasilar) circulation, a rate roughly equal to the proportion of the blood supply that goes into the vertebrobasilar arteries. The recipient artery destination depends on the size and nature of the particles. Calcific particles from heart valves or mitral annular calcifications are less mobile and adapt less well to the shape of their recipient artery resting places than red (erythrocyte-fibrin) and white (platelet-fibrin) thrombi. The circulating blood stream seems to be able to somehow bypass obstructing cholesterol crystal emboli, especially in the retinal arteries. Within the anterior and posterior circulations there are predilection sites for the destination of embolic particles. Large emboli entering a common carotid artery may become lodged in the common or internal carotid artery, especially if atheromatous plaques have already narrowed the lumens of these vessels. If the emboli were able to pass through the carotid arteries in the neck, the next common lodging place is the intracranial bifurcation of the internal carotid arteries (ICAs) into the anterior cerebral (ACA) and middle cerebral arteries (MCAs). Bifurcations are common resting places for emboli. Emboli that pass through the carotid intracranial bifurcations most often go into the MCAs and their branches. Gacs et al. showed that balloon emboli placed in the circulation nearly always followed the same pathway and ended up in the MCAs and their branches (13). Embolism in experimental animals produced by the introduction of silicone cylinders or spheres, elastic cylinders, and autologous blood clots, also showed a very high incidence of MCA territory localization (14). Emboli often pass into the superior and inferior divisions of the MCA and the cortical branches of these divisions. The superior division supplies the cortex and white matter above the sylvian fissure including the frontal and superior parietal lobes. The inferior division supplies the area below the sylvian fissure including the temporal and inferior parietal lobes. The ACA supplies the paramedian frontal lobe. Emboli seldom go into the penetrating artery (lenticulostriate arteries) branches of the MCAs or the penetrators from the ACAs because these vessels originate at about a 90° angle from the parent arteries. Embolism into the MCAs causes a variety of different patterns of infarction (1,15). Blockage of the mainstem MCA before the lenticulostriate branches can cause a large infarct that encompasses the entire MCA territory including the deep basal ganglia and internal capsule as well as the cerebral cortex and subcortical white matter of both the suprasylvian and infrasyllian MCA territories. In some patients, an embolus has blocked the intracranial ICA causing infarction of the ACA territory as well as the entire MCA territory. In young patients, when the mainstem MCA is blocked, the rapid development of collateral circulation over the convexity of the brain often leads

to sparing of the superficial territory of the MCA. The lenticulostriate branches are blocked by the clot in the mainstem MCA and collateral circulation to the deep MCA territory is poor. The resultant infarct is limited to the basal ganglia and surrounding cerebral white matter and is usually referred to as a striato-capsular infarct. Passage of an embolus into the superior division of the MCA leads to a cortical/subcortical infarct in the region of the suprasylvian convexity and embolism to the inferior division leads to an infarct limited to the temporal and inferior parietal lobes below the sylvian fissure. When an embolus rests first in the mainstem MCA and then travels to one of the divisional branches, infarction involves the deep territory and cortex above or below the sylvian fissure. Small emboli block cortical branches and cause small cortical/subcortical infarcts involving one or several gyri. Occasionally emboli block the ACA or its distal branches. This causes an infarct in the paramedian area of one frontal lobe.

Emboli that enter the posterior circulation can block the vertebral arteries in the neck or intracranially. Emboli that pass through the intracranial vertebral arteries (ICVAs) will usually be able to pass through the proximal and middle portions of the basilar artery which are wider than the ICVAs. The basilar artery becomes narrower as it courses craniad. Emboli often block the distal basilar artery bifurcation—"top of the basilar"—or one of its branches (16–18). The main branches of the basilar artery bifurcation are penetrating arteries to the medial portions of the thalami and midbrain, the superior cerebellar artery that supplies the upper surface of the cerebellum, and the posterior cerebral arteries (PCAs), which supply the lateral portions of the thalami and the temporal and occipital lobe territories of the PCAs. The most frequent brain areas infarcted are the posterior inferior portion of the cerebellum in the territory of the posterior inferior cerebellar artery (PICA) branch of the ICVA; the superior surface of the cerebellum in the territory of the superior cerebellar artery; the thalamic and hemispherical territories of the PCAs. The clinical and imaging findings in patients with these lesions are described in detail elsewhere (16). Table 5 notes the most frequent locations of brain infarction in the Lausanne Stroke Registry in patients with potential cardiac sources of embolism (7).

When emboli arise from arteries, the emboli can of course, only go into more distal portions of that artery. Emboli that originate in the ICA usually go into the MCA and its branches but occasionally must go into the anterior cerebral, and anterior choroidal arteries and their branches. Occasional emboli go into penetrating artery branches. Within the posterior circulation, emboli that originate from the vertebral arteries in the neck go to the ipsilateral intracranial vertebral artery and its PICA branch and more distally into the basilar artery and any of the branches on either side of the basilar artery and the SCAs and PCAs.

Ultrasound studies show that microembolic particles often pass through the intracranial arteries without causing symptoms or brain infarcts. The adequacy

Table 5  
Location and Distribution of Infarcts  
in the Lausanne Stroke Registry in Patients  
With Potential Cardiac Sources of Embolism

<b>Anterior circulation</b>	213 (70%)
Global MCA	33 (11%)
Superior division MCA	60 (20%)
Inferior division MCA	54 (18%)
Deep subcortical	56 (18%)
Anterior cerebral artery (ACA)	9 (3%)
ACA and MCA together	1 (0.3%)
<b>Posterior circulation</b>	69 (23%)
Brainstem	18 (6%)
Thalamus (deep PCA)	12 (4%)
Superficial PCA	21 (7%)
Superficial and deep PCA	3 (1%)
Cerebellum	10 (3%)

MCA, middle cerebral artery; PCA, posterior cerebral artery.

of flow through proximal arteries undoubtedly effects the fate of artery-to-artery emboli. When there are proximal vascular occlusive lesions that diminish flow, particles may not be cleared (washed out) as adequately as when the circulation is normal (19). These particles are often distributed within the distal fields causing so-called border-zone ischemia between intracranial arterial territories.

## *IN SITU* ARTERIAL DISORDERS — THROMBOSIS

### *Atherosclerosis of Large Arteries*

Atherosclerosis is by far the most common condition leading to stenosis and occlusion of large extracranial and intracranial arteries. The initial arterial lesion is a fatty streak that develops in the intima and then enlarges into a raised atherosclerotic plaque. Atherosclerotic plaques have been more thoroughly studied within the coronary arteries but the process is similar in the carotid arteries (20–23). Plaques contain a mixture of lipid, smooth muscle, fibrous and collagen tissues, macrophages, and other inflammatory cells. Plaques can enlarge quickly when hemorrhages occur within the plaques (23). When a critical plaque size and reduction in the lumen are reached, the atherosclerotic process accelerates. Reduced luminal area and the bulk of the protruding plaque alter the physical and mechanical properties of blood flow and create regions of local turbulence and stasis. Platelets adhere to the irregular surfaces of plaques. Secretion of chemical



mediators within platelets and within the underlying vascular endothelium causes aggregation and further adherence of platelets to the endothelium. A “white clot” composed of platelets and fibrin develops and, at first, is rather loosely adherent to the vascular wall. Plaques often interrupt the endothelium, ulcerate, and rupture. Breaches in the endothelium allow cracks and fissures to form allowing contact of the constituents of the plaque with the luminal contents. The coagulation cascade is activated by this contact and a “red thrombus” composed of erythrocytes and fibrin forms within the lumen. Platelet secretion can also activate the serine proteases that form the body’s coagulation system and promote red clot formation. When thrombi first form they are poorly organized and only loosely adherent. They often then propagate and embolize. Within a period of 1 to 2 wk, thrombi organize and become more adherent. Fragments are less likely to break off and embolize from organized thrombi. There are important sex and racial differences in the distribution of atherosclerotic occlusive lesions (24–28). In white men, the predominant cerebrovascular occlusive lesions are in the carotid and vertebral arteries in the neck (15,21,29–31). African-Americans, individuals of Asian origin, and women are more likely to have occlusive lesions in the large intracranial arteries of the circle of Willis and their main branches, and less likely to have severe occlusive vascular lesions in the neck. Caucasian men who have carotid artery disease in the neck also have a high frequency of coexisting coronary artery and occlusive lower limb artery disease, as well as hypertension, hypercholesterolemia, and a history of smoking. After menopause, the frequency of extracranial occlusive disease increases in women.

Within the anterior circulation, the most frequent and important occlusive lesion in Caucasian men is within the ICA in the neck. Atherosclerotic lesions usually begin within the common carotid artery (CCA) along the posterior wall of that vessel opposite the flow-divider between the ICA and the external carotid artery (ECA) (19,20,25). Atherosclerotic plaques grow in diameter and often spread rostrally within the CCA, and the proximal ICA, and ECAs. The next most common atherosclerotic lesions in white men are found within the intracranial ICA in the proximal intracranial portion of the artery, the carotid siphon, and within the proximal portions of the MCAs. These lesions all produce symptoms by causing hypoperfusion of supplied brain territories or by clot-fragment embolism.

Women, African-Americans, and Asians often develop occlusive lesions within the MCAs and their branches (25–28,32). ICA siphon and neck lesions are found less often. African-Americans, Asians, and women who develop occlusive neck lesions usually smoke and have important co-existing atherosclerotic risk factors such as hypertension and hypercholesterolemia. Asian patients who have stenosing neck atherosclerotic lesions often have accompanying intracranial disease (28,32).

Within the posterior circulation among Caucasian men, occlusive lesions are found most often at the origins of the vertebral arteries in the neck and within the adjacent subclavian artery. The next most common site is within the ICVAs and the basilar artery. Caucasian men with occlusive extracranial vertebral artery (ECVA) disease also have a high frequency of co-existing carotid artery disease (16,30,31) as well as hypertension and hypercholesterolemia. Intracranial posterior circulation lesions are also common in Caucasian men and women, African-Americans, and Asians. The predominant lesions are within ICVAs. Atherosclerotic lesions within the ICVAs are often bilateral. Atherosclerotic lesions involving the posterior cerebral arteries are more common in women, African-Americans, and Asians (16).

### *Arterial Dissections*

Arterial dissection is probably the second most common disease that leads to thrombi forming within arteries. Dissections are often related to mechanical injury. When there is an obvious direct injury the dissections are usually called traumatic, but even so-called “spontaneous” dissections usually involve some mechanical perturbation of the arterial wall. Stretching or tearing within the arterial media causes formation of an intramural hematoma. Blood within the media dissects longitudinally along the vessel wall and expansion of the arterial wall subsequently compromises the lumen. The expanding intramural hematoma can tear through the intima and inject fresh, congealed, hematoma-containing, thrombus-like material into the arterial lumen. This material is, at first, not adherent to the endothelium and often embolizes. The intimal tear and the underlying medial hematoma cause some irritation of the endothelium, which in turn causes activation of platelets and the coagulation cascade, promoting the formation of a luminal thrombus *in situ*. Compromise of the lumen by the expanding intramural lesion alters blood flow, which also promotes thrombus formation. Thus, thrombus can form *in situ* within the dissected artery or reach the lumen by introduction of the intramural contents. In either case, the acute luminal thrombus is poorly organized and nonadherent and readily embolizes distally (15,16).

Arterial dissections most often involve the pharyngeal portions of the extracranial carotid and vertebral arteries (15,16,33–36). The pharyngeal portions of the neck arteries are relatively mobile whereas the origins of the arteries and their penetrations into the cranial cavity are relatively anchored and much less mobile. Tearing most often occurs in portions of arteries that are flexible and stretch with motion. Within the ECVAs, the most common site of dissection is the most distal portion of the artery, which emerges from the intervertebral foramina and courses around the atlas to penetrate the dura mater and enter the foramen magnum (16,34,35). Dissections also occur in the mobile part of the proximal portion of

the ECVAs above the origin of the arteries from the subclavian arteries but before the arteries enter the vertebral column at the intervertebral foramen of the sixth or fifth cervical vertebrae.

Intracranial dissections are much less common than extracranial dissections. In the anterior circulation, dissections most often affect the intracranial ICA and extend into the middle and anterior cerebral arteries (37). Within the posterior circulation, the most common site is the intracranial vertebral artery (16,35,38). Dissections within the ICVAs often spread into the basilar artery. Occasionally the basilar artery is the primary site of dissection (16,35).

## OTHER LARGE-ARTERY DISEASES

Other vascular conditions cause large-artery occlusions at a much lower frequency than atherosclerosis and arterial dissections. FMD is a heterogeneous condition characterized mostly by abnormalities in the smooth muscle and connective tissue within the arterial media (15,16). The lesions can occur in the pharyngeal carotid artery and in the vertebral arteries within the vertebral column. Occasionally, the lesions involve the intracranial large arteries. Thrombi can develop in regions of narrowing of arteries related to FMD. Various types of arteritis can, on rare occasions, cause arterial occlusions. The most important such disorder is arteritis related to the Herpes zoster-varicella virus (39). The virus can spread from the trigeminal ganglion to the middle cerebral artery and cause endothelial lesions that promote thrombus formation. Although other forms of arteritis are frequently mentioned as part of obligatory differential diagnoses, they are extremely rare causes of brain infarction and are not often complicated by thrombosis of sizable intracranial arteries. Migraine can be accompanied by arterial vasoconstriction. Narrowing of intracranial arteries, especially the PCA, and perturbation of the endothelium can promote thrombus formation (16,40).

### *Hypercoagulable States (41,42)*

Occasionally, occlusion of extracranial arteries is caused by hypercoagulability. There may also be an underlying endothelial lesion (e.g., a plaque within the carotid or vertebral arteries). Polycythemia, thrombocytosis, hereditary and acquired deficiencies of coagulation factors (antithrombin III, protein C, and protein S), cancer, increased serum levels of fibrinogen, and deficiencies of fibrinolytic factors can all cause or contribute to hypercoagulability. Cancer—especially mucinous adenocarcinomas and inflammatory diseases such as Crohn's and ulcerative colitis—can also lead to increased coagulability. Acute and chronic infections induce an increase in acute phase reactants that increase coagulability.

In hypercoagulable patients, thrombi can form anywhere. Thrombi can form in regions of endothelial abnormalities. Often, there are multiple small intracranial thrombi.

### *Penetrating Artery Disease*

The arteries that penetrate into the deeper regions of the brain are susceptible to somewhat different disease processes than the superficial branches of the same intracranial arteries. These vessels supply the basal ganglia, caudate nuclei, thalami, pons, portions of the midbrain and medulla, as well as regions of the internal capsules, corona radiata, and centrum semi-ovale. The small, penetrating artery branches arise mostly at nearly right angles from the anterior, middle, and posterior cerebral arteries and the basilar artery. The predominant conditions that affect these penetrating arteries are lipohyalinosis (43–45) and intracranial atheromatous branch disease (46–48).

Lipohyalinotic arteries have walls thickened by the deposition of hyaline material and lipids. This process can lead to arterial narrowing with subsequent brain infarction in tissue supplied by the compromised penetrating artery (43–45). Because few patients die immediately after lacunar infarction, the precipitating pathology has not been defined. Choking off of the lumen by progressive medial wall hypertrophy is possible as is a superimposed occlusive white or red thrombus. Atheromas can also develop within the parent arteries and block or extend into the orifices of the penetrating branches (46–48). Microatheromas can also form within the proximal portion of the branches. Pathological studies are scant and it is not well known how often microthrombi form in these penetrating arteries. Microdissections have been discovered at necropsy within the proximal portions of relatively large penetrating arteries (47).

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