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Review: Cerebral microvascular pathology in aging and neurodegeneration

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Abstract

This review of age-related brain microvascular pathologies focuses on topics studied by this laboratory, including anatomy of the blood supply, tortuous vessels, venous collagenosis, capillary remnants, vascular density, and microembolic brain injury. Our studies feature thick sections, large blocks embedded in celloidin, and vascular staining by alkaline phosphatase (AP). This permits study of the vascular network in three dimensions, and the differentiation of afferent from efferent vessels. Current evidence suggests that there is decreased vascular density in aging, Alzheimer's disease (AD), and leukoaraiosis (LA), and cerebrovascular dysfunction precedes and accompanies cognitive dysfunction and neurodegeneration. A decline in cerebrovascular angiogenesis may inhibit recovery from hypoxia-induced capillary loss. Cerebral blood flow (CBF) is inhibited by tortuous arterioles and deposition of excessive collagen in veins and venules. Misery perfusion due to capillary loss appears to occur before cell loss in LA, and CBF is also reduced in the normal-appearing white matter. Hypoperfusion occurs early in AD, inducing white matter lesions and correlating with dementia. In vascular dementia, cholinergic reductions are correlated with cognitive impairment, and cholinesterase inhibitors have some benefit. Most lipid microemboli from cardiac surgery pass through the brain in a few days, but some remain for weeks. They can cause what appears to be a type of vascular dementia years after surgery. Donepezil has shown some benefit. Emboli, such as clots, cholesterol crystals, and microspheres can be extruded through the walls of cerebral vessels, but there is no evidence yet that lipid emboli undergo such extravasation.

Keywords

Alzheimer's disease; Vascular dementia; Leukoaraiosis; Tortuous vessels; Capillary loss; String vessels; Periventricular venous collagenosis; Cerebrovascular lipid emboli

Introduction

Cerebral microvascular pathology precedes and accompanies age-related cognitive dysfunction and neurodegeneration [1–3]. Therefore, knowledge of this pathology is essential to understanding neurodegeneration. This review focuses on several topics studied by this laboratory, including anatomy of the blood supply, tortuous vessels, venous collagenosis, string vessels (capillary remnants), decreased vascular density, and microembolic brain injury. In addition, we will discuss basement membrane (BM)

thickening, cerebral perfusion, and extravasation of emboli. These vascular factors are involved in vascular dementia, Alzheimer's disease (AD), cognitive decline following microembolic injury of the brain, and leukoaraiosis (LA). LA is an age-related white matter degeneration characterized by spongiosis, gliosis, demyelination, and capillary degeneration [4], as well as endothelial dysfunction [5], increased blood-brain barrier (BBB) permeability [6], and cognitive impairment [7–14]. The studies in this laboratory have featured two methods; cutting thick sections from large tissue blocks embedded in celloidin and staining vessels via the endogenous enzyme, alkaline phosphatase (AP) [15]. Large, 100 μm -thick tissue sections provide an overall view of the vascular network in three dimensions, and AP histochemistry stains the afferent vasculature, distinguishing it from the efferent vessels.

Cerebrovascular Anatomy and Pathology

Perilous blood supply

An arterial network covers the surface of the brain and penetrates the brain in the form of end arteries, i.e., they terminate in a capillary bed and do not have shunts to arterioles or veins within the brain [16]. This vascular supply is not uniform, thus some brain regions are more vulnerable than others to chronic hypoperfusion. The deep white matter is particularly vulnerable because its major blood supply is via long medullary arterioles which arise from the border-zone between the middle cerebral artery and the anterior cerebral artery (Figure 1) [17]. Some regions of the deep white matter also receive blood supply from the medial and lateral brain surfaces. An additional blood supply to the deep white matter has also been proposed to originate from the lenticulostriate arteries projecting upward and around the lateral ventricles. In our studies, using AP staining, we have seen no evidence of a lenticulostriate supply to the white matter above the lateral ventricles, although these arteries do appear to project into the white matter lateral to the ventricles. In earlier studies, which used media injected into vessels [18,19], there may have been overfilling of some afferent vessels resulting in unintentional filling of some of the veins that project up from the ventricle into the deep white matter. Those areas supplied by short penetrating vessels, such as the corpus callosum do not exhibit LA, possibly because they are less susceptible to hypoperfusion. Conversely, the deep white matter is subject to both hypoperfusion and LA.

Tortuous vessels

The arterioles supplying the deep white matter have the longest course through the brain, and with aging they often become tortuous [20–29]. Hassler [30] found that they were sparse in subjects under the age of 60, but were common after the age of 70. Akima et al. [24] found them to appear in the 5th decade and to occur in all specimens above 80 years old. Hassler et al. [27] reported that there was no correlation with dementia score. Tortuosity usually begins abruptly as the arteriole passes from the cortex into the white matter (Figure 2), suggesting an intrinsic vulnerability of the white matter. With collagen IV staining in thick celloidin sections, these vessels can be seen to be coiled in a cavity where some brain parenchyma has been lost. We refer to these tortuous vessels and cavities as tortuosity lesions. Tortuosity increases the vessel length, and with each turn and loop there is a loss of kinetic energy such that increased blood pressure is needed to maintain flow in these vessels [22]. We found large amounts of tortuosity after age 50 [25], and there was a trend toward an increase in tortuosity in LA. Thus, tortuous vessels may be a contributing factor to the development of LA in a subset of cases.

Periventricular venous collagenosis

In 1995, we identified a new type of cerebral vascular pathology, periventricular venous collagenosis (PVC), in subjects with LA (Figure 3) [20,31]. An increase in the thickness of the walls of veins and venules in the periventricular white matter was evident with normal

aging. In cases with LA, we found a much greater degree of venous wall thickening in the LA lesions, which resulted in narrowed lumina and even occlusion. Using routine stains, these thick-walled veins could be easily mistaken for hyalinized arterioles, but with AP histochemistry it was shown that the affected vessels were exclusively venous. The thickened walls stained for collagens type I and III, which corresponds to excessive collagen deposition as occurs in hyalinization. Staining for collagen IV marked the basal lamina of the endothelium and the glia limitans at the brain parenchyma. These observations have not been repeated by other laboratories, but somewhat similar findings have been reported in multiple sclerosis lesions [32] and in brain capillaries in aging rats and hypertensive rats [33,34].

We found an association between severe PVC and LA [31]. Although hypertension is often associated with vascular dementia and LA, most of our cases did not have hypertension. Pantoni and Garcia [4] observed that hypertension is not always found in LA cases. In a magnetic resonance imaging (MRI) investigation of PVC, tapering or occlusion of veins at the margin of confluent LA was found, suggesting that LA may involve venous insufficiency [35]. Inhibition of blood flow by the venous stenosis of PVC might induce chronic ischemia and/or edema in the deep white matter, leading to LA.

The thickened venous walls could impair passage into the veins of fluids, solutes, and toxins destined for removal from the brain via the blood stream. In addition, PVC might hinder the function of the perivascular route for drainage through the brain [36,37]. It has been shown that cerebrospinal fluid (CSF) is pumped through the brain via the periaxonal spaces by the pulsations of the arterioles [37]. Also, arteriolar sclerosis might impede the pulsatile pumping that moves CSF along the arterioles. Among the substances which drain through the perivascular pathway is A β [38,39]. The low concentrations of A β in the CSF of AD patients is thought to be due to decreased cerebral clearance of A β into CSF [40]. Roher et al [41] have speculated that the A β deposits in the walls of capillaries could close the lumen and cause degeneration and disappearance of the capillary, leaving a deposit of A β that may form a neuritic plaque. Furthermore, A β deposition in the perivascular drainage pathway may cause cerebral amyloid angiopathy (CAA) that may block the function of this pathway [39]. In CAA, A β deposition occurs in and around the vascular walls (Figure 7), disrupts the BM of small vessels, causes endothelial cell damage, and can reduce the vascular lumen [42]. Perhaps sluggish perivascular flow caused by cerebrovascular pathology, such as venous collagenosis, tortuosity lesions, and thickened arteriolar walls facilitate A β deposition in this pathway and further block the clearance of toxins. Clearance of A β may be disrupted by microvascular pathology and the reduction of A β clearance may contribute to further microvascular pathology.

It is unknown why the veins become thickened in the deep white matter and why PVC is associated with LA. We suggest three mechanisms for the development of PVC and ischemia leading to LA: i) a genetic predisposition to excessive collagen deposition in veins; ii) a genetic predisposition to chronic periventricular ischemia that causes overproduction of collagen in the veins; and iii) mechanical damage to small vessels due to abnormally high pulsatile motion in the periventricular white matter, as proposed by Marie-Cecile Henry-Feugeas [43]. These mechanisms need not be mutually exclusive.

String vessels

String vessels (Figure 4) are BM remnants of capillaries that have lost their endothelium [44]. They cannot transport blood or plasma [45,46]. In studies of retinal digest preparations, it was found that ischemia caused string vessels to begin to form at 3 to 5 days, with the loss of endothelial cells [47]. By 8 days, some of the acellular capillary remnants were reduced to thin strands, which were still present at 40 days [47]. When capillaries first lose their

endothelial cells, the residual BM often shows accordion-like pleating [48]. Shutdown of blood flow for about 1 to 2 days can cause capillary loss [49]. After shutdown, capillary regression occurs by apoptosis, synchronously along capillary segments from one vascular junction to the next, often with macrophage engulfment of apoptotic endothelial cells [50]. During apoptosis, the endothelial cells can bulge into the lumen and detach from the BM [51]. The synchronous apoptosis of endothelial cells may be due to the loss of availability of vascular endothelial growth factor (VEGF), due to the lack of blood flow [50,52]. A second mechanism is the loss of fluid shear stress on the endothelial cell surface, which helps maintain endothelial cell survival [50,53].

String vessels occur commonly in the normal brain, spinal cord, and eye of humans and animals [54], and they are increased in ischemia [47], irradiation [55], mesial temporal sclerosis [56], and AD [57–62]. In normal brains, we found string vessels at all ages from preterm babies to the very old [63]. The number of string vessels was highest in pre- and post-natal subjects, when vascular remodeling is prominent. Because string vessels were fewer at older ages, we concluded that they disappear after some months or years. Although string vessels increase in the aged brain and in brain pathology [44], we found the density of string vessels in LA lesions to be decreased (unpublished). The density of capillaries in the deep white matter in LA is also decreased [64,65], but the decrease in string vessels was greater than that of the capillaries. Our data indicate that LA may begin as early as mid-life, with a progressive loss of vessels in the deep white matter. An early loss of capillaries in LA would be marked by an increase in string vessels, but the string vessels gradually disappear as they are resorbed. By the time of death and autopsy, most of the string vessels in LA lesions may have disappeared.

Basement membrane thickening

The BM becomes thicker with age [34,48,66] and in AD [62,67–69] (see review by Kalaria [70]). BMs are highly crosslinked insoluble material made up of approximately 50 proteins, of which about 50% is collagen, especially collagen IV [71]. The molecular composition of the BM is unique for each tissue and the two BM polymer sheets of collagen IV and laminin expose various signaling constituents, such as VEGF, to the endothelial cells [71]. Age-related BM thickening occurs via the deposition of collagen fibrils in and around the BM, and this thickening is correlated with atherosclerosis in large peripheral vessels [34]. BM thickening can also occur when a string vessel is invaded by a newly forming capillary [72]. Empty BM tubes can provide a scaffold and signaling molecules for vessel regrowth [52,71]. Invading capillaries lay down a new BM within the old one, creating a lamellar reduplication. This would likely be rare in aging, AD, and LA.

Capillary Growth and Loss

Hypoxia and angiogenesis in aging

Angiogenesis can occur when VEGF is induced in response to hypoxia via the transcription factor, hypoxia-inducible factor-1 (HIF-1) [73]. The endothelial cells of vascular sprouts have tips that are similar to axonal growth cones, and many of the signaling pathways are shared between the nervous system and the vasculature [74]. For example, VEGFs are growth factors for both endothelial and neural cells, and semaphorins control both axon guidance and vascular patterning [74]. Another factor in capillary stability is pericyte signaling via Tie-2 receptors on endothelial cells [75]. Normally, angiopoietin-1 is released by pericytes and activates the Tie-2 receptors on endothelial cells, helping to maintain vascular integrity [76]. Hypoxia causes the induction of angiopoietin-2 which occupies the Tie-2 receptors, preventing angiopoietin-1 activation and causing the pericytes to move away from the capillaries and destabilize them [76]. In the presence of VEGF, angiogenesis

occurs, but in the absence of VEGF, the capillaries undergo apoptotic regression [77]. During angiogenesis, the developing capillaries are more permeable than established vessels. Chronic hypoxia in 2 month-old mice caused an increase in brain vascular density, likely due to angiogenesis [78]. However, there appears to be an age-related decline in the capacity for cerebral angiogenesis [79,80]; the responsiveness of HIF-1 to hypoxia wanes with age, reducing VEGF expression [81–83]. This HIF-1 decline is associated with neuronal loss [84]. Thus, in aging, AD, and LA, there may be a failure of vascular recovery from hypoxia-induced bouts of capillary loss. This failure of vascular recovery and other cerebrovascular changes represent a loss of brain vascular reserve and functional reserve.

Age-related capillary loss

There is considerable evidence of an age-related failure of cerebral vascular recovery in the studies of vessel density in aging, AD, and LA. As described in review by Kalara [70], in 1996 there were mixed findings. At the time of the review by Riddle et al. [85] in 2003, the preponderance of the 22 studies cited showed declines in vascular density. In the present review of 37 studies, there is strong evidence of decreased vascular density in aging animals, aging humans, AD, LA, and a mouse model of AD. Detailed results are discussed below.

There have been several vascular density studies in aging rats: Jucker et al. [86] reported decreases in capillary number (20%) and length (3%), in the hippocampus, and increased intercapillary distance (24%). In the cortex, they observed reductions in capillary number (25%) and length (7%), and increased intercapillary distance (39%). In brain white matter, Shao et al. [87] found a decrease in capillary length (19%) and volume (24%). Klein and Michel [88] reported a 33% decline in vascular density. Buchweitz-Milton and Weiss [89] found a decrease in capillary length (29%) and volume (16%). Casey and Feldman [90] observed a decreased vascular density (30%) in the brain stem. Hinds and McNelly [91] found a 15% decrease in capillary density. Data from Wilkinson et al. [92] demonstrate a decrease in vessel numbers (11%) and brain blood volume (32%). Sonntag et al. [93] observed a decrease in vascular density (39%) on the cortical surface. Hutchins et al. [94] reported a 39% decrease in arterioles penetrating the cortex. Amenta et al. [95] found a decrease in capillary numbers (43%) and length (20%). Amenta et al. [96] showed decreases in capillary numbers (23%) and length (5%), and increased in intercapillary distance (48%). Data from Burns et al. [97] showed a decrease in capillary density (12%) and an increased intercapillary distance (6%). Knox and Oliveira [98] found a decrease in the capillary numbers (8%). Villena et al. [99] reported decreases in capillary numbers (9%), volume (19%), and length (11%) from 18 to 24 months, but from 24 to 28 months there were increases in capillary numbers (7%), volume (15%), and length (9%). Meier-Ruge and Schulz-Dazzi [100] reported no significant change in capillary density, but their data show decreases in capillary length (7.5%) and number (5%). Black et al. [79] found no change in vessel density. Hughes and Lantos [101] found increases in vessel number, but their old rats were not very old. Bar [102] reported a 3% decrease in vascular volume, but a 16% increase in vessel length. In mice, Sturrock [103] found no change in vessel density. Also, Vaugan and Calvin [104] showed a decrease in hemoglobin in the brains of older mice, which they concluded was due to decreased blood volume.

In studies of human aging, Bell and Ball [105] reported decreases in capillary density in all six brain areas measured (average 16%). They also found a decrease in capillary density (16%) in the calcarine cortex [106,107]. Abernethy et al [108] observed a decrease in vascular density (50%) in the human paraventricular nucleus, but no change in the supraoptic nuclei. Brown et al. [64] found a decline in vessel density between 57 and 90 years in the white matter (Figure 5). Buée et al. [57] reported that the vascular density in two normal elderly subjects (79 years) compared to one young subject (49 years) was decreased by 26%. Mann et al. [109] found a decrease in vessel density in frontal cortex, but not in

temporal cortex. Hunziker et al. [110,111] found increased vascular density in subjects 64–74 years of age, compared to young subjects, but those 75 and older had a similar vascular density to the young. Meier-Ruge et al. [112] reported that vascular density was increased in the putamen, but unchanged in the cortex. However, their data for cortex showed decreases in capillary length and volume from ages 65–74 to 75–94. Farkas et al. [34] found no age-related change in vascular density in the white matter.

Capillary loss in AD

Bell and Ball [105] reported age-related decreases in capillary density in AD in the six brain areas measured (average 17%). Bell and Ball [106,107] found a decrease in capillary density (18%) in the calcarine cortex in AD. Brown et al. [64] observed an age-related decrease in vessel density in the white matter in seven AD subjects, and the AD vessel densities were lower than those of age-matched controls (Figure 5). Fischer et al. [26] found a decrease in vascular density in AD versus control (30%). Buée et al. [57] reported vascular density in AD to be decreased by 16% compared to age-matched controls, and 38% compared to a 49 year old. Suter et al. [113] commented that small cortical arterioles and capillaries were decreased in three AD cases compared with an age-matched control. Bailey et al. [114] showed a decline in vascular density with increasing Clinical Dementia Rating (CDR) score. In contrast to those studies, Perlmutter et al. [62] reported an anecdotal finding of focal regional increases in capillary density in AD subjects and Desai et al [115] found that vascular density was increased in one of five areas examined. They also found that an endothelial marker of angiogenesis was elevated in AD brains [115]. In a mouse model of AD, Paris et al. [116] found a decrease in vascular density of about 30% in both the hippocampus and cortex. Lee et al. [117] reported a 21% decrease in capillary numbers in the corpus callosum in a mouse model of AD.

Amyloid β ($A\beta$) accumulations on capillaries may contribute to the reduced brain capillary density in AD via anti-angiogenic activity [116,118]. Although the angiogenic factor VEGF is increased in AD [119], as would be expected in hypoxic conditions, VEGF binds to $A\beta$ and is heavily deposited in plaques. Thus, $A\beta$ may act as a molecular sink for VEGF, reducing its availability in AD [120].

Capillary loss in LA

Our laboratory has published vascular density studies in subjects from 57 to 90 years old comparing vessel density in the deep white matter from non-LA subjects to that in LA lesions, normal-appearing white matter, and cortex [64,65]. Vascular density in LA lesions was decreased (20%). Because there was an age-related decline in vessel density between years 57 and 90 in normal subjects, whereas vessel density in LA lesions did not decrease with age, vessel densities after 80 years were equivalent in the deep white matter of the LA and non-LA subjects (Figure 5). We observed a non-significant decrease in vascular density (11%) in the subcortical white matter in subjects with LA lesions, but in those LA subjects who died before 60 years, the decrease was 47%. Vessel density was also decreased (7%) in the cortex of LA subjects, but in those LA subjects who died before 60 years, the decrease in the cortex was 38% [64,65]. We also studied LA-like white matter lesions in four patients who received whole-brain irradiation for brain tumors. The deep white matter in these patients had low vessel densities, similar to those found in LA (Figure 5). Furthermore, there did not appear to be an age-related decline in vessel density in irradiated patients. After about 80 years of age, vascular density in the white matter tends to drop to levels typical of LA and irradiation. Similarly, it has been shown that the association between $A\beta$ plaques and dementia was strong at 75 years of age, but reduced at 95 years of age [121]. This presents a problem with studies using heavy sampling in subjects over 70 years of age. Younger subjects are more likely to show significant differences in vessel density due to

pathologies such as LA and AD. This problem can be partially circumvented by presenting the findings graphically and analytically as age-related changes as in Figure 5.

It is interesting that vascular density in LA lesions does not fall below a level that would cause infarcts and cavitation. Instead, the white matter appears to become hypoxic because of capillary loss, followed by spongiosis and enlargement of the ventricles as cells in the white matter gradually die. In LA we find apoptosis with a loss of oligodendrocytes and perhaps astrocytes [122–124]. Alternatively, a loss of neuropil would result in a decreased need for oxygen and glucose, and lead to a loss of capillaries. However, studies have revealed increased oxygen extraction from the blood in the deep white matter in LA, which would imply that there are too many cells for the existing oxygen supply [125–127]. This suggests that the capillary loss occurs first, causing misery perfusion in the white matter. The capillaries appear to die first, but why do they stop dying? Perhaps a hemodynamic imperative is reached, i.e., the number of capillaries needed to simply transport the arterial blood to the venous system is reached (Figure 6). At that point, capillary loss would cease and no more string vessels would be formed, and as string vessels are resorbed, there would be very few left in the LA lesions at autopsy.

Decreases in brain vascular density may be limited by physiological factors. As vessels are lost, hypoxia stimulates angiogenesis, but this may fail in old age. In this case, vessel density may decline, causing neuronal dysfunction and then neuronal and glial cell death. As cell death causes a loss of parenchymal volume, the packing effect reduces the amount of reduction in vascular density. However, some hypoxia can be tolerated by neurons and glia without causing cell death. At that point, there would be some reduction in vascular density.

Cerebral Perfusion

Elevated blood pressure, cerebrovascular pathology, and cognitive dysfunction

Hypertension, elevated blood pressure (BP), and fluctuations in BP are associated with cerebrovascular pathology [128], including the recently described cerebral microbleeds [129,130]. LA lesions were found to be increased with age and linearly increased with increasing BP levels [128]. Hypertension is also associated with decreased cognitive function [131]. In midlife, hypertension appears to injure the vascular system, but with advancing age, the lower boundary of autoregulation in the brain shifts upward, causing vulnerability to hypoperfusion [132]. Such hypoperfusion may cause white matter ischemia and LA [133]. Thus, aggressive treatment of hypertension in old age may cause brain hypoperfusion [133]. On the other hand, hypertension treatment in the elderly has been shown to improve BP levels and restore BP regulation [134], so hypertension treatment may induce some recovery of vascular pathology. Consequently, BP control in the elderly becomes a balancing act between risk and benefit.

Reduced cerebral blood flow and cognitive dysfunction

Reduced vascular density is consistent with findings of reduced cerebral blood flow (CBF) in LA and AD [135,136]. The following are among the factors that influence CBF: perivascular nerves can constrict or dilate arteries and arterioles [137,138], astrocyte end feet can influence arteriolar diameter [139], endothelial cells can release vasodilators such as nitric oxide and vasoconstrictors such as endothelin [140], and pericytes can cause capillary contraction and relaxation [141]. In AD, loss of cholinergic innervation of brain blood vessels [138], even down to the microvessels [142], may contribute to brain hypoperfusion.

LA lesions show increased expression of the hypoxia-inducible factor HIF1 α [143], and white matter lesion load correlates with the degree of hypoperfusion [144] and cognitive impairment [7–14]. The cognitive impairment may be affected by the location of the lesions.

CBF is also reduced in normal-appearing periventricular white matter in patients with LA [144]. This is consistent with hypoperfusion preceding and inducing LA lesion development. Recent diffusion-weighted imaging studies of normal-appearing white matter in LA patients have shown increased diffusivity in white matter outside of the LA lesions [145,146] and this was more strongly correlated with cognitive decline than was lesion load or brain atrophy [145]. This indication of moderate damage adjacent to the LA lesions parallels our findings of a trend toward decreased vascular density in these areas and in the cortex [64,65]. Regional decreases in white matter integrity (fractional anisotropy) are linked to gray matter hypometabolism in the areas affected in AD and vascular dementia [147].

Hypoperfusion in AD induces white matter lesions and cortical watershed microinfarcts [113]. CBF reductions correlate with dementia and co-localize with cortical atrophy and vascular disease in the white matter [136]. Reduced CBF occurs early in the development of AD, most significantly in areas where tau pathology is associated with AD [148,149]. These perfusion deficits develop in presymptomatic stages before brain atrophy [135,148,149]. Subjects with mild cognitive impairment also exhibit hypoperfusion in the areas most affected in AD [135,149].

Cholinergic stimulation of brain perfusion

The human basal forebrain cholinergic system plays a major role in cognitive function and cholinergic agonists have been shown to enhance cognition in both animals and humans [150]. Baroreceptors monitor BP and induce neural responses to modulate BP [151] and regional blood flow [152]. This function is reduced in the elderly [153]. Cholinergic deficits are observed following chronic hypoperfusion [154] and cholinesterase inhibitors, such as donepezil, can enhance cholinergic transmission [155]. Ischemia of cholinergic nuclei can result in cholinergic neuron loss [156], and this injury may be exacerbated if the damage to the cholinergic nuclei reduces their function. This may occur in vascular dementia [157–159] and AD [160]. Cholinesterase inhibitors have some benefit in treating vascular dementia, although not as much as in AD [161]. In vascular dementia, cholinergic reductions are correlated with cognitive impairment [162]. In AD, excitation of acetylcholine receptors by physostigmine improved the impaired CBF [150]. Furthermore, cholinesterase inhibitors enhanced CBF and cognition in AD patients [163]. Cholinergic fibers are often severed in white matter lesions, resulting in disconnection of the cholinergic projections to the cortex [138]. Possibly, this disconnection contributes to white matter lesion-induced cognitive dysfunction. Indeed, cholinesterase inhibitors can restore CBF after ablation of the nucleus basalis of Meynert [164]. There is reason for optimism that the brain can be rescued from extended periods of hypoperfusion. In Norrie disease, where retinal hypovascularization causes ischemia and vision loss [165], the rods and cones remain intact but unable to transmit signals in their hypoxic milieu. However, their function can be revived with oxygenation.

Cerebrovascular Microemboli and Their Clearance

Microemboli from cardiac surgery

Microemboli released during cardiac surgery assisted by cardiopulmonary bypass (CPB) are a source of microvascular pathology. In brain tissue sections from patients who die within days after cardiac surgery, lipid microemboli can be seen as SCADs (small capillary and arteriolar dilatations) (Figure 8) [166]. The microemboli tend to pump through the vessels, breaking into smaller emboli at branch-points [167]. While most of these emboli pass through the brain in a few hours to a few days, some remain impacted for weeks or longer [168]. This can block blood flow and cause ischemia and capillary loss.

Our findings suggest that SCADs come primarily from fat that drips into the blood in the chest wound during surgery, especially from the fatty marrow of the sternum [167]. When this lipid-laden blood is suctioned into the CPB circuit, the lipid globules can slip through the filters and travel to the brain and other organs. Microvascular occlusion by lipid emboli may be the major contributor to post-CPB encephalopathy. Our studies with experimental dog surgeries have led to strategies of blood return and blood temperature management to improve surgical outcomes. For example, suctioned blood is cleansed of lipid emboli by passing it through a cell saver, which washes and separates red blood cells by centrifugation [169,170].

Other vascular surgical procedures that can cause lipid microemboli to circulate to the brain include disruption of atheromatous plaque during carotid endarterectomy [171], and left heart catheterization during angioplasty [166,172]. These procedures can also result in cognitive decline [173]. Orthopedic surgery of large bones can also release lipid emboli from the bone marrow into the venous system [174], some of which can pass through the lungs [174,175]. Patients with a patent foramen ovale are especially in danger of having emboli pass into the left side of the heart and travel to the brain. This can cause cognitive dysfunction, stroke, coma, or death [167,176,177]. Another major source of fat embolism is broken bones, as in car accidents, which can cause petechial hemorrhages in the brain, skin, and conjunctiva, and sometimes death [167]. Since fat emboli float in the blood, positioning the patient head down can alter their route [178]. Fat embolism affects the white matter more than it does the cortex [167], perhaps because of its vulnerability to hypoperfusion.

Post-pump encephalopathy appears to be a type of vascular dementia resulting from lipid microemboli [167]. This can cause accelerated cognitive decline some years after surgery [179–183]. With aging, lost capillaries are less likely to be replaced, and this may cause chronic hypoperfusion and exacerbate any bouts of hypoxia. There is an accelerated cognitive decline 5 years after CPB surgery [179–182]. Embolic injury may accelerate age-related cerebrovascular pathology and reduce vascular reserve and brain reserve. It is of interest that the cholinesterase inhibitor, donepezil, has shown some benefit for cognitive decline following CPB surgery [184]. Because cardiac surgery is the most common surgery in the world [185], it may be worth recording as a risk factor in studies of dementia.

Extravasation of emboli

Grutzendler and colleagues have recently shown that certain types of emboli were extruded through the walls of mouse cerebral vessels within 2 to 7 days after injection into the carotid artery [186]. The emboli included fibrin clots and cholesterol crystals filtered through sieves of 8–20 μm pore size, and polystyrene microspheres of 10 or 15 μm diameter. Using new techniques such as a thinned-skull cranial window, high resolution imaging with two-photon laser scanning microscopy, and live video, the process of emboli extravasation was shown in live mice. The emboli that lodged in the microvasculature became covered by endothelial cell membrane projections which completely enveloped them within 24–48 hours. The endothelial projections frequently formed transient adhesions, resembling adherens junctions, with the endothelium of the opposing wall of the vessel. The emboli were then pushed toward the parenchyma as the endothelial cells withdrew from the abluminal side of the embolus, exposing the embolus to the BM. The embolus then passed through the BM into the extravascular space adjacent to the brain parenchyma. Matrix metalloproteinases were detected adjacent to the emboli and extravasation was decreased after treatment with matrix metalloproteinase inhibitors.

There was some vascular degeneration with 15 μm microspheres, but none with 10 μm microspheres [186]. With the numbers of microemboli they administered, they typically found transient hypoxia and transient synaptic pruning rather than cell death. In aged mice,

however, extravasation of emboli was delayed and accompanied by persistent hypoxia, dystrophic synapses, and caspase-positive (apoptotic) perivascular cells. Thus the degree of embolic brain injury depends on the number, size, and type of the emboli, as well as the age of the person or animal.

This extravasation of clots, cholesterol crystals, and microspheres appears to differ from what occurs in the case of lipid emboli. We have not seen evidence of lipid embolus extravasation and numerous lipid emboli remain within the cerebral microvasculature for some weeks after cardiac surgery, often in degenerated capillaries (Figures 9 and 10) [167,168]. Antifoam emboli, with fat-like consistency, have also been found up to 8 months after CPB [187]. After fat embolism, excretion occurs via small lipid droplets in the urine and sputum [188]. If lipid emboli are not extravasated, one explanation could be that endothelial cells are unable to extend cell projections over the flexible and motile surface of lipid droplets. Also, the lipid emboli may not trigger an endothelial cell recognition event that induces membrane projections to cover the embolus.

Conclusions

Current evidence suggests that there is an age-related decline in microvascular structure. The decline in the capacity for cerebrovascular angiogenesis may result in a failure of vascular recovery from hypoxia-induced bouts of capillary loss in aging, AD, and LA. In concordance with this, there is strong evidence of decreased vascular density in aging, AD, and LA. Reduced capillary density in AD may be due in part to a reduction in angiogenesis caused by VEGF becoming bound to A β and sequestered in plaques.

The white matter is vulnerable to suffering hypoperfusion because its major blood supply is via long arterioles which arise from the border-zone. Blood flow can also be inhibited by tortuous arterioles which form in the white matter, coiled in a cavity where brain parenchyma is lost. Another change is the deposition of excessive collagen in the walls of veins and venules in the deep white matter. These deposits can be severe in LA, and they likely contribute to the development of LA. Vascular collagen deposition also occurs in multiple sclerosis lesions. It would be interesting to know its significance and whether the veins are specifically affected. Venous collagenosis in LA likely inhibits blood flow. The thickened walls may inhibit the passage of fluids and toxins into the veins for removal from the brain, and the perivascular drainage may also be impaired, affecting the clearance of A β along this channel.

Hypertension appears to injure the vascular system, and with aging, the boundary of autoregulation in the brain shifts upward, causing vulnerability to hypoperfusion. Misery perfusion due to capillary loss appears to occur before cell loss in LA, as there is increased oxygen extraction in the deep white matter, which implies reduced oxygen supply. CBF is also reduced in normal-appearing white matter in LA. This is consistent with hypoperfusion preceding and inducing LA. LA lesions correlate with the degree of hypoperfusion and cognitive impairment. Normal-appearing white matter in LA also has increased diffusivity and this is correlated with cognitive decline. Hypoperfusion in AD induces white matter lesions, and CBF reductions correlate with dementia and vascular disease in the white matter. Reduced CBF occurs early in AD, in areas where tau pathology is associated with AD. These perfusion deficits develop in presymptomatic stages before brain atrophy. Also, in mild cognitive impairment, hypoperfusion occurs in the areas most affected in AD.

In AD, loss of cholinergic innervation of brain blood vessels may contribute to brain hypoperfusion. Neural responses modulate BP and regional blood flow, but this function is reduced in the elderly. Cholinergic deficits occur following chronic hypoperfusion, and

ischemia of cholinergic nuclei can cause cholinergic neuron loss. Such injury may be exacerbated if damage to the nuclei reduces cholinergic activity. In vascular dementia, cholinergic reductions are correlated with cognitive impairment, and cholinesterase inhibitors have some benefit, although not as much as in AD. Cholinergic fibers are often severed by lesions in the white matter, disconnecting cholinergic projections to the cortex, which might contribute to cognitive dysfunction. In AD, excitation of acetylcholine receptors improved the impaired CBF, and cholinesterase inhibitors enhanced CBF and cognition.

Lipid microemboli from cardiac surgery pump through the vessels, breaking into smaller emboli at branch-points and occlude some microvessels. Most of the emboli pass through the brain in a few hours to days, but some remain for weeks. They can cause cognitive dysfunction, stroke, coma, or death. Microemboli-induced encephalopathy appears to be a type of vascular dementia which can develop some years after surgery. Donepezil has shown some benefit. It has been recently shown that emboli, such as clots, cholesterol crystals, and microspheres, can be extruded through the walls of cerebral vessels. The emboli became enveloped by endothelial cell membrane projections and then pushed out as the endothelial cells withdrew at the abluminal side of the vessel. Emboli then passed through the BM into the extravascular space. In aged mice, extravasation of emboli was slower. There is no evidence yet that lipid emboli undergo such extravasation.

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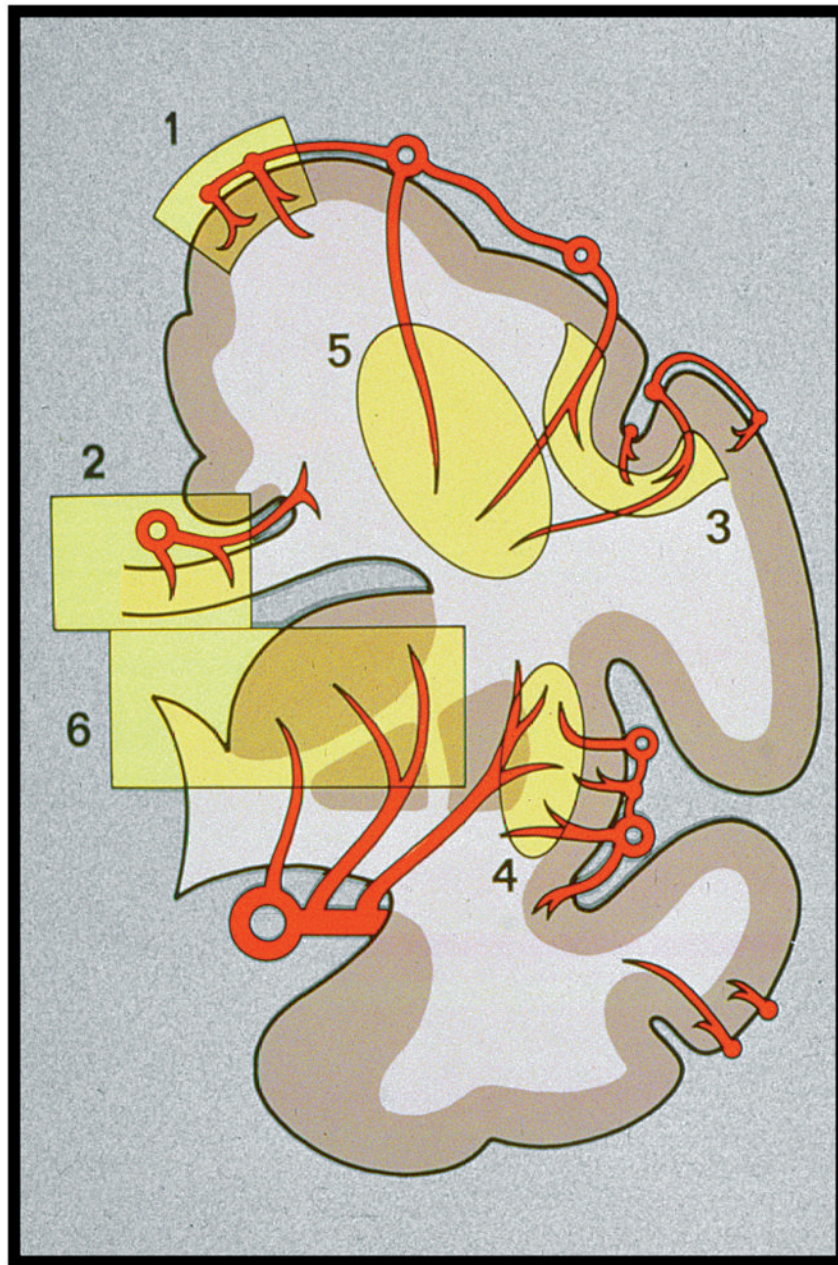


Fig. 1. Schematic of the cerebral blood supply. (Reprinted from [17]).

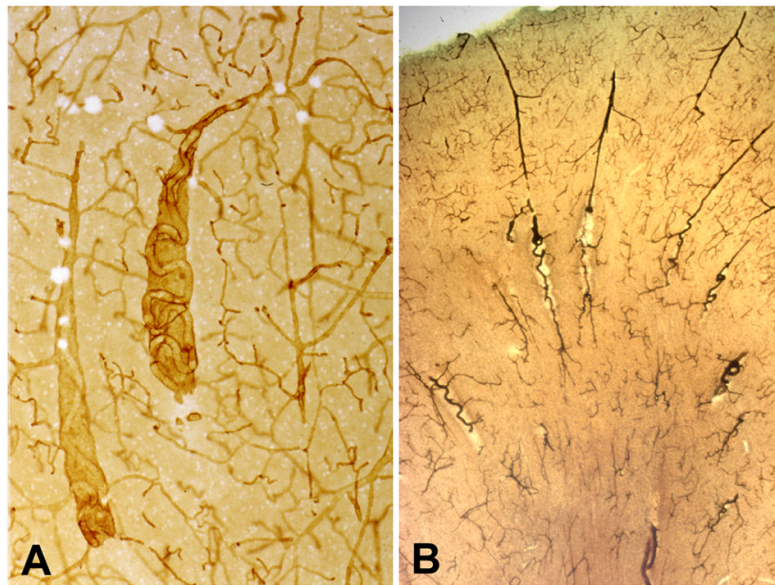


Fig. 2. Tortuous arterioles in the white matter. (A) This thick celloidin section stained with collagen IV shows two tortuous arterioles in cavities. (B) This thick celloidin section stained with AP shows several arterioles with tortuosity beginning as they enter the white matter. (Reprinted from [20]).

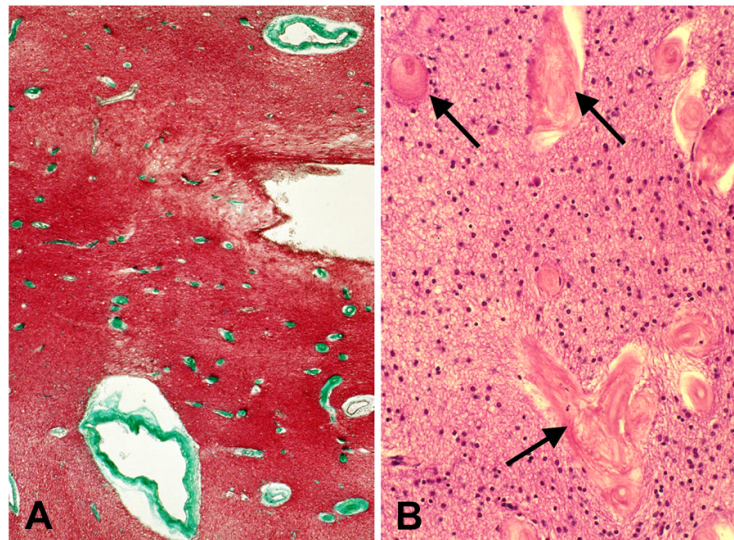


Fig. 3. Severe periventricular venous collagenosis in the brain of a subject with leukoaraiosis. (A) This thin paraffin section stained with trichrome shows numerous affected veins (green) near the lateral ventricle. (B) This thin paraffin section stained with &E shows veins with collagenosis (arrows) at higher magnification. (Reprinted from [20]).

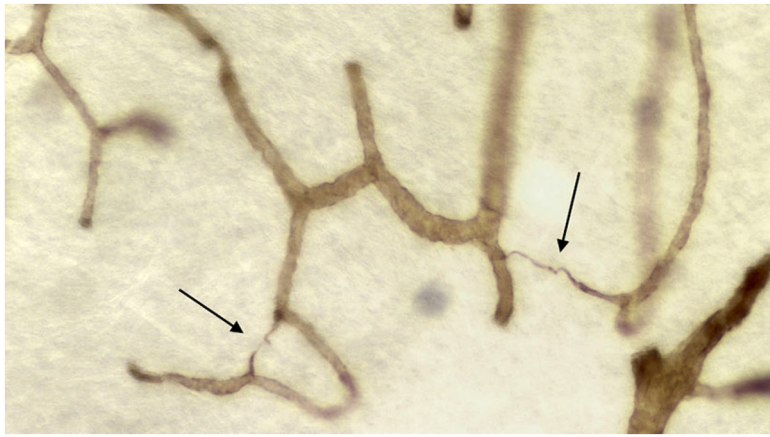


Fig. 4. String vessels (arrows) in a thick celloidin section stained with antibody to collagen IV.

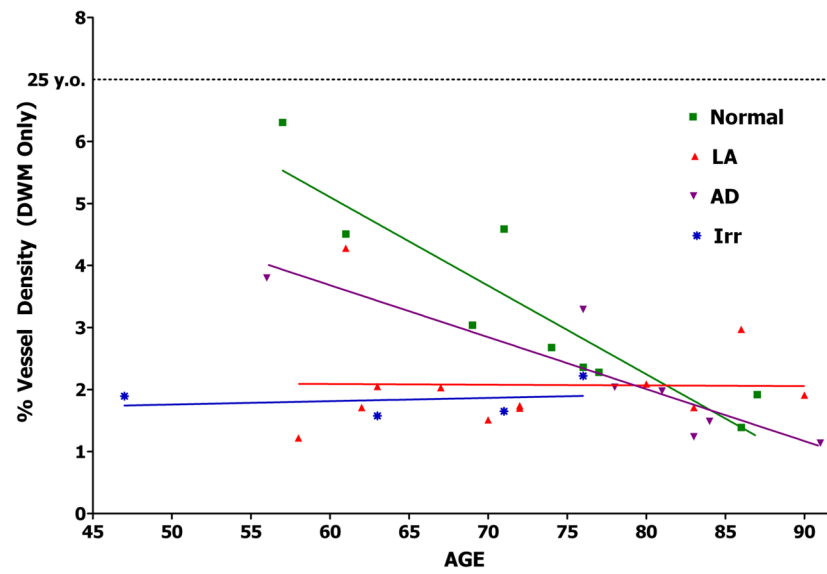


Fig. 5.
Graph of vascular density in normal, AD, LA, and brain irradiation.

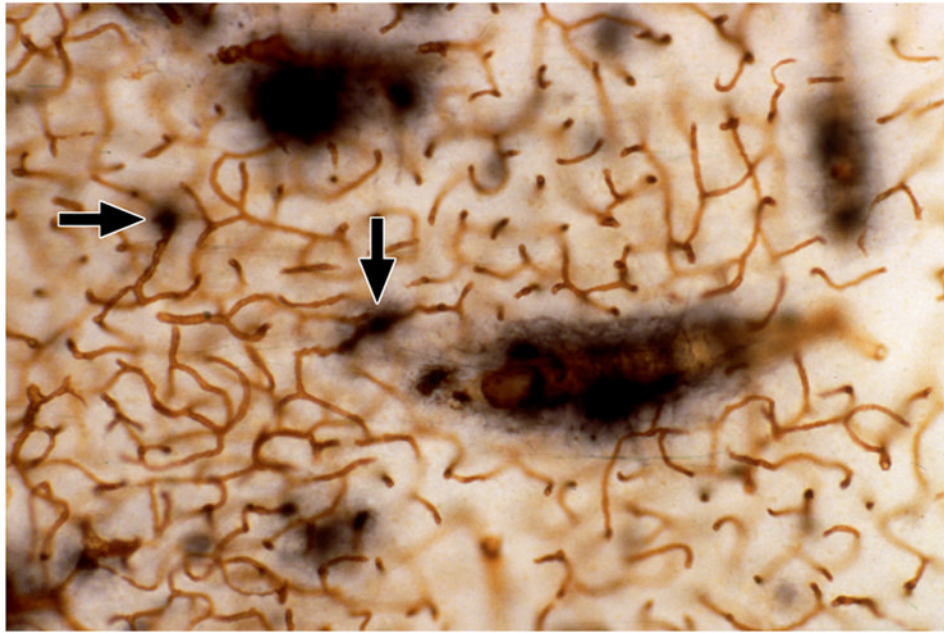


Fig. 6. Amyloid β deposited in and around capillaries (arrows) larger blood vessels. Thick celloidin section stained with antibodies to collagen IV and A β . (Reprinted from [189]).

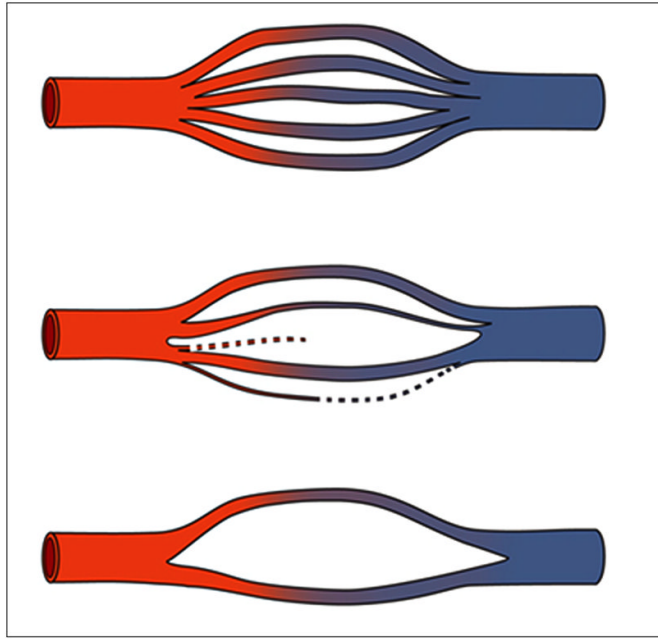


Fig. 7. Schematic of capillary loss and string vessel formation. (Reprinted from [44]).

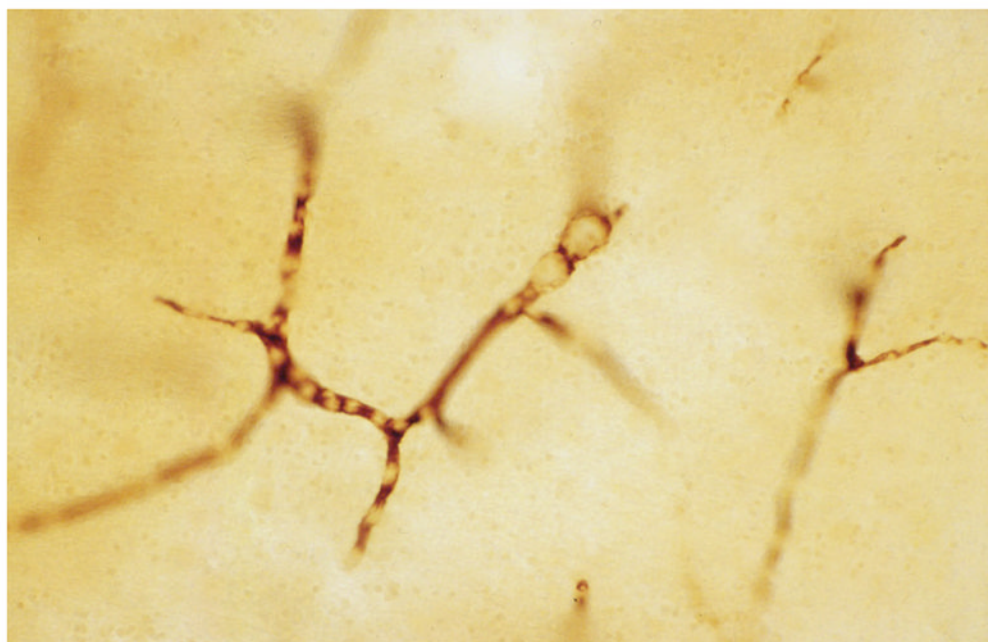


Fig. 8. Lipid microemboli in brain capillaries in a patient one day after cardiac surgery assisted by CPB. (Reprinted from [190]).

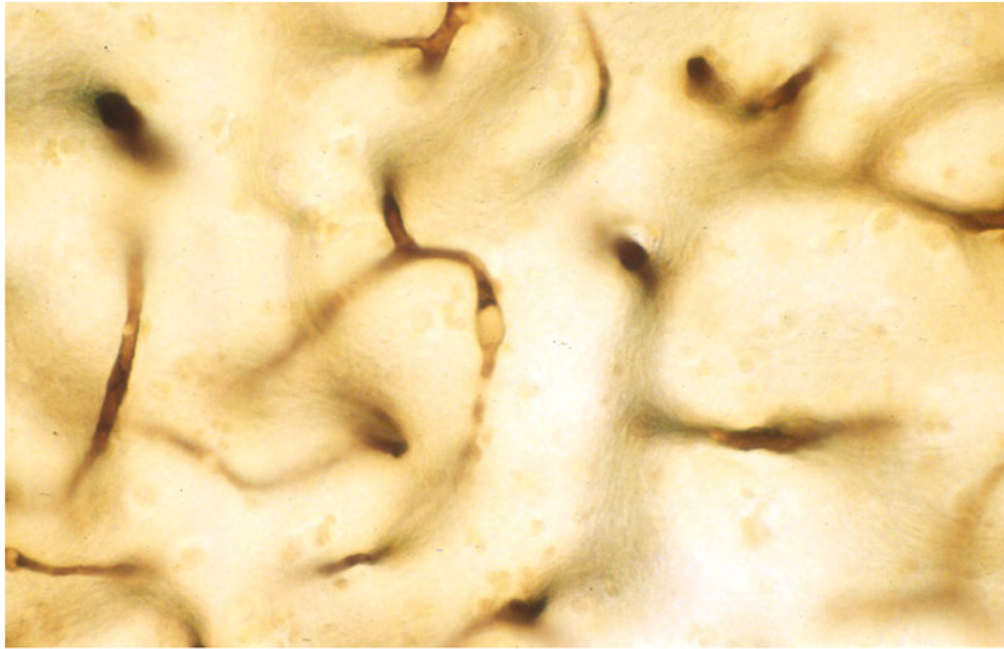


Fig. 9. A lipid embolus (large arrow) in a brain capillary in a patient 17 days after cardiac surgery assisted by CPB. Note the loss of AP staining and apparent degenerative changes in the capillary down stream from the embolus. (Reprinted from [167]).

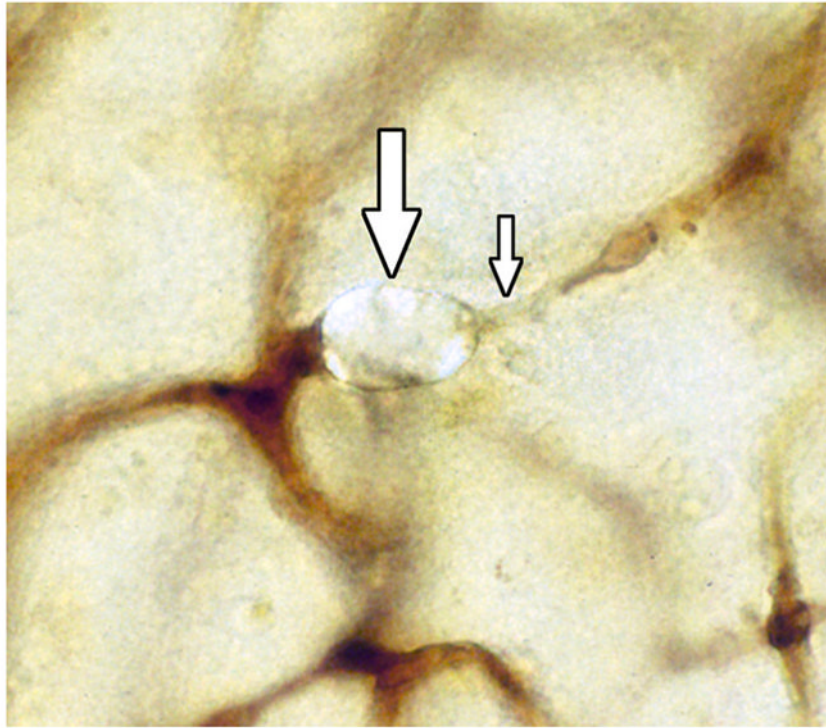


Fig. 10. A lipid embolus (large arrow) showing birefringence in a photograph with a polarizing filter. Note the loss of AP staining and apparent degenerative changes in the capillary down stream from the embolus. (Reprinted from [167]).