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Histopathologic Analysis of Intraarterial Polyvinyl Alcohol Microemboli in Rat Cerebral Cortex

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Polyvinyl alcohol (PVA) foam particles have been used with success in both experimental and clinical embolization of vascular lesions. Cellular response to PVA has been well documented outside, but not within, the central nervous system. This study was directed specifically at the cellular response to PVA in rat brain vasculature. By using small numbers of microparticles, an effort was made to define the response to PVA alone, rather than associated occlusions or infarctions. It was determined that PVA elicited no significant inflammatory response in the embolized vessels nor in the surrounding tissue. The isolated fragments did not appear to alter the blood-brain barrier. The PVA microemboli were extremely adherent to vascular endothelium, lodging in vessels of larger diameter and in relatively high-flow locations without actually wedging within the vessel lumen. On the basis of this analysis, it was determined that PVA foam has properties suitable for an intracerebral vascular embolic agent.

Polyvinyl alcohol (PVA) foam microemboli (Unipoint Labs., High Point, NC) represent a type of particulate material suitable for many interventional neuroradiographic procedures [1–5]. Its natural biologic behavior, based on histologic evidence in visceral organs and extracranial use, has been reported [5–7]. Injection of PVA into canine renal and splenic arteries revealed progressive, nonrecanalizing thrombosis and eventual fibrosis of the injected artery with only a transient minimal inflammatory response [6, 7]. PVA has also been used for artificial dura, cardiac patch grafts, and as a skin prosthesis [8–12]. It elicited minimal inflammatory response and progressive fibrosis, while demonstrating a high degree of biocompatibility. To date, a laboratory investigation assessing the histopathologic response of the intracerebral circulation has not been reported. Since PVA foam microemboli represent a potential intracerebral embolic agent, further investigation is warranted. The purpose of this project was to examine the cerebrovascular histologic changes of small numbers of PVA emboli introduced directly into the rat internal carotid artery.

Materials and Methods

Thirty-five Sprague-Dawley rats weighing 250–200 g were anesthetized with a combination of Ketaject (ketamine hydrochloride, Bristol Labs., Syracuse, NY: 0.87 ml/100 g intramuscularly) and Rompun (zylazine, Bayvet Div. of Cutter Labs., Shawnee, KS: 0.31 ml/100 intramuscularly). Under ×3 and ×20 magnification, dissection was performed of the right common, external, and internal carotid arteries. The procedure was surgically clean, but nonsterile. Preoperatively, the PVA fragments were suspended in saline, fragmented in a high-shear blender, sterilized in a steam autoclave at 121°C for 30 min, and separated by direct observation. Temporary vascular occlusion clips (Kliner-Kutz Temporary Microvascular Occlusion Clips, Edward Weck, Research Triangle Park, NC) were placed on the proximal and distal common and external carotid arteries. The internal carotid was selectively cannulated with a Silastic catheter having a 1-mm-thick tip via a common carotid arteriotomy. Ten 50–150-μm-diameter PVA emboli, suspended in 0.5 ml of normal saline, were injected with

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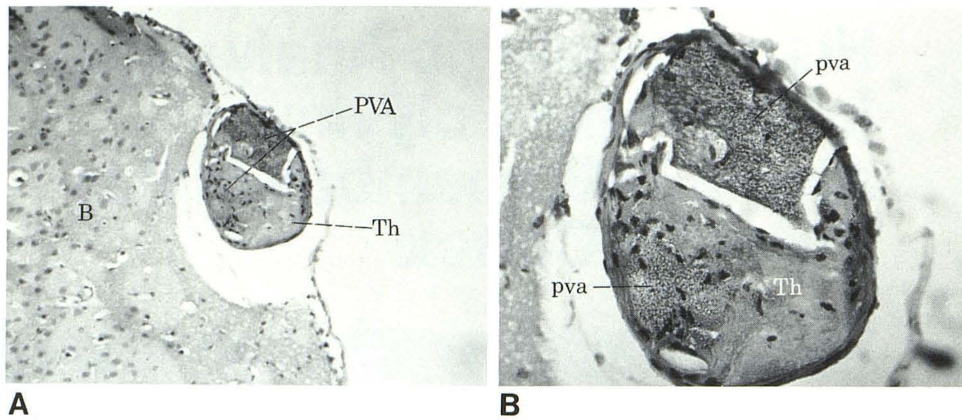

Fig. 1.—**A**, Photomicrograph ×250 of occluded middle cerebral artery in animal sacrificed 12 hr postembolization. Separation of organized thrombus (Th) from PVA fragment is artifactual. No acute histologic changes were noted in brain (B) to suggest infarction. **B**, ×400 magnification reveals a few inflammatory cells limited to thrombus. No alteration of endothelium or vessel wall is evident.

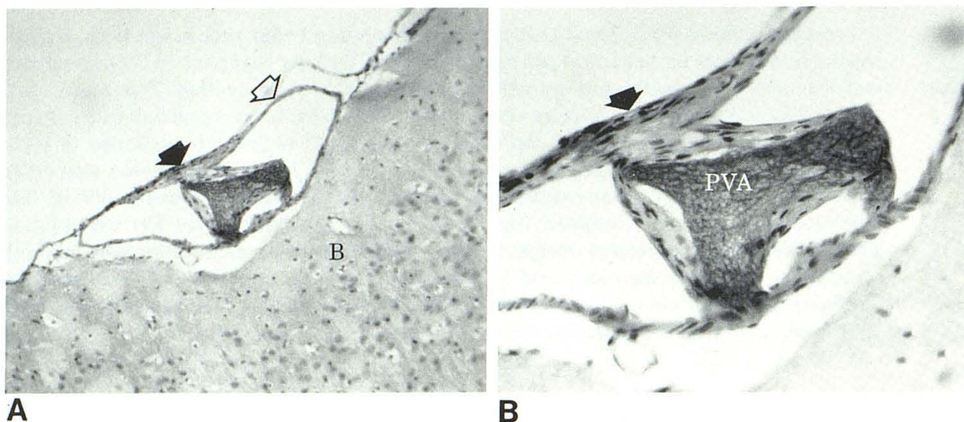

Fig. 2.—**A**, An approximately 100 μm PVA embolus from a rat sacrificed 3 months postembolization. Vessel lumen is patent, and there is no evidence of inflammatory response affecting vessel wall (*open arrow*) or brain (B) parenchyma. Endothelial proliferation (*solid arrow*) at points where PVA touches intima. **B**, ×400. Embolus is enveloped in endothelial and fibrous tissue. Focal endothelial proliferation (*arrow*) at points in contact with PVA fragment; otherwise, no alteration of intima, vessel wall, or perivascular space. Brain parenchyma adjacent to polyvinyl embolus is normal also.

clip occlusion of the external and proximal common carotid arteries. Back-flow through the internal carotid postembolization, without evidence of reflux of emboli, was assured in each instance. The arteriotomy was closed with interrupted 10–0 suture. The procedure was repeated on the left carotid arteries with 0.5 ml normal saline only, as a control. The dermal incision was approximated with Michael wound clips (Codman Shurtleff, Randolph, MA). Two animals were sacrificed at 0, ½, 1, 3, 12, and 24 hr and daily at 2–5 days. The other 15 animals were then examined weekly from 1 to 12 weeks and then at 6 and 9 months and were also sacrificed.

One population (15 of 35 rats) arbitrarily chosen from the 35 rats at varying intervals was perfused with 2% Evans blue solution, 0.1 ml/100 g intravenously, 15 min before sacrifice. A second population received no Evans blue. Both were sacrificed at the above-noted intervals after embolization by cardiac (left-ventricular) perfusion with 100 ml of normal saline followed by 50 ml of a 10% phosphate-buffered formalin solution. The brains were removed and allowed to fix in the perfusate. They were imbedded in paraffin, sectioned at 150 μm intervals, and stained with hematoxylin and eosin. Both carotid arteries from each animal were removed and examined for patency.

Results

All carotid arteries were patent at the time of sacrifice. Routine light microscopic examination revealed no pathologic abnormalities in the control left hemispheres. One animal developed a right parietooccipital meningitis and brain abscess from which it died at 8 weeks. The exact location or origin of the abscess was unclear from histologic examination. Another animal sacrificed at 12 hr was found to have neuronal dropout in the right hippocampal region suggesting a hypoxic event. This animal was also found to have a proximal middle cerebral artery branch occlusion with an approximately 100 μm diameter PVA embolus. However, there was no evidence of a middle cerebral artery distribution infarct. No other direct procedural complications were noted.

The PVA emboli were found in 34 of 35 of the brains examined. Most of the emboli were located in the intracranial internal carotid, proximal anterior, and proximal middle cerebral arteries. All the intracerebral emboli (except one) were detected in proximal cerebral vessels measuring 100–200 μm in diameter. No emboli were detected in the ipsilateral posterior circulation nor in the contralateral vessels. A single case demonstrated PVA fragments in a distal middle cerebral cortical arterial vessel with complete thrombosis of the embolized vessels. No other cases of thrombosis were identified. In no cases did the appearances suggest recanalization after previous thrombosis.

Most of the cerebral emboli were about 50 μm in diameter. In only two animals were the fragments larger (about 100 μm in size). In both these cases the emboli were adherent to larger proximal cerebral vessels. In the single case of vessel thrombosis associated with a PVA fragment (fig. 1), acute

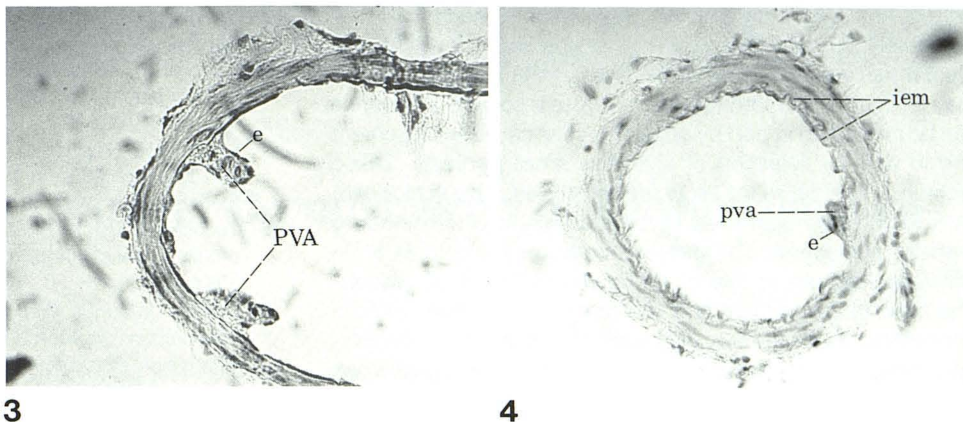

Fig. 3.—Photomicrograph demonstrates supraclinoid internal carotid artery and branch in animal sacrificed 7 days postembolization. Small fragments of PVA have adhered to vessel wall without actually wedging within confines of vessel lumen. Already microemboli have become surrounded by endothelium. No inflammatory cells are evident in vessel wall or adjacent to PVA microparticles.

Fig. 4.—Photomicrograph of proximal cerebral artery 6 months after embolization reveals small fragment of PVA surrounded by endothelium (e). Note endothelial response to intravascular PVA microembolus is essentially the same as in fig. 3A, where PVA fragments had been present for only 7 days. No chronic vessel wall inflammatory changes are evident. No degeneration of arterial musculature or internal elastic membrane (IEM) has occurred.

inflammatory cells were evident within the organized thrombus. However, no mural, perivascular, or contiguous brain inflammatory changes occurred nor were changes indicative of infarction seen in brain sections distal to the emboli. PVA fragments of 150 μm in diameter were not found, suggesting that these emboli were stopped short of the cerebral circulation. Numerous fragments were found adherent to the endothelium of vessels about three times their diameter without mechanically wedging in the vessel lumen (figs. 2–4).

All the fragments adherent to the endothelium elicited no apparent response for the first 5 days. Envelopment of the PVA emboli by endothelium was observed between 5 and 7 days. Specimens at 7 days were found to have incorporated the PVA into the vessel wall by sandwiching it between endothelial cell layers (fig. 3). From 7 days to 9 months, there were no further changes noted either in the vessel walls or the PVA fragments (figs. 2 and 4).

There was no evidence of any inflammatory response to the PVA in the absence of occlusion. The arterial wall remained free of acute or chronic inflammatory cells for the entire period of review, its only response being that of endothelial overgrowth. The adventitia, Virchow-Robin spaces, and underlying cerebral parenchyma were all free of any response to the PVA. No endothelial, internal-elastic-membrane, or vessel-wall degeneration was observed (fig. 4). There was no early or late staining of cerebral tissue with the Evans blue solution, indicating that disruption of the blood-brain barrier from either the isolated PVA fragments or from the single observed occlusion did not occur.

Discussion

Numerous experimental and clinical investigations with PVA foam have shown it to be a biocompatible material eliciting a mild, nonspecific inflammatory response [3, 5–7]. Casteneda-Zuniga et al. [6] have reported intimal proliferation and a mild polymorphonuclear leukocyte response in the media of canine splenic arteries. They found this to evolve to vessel fibrosis in 9 months. Previously reported analyses of intravascular PVA embolization have been limited to vessels, which have been completely occluded. Thus, it is unclear what role occlusion and/or infarction had in producing the observed cellular response.

Since in this study PVA emboli were introduced in small numbers and at small sizes, all but one of the cases demonstrated PVA fragments without complete lumen occlusion. This helped to eliminate cellular response to tissue or vessel infarction and permitted analysis of the response to PVA in the absence of vessel thrombosis or brain infarction. An inflammatory response was seen only in the one instance of a vascular occlusion, and was absent in the specimens without occlusion. The PVA fragments were unchanged over 9 months, confirming the inert biologic behavior and the permanence noted in other studies [4, 6, 7].

PVA microparticles were readily adherent to vascular endothelium. Rather than simply clogging arteries of critical diameter, the emboli adhered to endothelium in large-lumen vessels with high vascular flows. Endothelial overgrowth occurred between 5 and 7 days. The relative absence of larger (100–150 μm) emboli suggests these larger fragments lodged against the endothelium of the internal carotid or ophthalmic arteries proximal to the specimens examined, or less likely fragmented and were carried distally. However, no fragmentation of PVA has been noted in other multiple experimental and clinical uses [3, 4, 7]. It is most likely that the very small particles were created in the blending process and were washed distally by the intravascular blood flow.

This investigation illustrates several qualities of practical significance for PVA microparticles as an embolic agent. The biologic response in cerebral vasculature is benign with no significant inflammatory or degeneration response of either the vessels or adjacent brain. The eventual reaction is one of endothelial proliferation and vessel-lumen fibrosis. In addition to the benign histologic response, the adherence to vascular endothelium occurred mainly with small particles (under 100 μm), mainly in arteriolar-sized vessels (100 to 200 μm diameter), and in areas of rapid arterial circulation. This suggests that small-particle PVA foam emboli may be considered for embolization of lesions having relatively high flow and minimal capillary barriers with the expectation of the emboli adhering to the walls of the feeding vessels. Vessel thrombosis could be obtained by increasing the numbers of particles injected

both at any single injection or by repeated injections.

Emboli lodging in proximal large-vessel occlusion occurred uncommonly in this rat model and only with particles greater than 100 μm. Thus, proximal larger-vessel particle adherence can be minimized in part by superselective catheter placement and in part by selection of uniformly small particles. These technical considerations allow the embolization dynamics with PVA foam to be controlled by particle size and subselective catheter placement. The delivery method necessitates flow-controlled techniques in such selectively catheterized vessels. The ease of preparation and sterilization, combined with the above biologic properties, suggests that PVA foam microparticles may be considered an intracerebral embolic agent when a suitable delivery system becomes available.

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REFERENCES

1. Ausman JI, Gold LH, Tadavarthy SM, Amplatz K, Chow SN. Intraparenchymal embolization for obliteration of an intramedullary AVM of the spinal cord. *J Neurosurg* **1977**;47:119–125
2. Doppman JL, Di Chiro G, Ommaya. A. Obliteration of spinal cord arteriovenous malformation by percutaneous embolization. *Lancet* **1968**;113:477
3. Latchaw RE, Gold LHA. Polyvinyl foam embolization of vascular and neoplastic lesions of the head, neck and spine. *Neuroradiology* **1979**;131:669–679
4. Latchaw RE, Harris RD, Chou S, Gold HA. Combined embolization and operation in the treatment of cervical arteriovenous malformations. *Neurosurgery* **1980**;6:131–137
5. Tadavarthy SM, Knight L, Ovitt T, Snyder C, Amplatz K. Therapeutic transcatheter arterial embolization. *Radiology* **1974**;111:13–16
6. Casteneda-Zunga WR, Sanchez R, Amplatz K. Experimental observations on short and long-term effects of arterial occlusion with Ivalon. *Radiology* **1978**;126:783–785
7. Tadavarthy SM, Moller JH, Amplatz K. Polyvinyl alcohol (Ivalon)—a new embolic material. *AJR* **1975**;125:609–616
8. Chardack WM, Day CE, Fazekas G, Minsley BS. Synthetic skin: an experimental study. *J Trauma* **1961**;1:54–68
9. Grindlay JH, Clagett OT. A plastic sponge prosthesis for use after pneumonectomy: preliminary report of an experimental study. *Mayo Clinic Proc* **1949**;24:538–539
10. Hawe A, Rastelli CG. Late deterioration of intracardiac Ivalon sponge patches. *J Thorac Cardiovasc Surg* **1969**;58:87–91
11. Dodge HW, Grindlay JH, Winchell MC, Ross PJ. Use of polyvinyl sponge in neurosurgery. *J Neurosurg* **1954**;11:258–261
12. Payne WS, Kirklin JW. Late complications after plastic reconstruction of outflow tract in tetralogy of Fallot. *Ann Surg* **1961**;154:53–57