HHS Public Access

Author manuscript

Am J Med. Author manuscript; available in PMC 2017 August 07.

Published in final edited form as:

Am J Med. 2017 July ; 130(7): e287–e290. doi:10.1016/j.amjmed.2017.01.032.

Hydrophilic Polymer Embolism: An Update for Physicians

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Keywords

Catheter; Endovascular procedure; Hydrophilic polymer embolism; Iatrogenic complication; Inflammation; Vasculopathy

Hydrophilic polymers are widely used as surface coatings on vascular medical devices including guidewires, introducer and delivery sheaths, implantable stents and coils as well as cardiac, central and peripheral catheters. These surface coatings have unique properties that enhance biocompatibility and maneuverability of endovascular technologies, while decreasing friction and reducing trauma to vessel walls. Select polymers also enable targeted intravascular drug delivery while decreasing systemic toxicity and improving compliance. With increasing trends towards minimally invasive procedures and novel drug delivery systems, applications of polymer coatings on vascular devices are gradually increasing. Despite their advantages, unanticipated biological reactions and coating delamination from vascular device surfaces have been recognized worldwide and associated with significant morbidity over recent years[1–4].

Non-healing ulcers and painful access site nodules were first recognized over ten years ago in patients who underwent transradial catheterization using hydrophilic coated vascular sheaths [2]. Biopsies of these superficial lesions revealed localized inflammation resulting from intradermal deposits of polymeric foreign bodies. These reports established polymer coatings as a potential iatrogenic cause of inflammation and led to warning labels on specific Cook branded vascular sheaths (Cook Medical, Inc., Bloomington, IN). More significant reactions have subsequently been documented due to mechanical abrasion and embolization of polymer particles from the surfaces of various branded devices to sites downstream from areas of intravascular insertion or implantation (Fig 1A). This phenomenon of *hydrophilic*

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Conflicts of Interest: All authors declare no conflicts of interest

Verification: All authors had access to the data and a role in writing this manuscript

polymer embolization has steadily gained attention following initial reports of fatality in 2009[3,4].

The 2015 U.S. FDA safety communication pertaining to lubricious coating separation from intravascular medical devices (http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm473794.htm) disclosed approximately 500 Medical Device Reports of this phenomenon over a two-year period[5]. In this statement, the FDA acknowledged a rising clinical concern pertaining to polymer coating phenomena and reported 11 device recalls and 9 deaths associated primarily with peeling or flaking of interventional guidewire coatings since the start of 2010. Furthermore, the FDA acknowledged existing gaps in current national and international device standards and stated that the agency will work with stakeholders to further evaluate surface integrity and safety of coated vascular medical devices. Despite FDA acknowledgment, polymer complications remain clinically under-recognized by healthcare providers who routinely manage and treat patients using coated intravascular medical technologies.

Reported Adverse Events

Polymer-induced vascular effects may include luminal occlusion, intra- and peri-vascular inflammation and fibrous obliteration following embolism to small, intermediate, and large-sized vessels throughout the body (Fig 1B–F). Reported tissue injuries have most commonly involved the brain[1,3,4,6–8] and lungs[1,4,9], however involvement of the heart[10–13], kidneys[11,12], skin[14–16], arteriovenous grafts[11], transplanted organs[4,11], colon[17], small intestine[17], liver, and pancreas have also been documented, along with multisystem involvement and systemic effects in rare cases (Mehta, unpublished observations). Sequelae may include focal or multifocal hemorrhage, inflammation, arteritis, vasculopathy, thrombosis, transient ischemia or tissue infarcts, and fever among other effects[1–4]. The majority of polymer reactions are subclinical. However complications are often long-lasting and may lead to serious irreversible injuries. Outcomes have been shown to vary with embolic burden, site(s) of involvement, co-existing morbidities and severity of secondary reactions[1–4]. Symptom onset may occur during the acute, subacute or delayed post-procedure periods[8], with onset as late as 9 months post-procedure[7] and recurrence or persistence of reactive inflammation in some cases for over 3 years[11]. While sequelae are heterogeneous and organ specific, predictable vascular reaction patterns have been recognized (Fig 2)[1,8]. Postmortem data reveal a hospital autopsy frequency of at least 13%, although the clinical incidence of polymer embolism is unknown[1].

Diagnosis and Management

A heightened index of suspicion is required for clinical diagnosis of polymer coating embolism. Recognition of specific presenting patterns during the acute, subacute and delayed post-procedure intervals may facilitate empiric diagnosis of this iatrogenic phenomenon (Fig 2, upper panels)[1,8]. Preliminary data suggest the utility of routine serum markers as supportive evidence of the diagnosis (Fig 2, lower panel)[1,8]. Tissue sampling (e.g., biopsy, autopsy, or evaluation of evacuated embolic or clot material) is necessary for histologic confirmation, although sampling errors occur and negative biopsies do not

exclude the diagnosis[1,3]. On standard pathologic preparations, polymer emboli generally appear as nonrefractile, nonpolarizable, basophilic, granular lamellated foreign bodies (Fig 1B–D). For accurate diagnosis, infection and alternate causes of embolism or vasculitis should be ruled out. Recognition of this iatrogenic event may prevent misdiagnosis of unrelated medical disease (e.g., transplant organ rejection, parasitic infection or sarcoidosis)[12,17]. In some cases, steroids and immunomodulatory therapies have been effective in mitigating inflammatory reactions, although optimal dosages are unreported and risks of immunosuppression should be considered with long-term use. Antiplatelet therapy has additionally been reported to alleviate symptoms in some patients, while surgical resection may be necessary in others to exclude treatable conditions or to debride secondary necrotic wounds[9]. As no specific therapies are currently available, additional supportive measures should be implemented, as needed.

Clinical Implications

Post-procedural embolic phenomena have generally been attributed to air, septic, atheromatous, thrombotic or other foreign body embolism, however, polymer embolism is now a well-documented iatrogenic event attributed to catheterization and other vascular procedures. A recent analysis of material captured through use of an embolic protection device during mitral valve repair showed that polymer embolism occurred as frequently as acute thromboembolism (86%), with native tissue emboli (64%) and organizing thrombi (29%) noted less often[18]. Frequent polymer coating emboli have also been affiliated with other percutaneous procedures[19,20]. Thus, polymer embolism should be included in the differential of unanticipated ischemic or inflammatory complications as well as unexplained vasculopathies occurring during the post-procedural clinical setting. Iatrogenic polymer effects may be transient and self-limiting, as polymer emboli eventually biodegrade *in vivo*, although the time course is variable[1,4]. Unanticipated inflammation, particularly if persistent or associated with delayed onset following catheterization or endovascular treatment should raise clinical suspicion for this potential complication[8]. Onset of constitutional symptoms in the setting of temporally evolving vascular phenomena (eg., transient elevation of p-ANCA, with subsequent thrombosis, coagulopathy, sterile abscess or granulomata) should also prompt consideration for biodegrading polymeric reactions[1,3,8,9]. In cases with unclear embolic etiology, tissue evaluation may be considered if accurate detection will influence the need for medical or invasive therapies.

Future Directions

Given the millions of endovascular and catheter-based interventions performed worldwide each year as well as increasing trends toward polymer-based nanotherapies, there is an urgent need to better understand the effects of intravascular polymers in live patients. In large part, a lack of awareness on this subject and limitations of conventional diagnostic tools have hindered accurate assessments of polymer effects in the clinical setting[1,3,4]. However, methodologies such as use of embolic protection devices illustrate the feasibility of systematically analyzing particulates retrievable from the human bloodstream[18]. Heightened awareness and empiric diagnosis of this phenomenon would yield critical information regarding the incidence of polymer embolism in different contexts.

Investigations into novel biomarkers and alternative methods of analyzing blood particulates may allow for more sensitive and specific methods of noninvasive clinical detection. Moreover, examination of distinct populations such as patients with immunosuppression (e.g., cancer or chronic steroid use), hyperinflammation (e.g., sepsis or autoimmune disease), acidosis (e.g., impaired renal function), vascular risk factors (e.g., diabetes or hypertension), chronic indwelling devices (e.g., implanted stents or prolonged dialysis) or potential toxicological interactions (e.g., various therapeutic regimens) may elucidate effects of intravascular polymers in patient subsets. Large-scale prospective studies and investigations into patient specific factors may further clarify the natural evolution, specific biodegradative profiles and long-term consequences of polymer deposition within the distal vasculature. Further work in this area will help stratify risks and improve the safety and design of modern devices and therapies, while impacting beneficially on vascular health and patient outcome.

Acknowledgments

R.I.M. is supported by a grant from the National Institute of Neurological Disorders and Stroke (K08NS089830).

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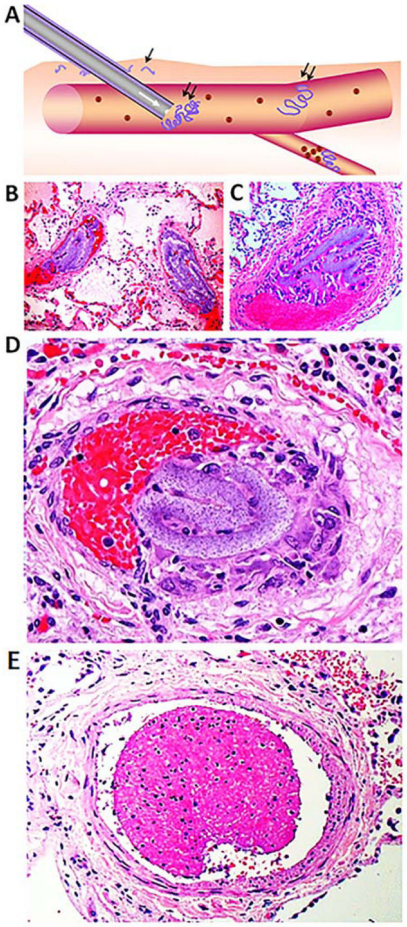

Figure 1. Hydrophilic Polymer Embolism Formation and Histologic Appearances

Schematic depiction showing polymer coating delamination from vascular device surface (A), with localized foreign body deposition at access site (single arrow) or associated embolic phenomena (double arrows). Histologic findings in a patient with pulmonary hydrophilic polymer embolism include non-refractile, basophilic, granular, lamellated intravascular foreign bodies (B,C) with associated congestion (B,C), inflammation (C,D), vasculitis (D), adjacent thrombi (E) and pulmonary infarct (not shown).

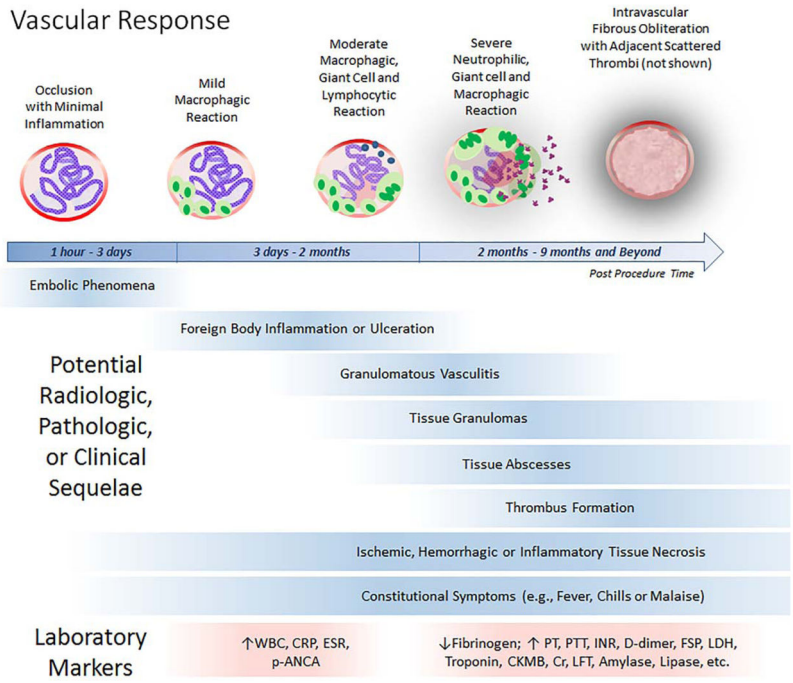

Figure 2. Summary of Vascular Changes Induced by Hydrophilic Polymer Emboli, with Diagnostic Features

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FSP, fibrin split products; INR, international normalised ratio; LDH, lactate dehydrogenase; LFT, liver function tests; p-ANCA, perinuclear anti-neutrophil cytoplasmic antibodies; PT, prothrombin time; PTT, Partial thromboplastin time; WBC, white blood cell