Embolic Materials: Understanding the Ocean of Choices

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Abstract

Embolization is a fundamental procedure that interventional radiologists perform on a daily basis to treat a variety of diseases. The disease processes for which embolization is considered a safe and effective treatment are continuously expanding, as are the embolization materials available for use. To achieve optimal clinical outcomes and minimize complications, it is imperative that the interventional radiologist understands the properties, strengths, and weaknesses of each class of embolic and specific embolic products. This is a continuous process as new materials are always becoming available. This article reviews the different classes of embolic materials, discusses strengths and weaknesses, and reviews areas of innovation.

Introduction

Embolization is a fundamental procedure for interventional radiologists with several applications.¹-⁴ The technique has continued to evolve and find new areas of clinical use, with current indications ranging from the treatment of benign and malignant tumors, acute trauma, and chronic pain.¹-⁴ Given the wide variety of clinical applications, it is not surprising that there is also a wide variety of materials available for the interventionalist to utilize for any embolization procedure.¹ Furthermore, there has been consistent evolution of these products, which continues at present. Knowledge of these materials as well as the strengths and weaknesses of each is paramount to allow the treating physician to achieve favorable results. This review examines the different classes of embolic materials, discusses strengths and weaknesses, and reports on current and future directives.

Coils

Coils are a commonly utilized embolic material with clinical applications in several different scenarios.¹,⁵ This likely explains why there are greater than 50 different coils commercially available.¹ One important aspect of coils to understand is that they rely on thrombosis to completely occlude the vessel.⁵-⁷ Therefore, it is beneficial for the materials that make up coils to have thrombogenic properties, an area of evolution over the years.⁵-⁷ For instance, companies have attached nylon fibers to a platinum backbone to increase the filling and thrombogenicity of the coil.⁸,⁹ Other types of fibers or coating have been used to provoke platelet aggregation as well, but it should be noted that some coils continue to be made of bare metal. While there is some disagreement on the importance of the presence or absence of fibers, it is generally accepted that cross-sectional packing represents the ideal embolization technique. The selection of the coil softness, size, and length plays an important role in the ability to densely pack the vessel and thus prevent recanalization.¹,¹⁰ Coils have many advantages including the ability to provide controlled and predictable embolization of a target vessel. This precise knowledge of embolization location can provide reassurance for providers and reduce complications, such as non-target ischemia, at times.
However, as with all materials, coils have weaknesses as well. One weakness of coils is the risk of incomplete vessel occlusion or vessel recanalization. A factor that has been shown to affect vessel occlusion and recanalization is packing density, as mentioned above.11,12 Therefore, significant research has been done on coil softness and shape formation.10 It is important for operators to understand the differences in shape formation for each coil as this may directly affect the technical success of any given embolization procedure. Some coils have “memory” and will form a predictable shape (loop, sine wave, complex 3D shape, etc.), while others are relatively amorphous but soft and designed to fill the entirety of a vessel. Another weakness of coils is their tendency to “run” down a target vessel and form a non-occlusive line. There are a few ways to combat this, one is by starting the coil in a small side branch vessel and letting it extrude into the target vessel. However, some coils have been designed with a stiff “anchor” portion at the beginning of the coil, which then becomes softer throughout its course, allowing anchoring and then filling of the vessel.13 Another consideration when using a coil is deliverability. Namely, the stiffness of a coil can result in the inability of that coil to be delivered to an area reached by a catheter or microcatheter. In general, softer coils are more amenable to delivery through tortuous vessels. Finally, coils can migrate, especially in high flow scenarios. Detachable coils were developed to compensate for this weakness. A detachable coil has a mechanism holding it to a wire, which can be released when desired by the operator. This differs from pushable coils that are attached to nothing and cannot be “retrieved” easily after delivery. While pushable coils are less expensive than detachable coils, in some scenarios a greater number of pushable coils are needed to achieve the same result as a single detachable coil, and therefore using them can drive up the overall procedural cost.14

As described above the inherent weaknesses of coils have provided opportunities to innovate, with several advancements being achieved. However, research continues and the areas of complex embolization and long-term vessel recanalization rates, particularly with newly developed coil materials, would benefit from further attention.

Vascular Plugs

Large arteries often require the delivery of multiple coils to achieve a successful occlusion, increasing the cost and time of a procedure. Vascular plugs were engineered to address this issue and provide permanent occlusion of larger arteries using a single device.15 The Amplatz Vascular Plug (AVP) (Abbott Medical, Chicago, IL, USA) was the first commercially available plug.15–17 Unfortunately, the AVP, which comprises a nitinol mesh, can only be delivered through access sheaths and large base catheters, limiting its usability in many target vessels. Furthermore, despite the initial goals, incomplete occlusion rates and lengthy time to occlusion requiring the concomitant use of coils to achieve rapid, complete occlusion is an issue.

In light of these issues, several new devices have been developed including the Microvascular Plug (MVP) (Medtronic, Dublin, IR), Azur Vascular Plug (Terumo, Tokyo, Japan), Caterpillar (BD, Franklin Lakes, NJ), Lobo vascular occlude (Okami Medical, Aliso Viejo, CA), Hourglass (EMBA Medical, Dublin, IR), Pillow Occluder (AndraTec, Kolbienz, Germany), and IMPEDE (Shape Memory Medical, Santa Clara, CA).18–26 Many of these plugs have been engineered with a polytetrafluoroethylene-covering or membrane which enables faster occlusion times.19,20 However, it should be noted that this membrane can also increase the risk of migration when delivered in high flow situations.23 Many of these second-generation devices are deliverable through smaller systems, and therefore can be used in smaller, more distal vessels relative to the AVP. While these newer plug technologies represent progress and address several key issues with vascular plugs remain. They still require larger catheters and sheath for larger vessels (5–8 mm or above based on the plug) and time to occlusion can still be less than ideal, at times still requiring coils. Furthermore, improvements in the areas of trackability and reliance on a patient’s clotting cascade would fill current needs.

Particles

As the earliest described embolics, particles have seen significant evolution since conception and have remained a primary embolic staple in interventional radiology.27 In fact, the application of particle embolization has surged in the past couple of decades, including uterine fibroid embolization, embolization for benign prostatic hyperplasia, and drug eluting–particles for oncologic purposes among others.28 Particles, as the name implies, are small (typically sizes are measured by micrometer) embolics that are delivered through a catheter/microcatheter. After leaving the catheter tip particles flow along with the blood to the distal vascular system. This distal embolization can often lead to tissue ischemia, sometimes a desired and other times an undesirable result. Both resorbable and permanent particles are available on the market. Resorbable particles are designed to provide temporary occlusion of the target vessels and the most commonly available material is Gel-foam.29 However, how quickly Gel-foam is resorbed appears highly variable and it is not clear whether vessels recanalize or undergo neovascular remodeling.29,30 Because of the allure of temporary occlusion, which theoretically could provide a desired clinical effect without enduring the long-term negative repercussions of permanent vessel occlusion, significant research into new resorbable materials is ongoing.30

In contrast, as the name suggests, permanent particles are so termed because they are never resorbed by the body. However, it is important to note that recanalization can occur despite the fact particles are not resorbed. Permanent particles are typically further subdivided into spherical and non-spherical categories. Non-spherical particles such as polyvinyl alcohol (PVA) have the advantage of being relatively inexpensive. Conversely, they can clog delivery catheters and due to their irregular shape, the exact level of occlusion is not predictable.31,32 Spherical particles, which are made of several materials including tris-acryl gelatin and
polymethylmethacrylate, polyethylene glycol PEG, are relatively uniform in size and shape and therefore have a more predictable level of occlusion and are less likely to clog a delivery system.\textsuperscript{33} It should be noted that they are also typically more expensive and that the advantages of spherical particles described above have not always translated to improved clinical outcomes.\textsuperscript{34}

Finally, drug-eluting beads (DEB) is another particle category worth mentioning. DEBs can be loaded with various drugs through an ion-exchange mechanism; however, only certain drugs are amenable to being loaded.\textsuperscript{35,36} After delivery, the DEBs slowly release the “loaded” chemical into the target tissue. This function has been utilized in cancer therapy\textsuperscript{1} but has theoretical applications in other areas as well.

While several features of particle embolics require consideration (including compressibility, shape, size, degree of inflammation, and injectability) and are therefore targets of innovation, two-particle features, visibility, and resorbability, have generated significant research interest.\textsuperscript{28} Because of the theoretical advantages of resorbable particles discussed above several studies have been evaluating new materials. For example, Sommer et al demonstrated reduced post-procedure complications when using a novel biodegradable microsphere in comparison with established permanent microspheres.\textsuperscript{37} Another theoretical advantage of particle resorption is minimizing the risk of long-term immune reactions. Similarly, the development of visible particles has been an active area of research with several studies reporting computed tomography (CT) and magnetic resonance imaging (MRI) visible particles.\textsuperscript{28,38} In theory, particle visibility on follow-up imaging would enable a greater understanding of collateral pathways, embolization dynamics, reduce non-target embolization, as well as aid in the understanding of the relationship between particle distribution and clinical failure. However, it is yet unknown how changing the chemical composition to make particles visible will affect other aspects of their performance.

**Liquid Embolics**

Liquid embolic agents represent perhaps the most actively developing category of embolic. Liquid embolics offer several advantages relative to other materials, in that, unlike particles, coils, and plugs they do not rely on the patient’s native clotting ability. In fact, liquid embolics can result in embolization through a biochemical response.\textsuperscript{39} Conversely, these properties as well as their ability to penetrate deep into the vascular arcade make liquid embolics very powerful and necessitate operator familiarity for safe usage. That said, liquid embolics, perhaps more than any other embolic material, have seen an increase in published indications over the last several years.\textsuperscript{39} In general, there are three categories of liquid embolics: polymerizing, precipitating, and phase transitioning agents.

Polymerizing liquid embolics comprise monomers or micro-monomers in a carrier, which solidifies when coming into contact with an initiating agent. Perhaps the most commonly utilized polymerizing liquid embolic agent is N-butyl-2- cyanoacrylate (NBCA), which consists of several different chemical derivations and resultant variations in properties. NBCA has demonstrated safety and efficacy in treating a variety of pathologies including arteriovenous (AVM) and venous malformations, as well as gastrointestinal (GI) hemorrhage and portal vein embolization.\textsuperscript{39–41} The disadvantage of polymerizing agents and NBCA is that if the polymerization occurs too quickly, the embolic can clog or “glue” the delivery catheter into the vessel, but if it occurs too late then non-target embolization can occur. Therefore, precise knowledge of the time to polymerization is required. NBCA is typically diluted with lipiodol; the degree of dilution affects polymerization time. Fortunately, there is a linear and reliable relationship between lipiodol dilution and time to polymerization.\textsuperscript{42}

Precipitating agents are comprised of a polymer in a solvent. When the polymer and solvent leave the catheter the change in conditions lead to precipitation of the polymer chains and subsequent solidification. One disadvantage of this system is the potential impact that the dissolving agent can have on the vascular system. Onyx (Medtronic, Dublin, Ireland), which is made up of ethylene-co-vinyl alcohol dissolved in dimethyl sulfoxide (DMSO), is a precipitating agent and has been reported as an effective treatment for a wide variety of pathologies including peripheral and central AVMs, GI hemorrhage, peripheral aneurysms, and varices.\textsuperscript{43–46} One disadvantage of Onyx is that it relies on tantalum powder to provide radiolucency, which requires it to be shaken for a significant period prior to use and leads to an artifact of CT and MRI follow-up imaging.

Phase transitioning embolics require an external stimulus, such as temperature, pH, or salt concentrations, which leads to the transition of the liquid to gel. While no phase transitioning embolics are available on the market currently, several are in the pipeline and may reach the market in the coming years.\textsuperscript{47,48}

As alluded to above, there is significant development ongoing in liquid embolics, with several new materials available in some markets but not others, or soon to be released. We will briefly review some of these materials to make the reader aware of them.

In terms of polymerizing agents, Hydrogel Embolic System (HES; Instyliia Inc., Bedford, MA, USA), is being developed and has been demonstrated to provide significantly higher occlusion rates when compared with 40 μm microspheres in a rabbit model, as well as distal penetration into the lumen of arterioles as small as 10 μm.\textsuperscript{49}

Given the clinical success of Onyx, significant effort has been placed into the development of precipitating agents including Squid (Emboflu, Gland, Switzerland), Precipitating hydrophobic injectable liquid (PHIL Terumo, Tokyo, Japan), Easylx (Antia Therapeutics AG, Berne, Switzerland) and Lava (Black Swan Vascular Inc, Hayward CA).\textsuperscript{50–55} These products aim to have improved features including distal penetration, a reduced beam-hardening artifact on post-procedural imaging, minimize adhesiveness and increase ease of delivery as compared with Onyx.\textsuperscript{39}
As described above no phase transitioning liquid embolic is available on the market at this time. However, GPX (Fluidx Medical Technology) and PuraMatrix (3D Matrix Co., Tokyo, Japan) are both phase transitioning liquid embolics, which are being actively developed and may come to market in the future. Finally, gel embolic material (GEM) (Obsidio Inc, Columbia, South Carolina) is a unique liquid embolic that is made of gelatin and nano silicates. It becomes a liquid when pressure is applied but forms a solid when that pressure is removed (after leaving the catheter), it has shown promise in preclinical studies.

Conclusions and Future Perspectives

The role of embolization in the treatment of a variety of diseases is likely to continue to expand. At the same time, research and commercial need has driven innovation with new and revised materials continually becoming available. This emphasizes the importance of understanding each embolic class and product’s strengths and weaknesses. While new materials often address weaknesses of previous devices, they require knowledge to use effectively and safely. Furthermore, the role of each embolic class is continuously changing, with new indications being reported frequently. These changes are exciting and allow interventional radiologists to help patients in new and exciting ways. However, it also leads to a requirement that these same physicians constantly update and refresh their knowledge, of this fundamental procedure and its materials.

Note

The contents of this paper, in whole or in part, have not been published or presented elsewhere.

Funding

None.

Conflict of Interest

None declared.

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