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Review

Particle Distribution in Embolotherapy, How Do They Get There? A Critical Review of the Factors Affecting Arterial Distribution of Embolic Particles

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Abstract—Embolization has tremendously evolved in recent years and has expanded to treatment of a variety of pathologic processes. There has been emerging evidence that the level of arterial occlusion and the distribution of embolic particles may play an important role in the clinical outcome. This is a comprehensive literature review to identify variables that play important role in determination of level of occlusion of blood vessels and distribution of embolic particles. The literature searches between 1996 to 2020 through PubMed and Ovid-MEDLINE yielded over 1030 articles of which 30 studies providing details on the level of occlusion are reviewed here. We divided the playing factors into characteristics of the particles, solution/injection and vascular bed. Accordingly, particle size, type and aggregation, compressibility/deformability, and biodegradability are categorized as the factors involving particles' behavioral nature. Infusion rate and concentration/dilution of the medium are related to the carrying solution. Hemodynamics and the arterial resistance are characteristics of the vascular bed that also play an important role in the distribution of embolic particles. Understanding and predicting the level of embolization is a complex multi-factor problem that requires more evidence, warranting further randomized controlled trials, and powered human and animal studies.

Keywords—Embolic agents, Particle, Embolization, Interventional radiology.

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ABBREVIATIONS

PVA	Polyvinyl alcohol
TGMS	Trisacryl gelatin microspheres
PVAMSs	PVA microspheres
AVMs	Arteriovenous Malformations
UAE	Uterine Artery Embolization

INTRODUCTION

Interventional radiology employs image-guided techniques to perform minimally invasive procedures for diagnosis and treatment.[5] Embolization has recently brought a leap in modern medicine as a minimally-invasive treatment.[51] Vascular embolization is a minimally invasive catheter-based procedure in which an occlusive material is placed into a blood vessel to block the arterial lumen and blood flow.[5,42,51] Before embolization, interventional radiologist puts an angiography catheter into the artery and performs selective diagnostic angiography to obtain an anatomic roadmap of the blood vessels, understands the flow dynamics of the artery, size of the arterial lumen, and plans for occluding the desired level of blood vessel depending on the clinical situation.[5,51] The goal of the embolization may be used to stop blood flow in active

bleeding (such as in patients with trauma or gastrointestinal bleeding), to block the blood flow to a tumor (such as hepatocellular carcinoma or liver metastatic colorectal cancer), or to decrease vascular flow in an area of hypertrophied tissue with abnormal vascularity (such as uterine fibroids, or benign prostatic hyperplasia, or knee osteoarthritis).[5,17,42,51] The ideal embolic material should effectively and rapidly occlude blood vessel at certain point of the artery (proximal, or distal to the target tissue), without any non-target embolization of arteries surrounding the target tissue or blood vessel. Embolization can be permanent or temporary. The former is more common and is performed utilizing liquid agents (such as *n*-butyl-2-cyanoacrylate (NBCA) or ethylene vinyl alcohol copolymer (EVOH)), Sodium tetradecyl sulfate (STS) (in the form of foam when mixed with Co_2 or air), mechanicals (coils and plugs), and particles (including spherical and non-spherical particles) that are the focus of this review.

The clinical application of particle embolization has surged in the past couple of decades, including uterine fibroid embolization, prostate artery embolization, embolization for sports medicine complaints, and drug eluting-particles for oncologic purposes among others.[42]

There are various particles available in the market with different shape, size, surface characteristics, loading capability, opacity, *etc*. An understanding of the characteristics of the particle and its expected behavior in a blood vessel is of paramount importance in order to ensure the desired clinical outcome. From an engineering standpoint, embolization is a multifactor problem of particle distribution. A complex interaction of particle-flow dynamics depends on the particle properties, particle to vessel size ratio, particle volume fraction (in the injected solution) in addition to the local Reynolds, Womersley and Stokes numbers. However, at times, the role of physics in the turn of events is neglected both in the procedure implementation and the design of relevant biomedical devices.

Previously, spherical particles and non-spherical particles have been compared to identify the properties that determine the distribution of the particles and level of the target vessel occlusion.[15,17,24] Polyvinyl alcohol (PVA) particles' irregular shape, tendency to aggregate, and their wide granulometric size range has led to a lack of correlation between target vessel size and particle diameter, leading to more proximal large vessel occlusion, non-target embolization, or catheter clogging. These lead to unpredictable results and sometimes complications, such as non-target embolization and early recanalization of the previously occluded blood vessel. Calibrated microspheres offer better target and distal vessel occlusion, with regular surfaces and less aggregation. This allows for a more predictable and reliable behavior and therefore better clinical results. Certain microspheres such as trisacryl gelatin microspheres (TGMS, Embosphere; Biosphere Medical, Roissy, France) and PVA microspheres (PVAMSs, Contour SE, Boston scientific Corp. Fremont, CA, USA) have new properties such as having a hydrophilic and microporous structure. These confer a better compressibility and malleability allowing the particle to flow relatively freely within the vessel lumen, resulting in deeper penetration and more distal occlusion.

Levels of occlusion of particles also depends on a number of other intrinsic and extrinsic factors such as particle type and size, aggregation, compressibility, local flow dynamics, arterial resistance, and the type of the microcatheter tip. In the quest to develop an ideal embolic particle with a predictable distribution and level of embolization, it is necessary to understand how particles behave in the blood vessels and which of the particle properties reliably predict the level of the arterial occlusion. This is a comprehensive review of the available literature to evaluate this complex clinical issue and bring this gap to the attention of the physical and engineering communities. We also provide an organized framework to comprehend the intricate physical properties of particles which affect the distribution of the particles in the blood vessels and the level of the embolization, based on the current clinical practice and literature review.

MATERIALS AND METHODS

Search Strategy and Data Sources

This systematic review was in-line with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).[36] A systematic search was performed to collect current evidence on factors affecting arterial distribution of particles and levels of occlusion. Literature searches were performed in PubMed over a period of two decades (Jan 1996 to Dec 2020). The following keywords were used to search for relevant literature: ''embolization'' and ''microspheres'' and ''polyvinyl alcohol'' or ''poly vinyl'' (using filter ''all fields'') and ''embolization therapeutic/methods'' (MeSH terms).

Eligibility Criteria and Study Selection

This review includes all randomized clinical trials (RCT), animal models, case reports, and *in vitro* studies discussing different properties of embolic particles. Additionally, review articles on this topic were studied and their results were included. Studies analyzing particle distribution, specificity in vessel occlusion and comparing different physical properties of

embolic particles were included in this review. We excluded studies on radioembolization, chemoembolization, preclinical studies on cancer treatment using embolic particles, and studies on loaded particles. Any studies dealing with other type of embolic agents such as liquid agent, coil, plug, vascular occlusion device, and balloons were not considered here. Only articles in English were included in this review.

Data Extraction and Quality Assessment

A total of 1030 articles were screened. 977 non-relevant articles were excluded based on title and/or abstract. These articles did not discuss the properties of embolic particles, particle distribution in vascular bed, or level of occlusion. Articles discussing radioembolization, chemoembolization, preclinical cancer treatments and loadable particles were excluded. In addition, articles pertaining to embolic devices other than embolic particles were excluded. Duplicates were also removed. The details of the algorithm are described in the diagram shown in Fig. 1. From the 53 articles left, all were critically reviewed by 3 authors and similar inclusion/exclusion criteria were applied. Finally, 30 articles were deemed relevant for the review. Abstracts and full texts were then reviewed to extract details on the type of the study (RCT, comparative animal/human study, *in vitro*, literature review, *etc*), the number of subjects, the type of embolic particles and the outcome of embolization. In order to quantify the clinical significance of the reviewed studies, we used the levels developed by the Centre for Evidence Based Medicine (CEBM) for treatment. We assigned a level of evidence (LOE) score to all reviewed articles in the scale of 1 to 5, with 1 being the highest level of evidence.[10]

RESULTS

General Review Information

We initially searched literature reviews, commentaries and comparative studies in order to collect information on the different studies available on particle characteristics affecting arterial distribution and occlusion. Studies by Sheth *et al.*,[42] Golzarian and Weng *et al.*,[20] Senturk *et al.*,[41] and Wenxiao *et al.*[25] helped greatly in this process as they summarized the main embolic particles used and the various intrinsic and extrinsic characteristics affecting their behavior. As addressed in the following, several characteristics were identified in these studies: particle size, particle type/aggregation, compressibility/deformability, infusion rate, concentration/dilution, and hemodynamics/arterial resistance, elastic recovery/viscous relaxation and particle density/constitution.

Study Composition and Description

We selected a total of 30 articles that specifically studied the topic of interest (RCT's, *in vitro*, comparative animal or human models) including 4 articles that were found in bibliographies of primary sources. Articles were grouped into 6 categories following the characteristics discussed: particle size, type/aggregation, compressibility/deformability, infusion rate, concentration/dilution, particle biodegradability, flow dynamics/arterial resistance. Seven studies were reported discussing the effect of the size on arterial distribution and occlusion of particles, including 4 animal models; Bilbao *et al.* (swine kidney, $n = 18$),[8] Pelage *et al.* (sheep uterine and renal artery, $n = 26$),[40] Stampfl *et al.* (porcine kidney, $n = 9$),[45] Kishimoto *et al.* (dog superior mesenteric artery, $n = 10$)[28] and 3 comparative human studies; including Laurent *et al.*, Beaujeux *et al.* ($n = 49$ and 105 patients, respectively)[6,29] as well as Bendszus *et al.* ($n = 60$, meningioma embolization with PVA vs. TGMS).[7] All 4 animal models compared different types of microspheres (different in type and/or size), while the human models studied for the most part, trisacryl gelatin microspheres and only one comparative TGMS vs. two different sizes of PVA. All of these studies were given a level of evidence score of 2B.

For the effect of the particle aggregation on distribution and arterial occlusion, we included a total of 9 articles including 1 commentary by Golzarian and Weng *et al.*,[20] 1 comparative human model by Chua *et al.* ($n = 17$),[15] and finally 7 animal models as follows; Choe *et al.* (rabbit renal artery, $n = 14$),[14] Derdeyn *et al.* (Swine rete mirabile, $n = 7$),[18] Siskin *et al.* (miniature pigs renal artery, $n = 11$),[43] Bilbao *et al.* (swine kidney, $n = 18$),[8] Andrews and Binkert *et al.* (swine renal artery, $n = 20$),[2] Pelage *et al.* (sheep uterine and renal artery, $n = 26$),[40] Laurent *et al.* (sheep uterine artery, $n = 10$).[30] Seven of the 9 studies compared microspheres (TGMS) with non-microspherical particles (PVA) and included 5 animal models, 1 human comparative study and 1 literature review. The two remaining articles were studies on specifically PVA particles and 4 types of microspheres. The level of evidence of all the study models was attributed a score of 2B, except for the literature review which was scored 4.

Seven studies were found discussing the impact of compressibility and deformability on the arterial distribution. Two studies, Lewis *et al.* comparing 4 types of microspheres,[32] Peixoto *et al.* comparing microspheres with non-microspheres,[39] were found and attributed an LOE score of 5. One Double-blinded randomized controlled trial (LOE = 1) on uterine artery embolization (Yu *et al.*, $n = 56$) compared two

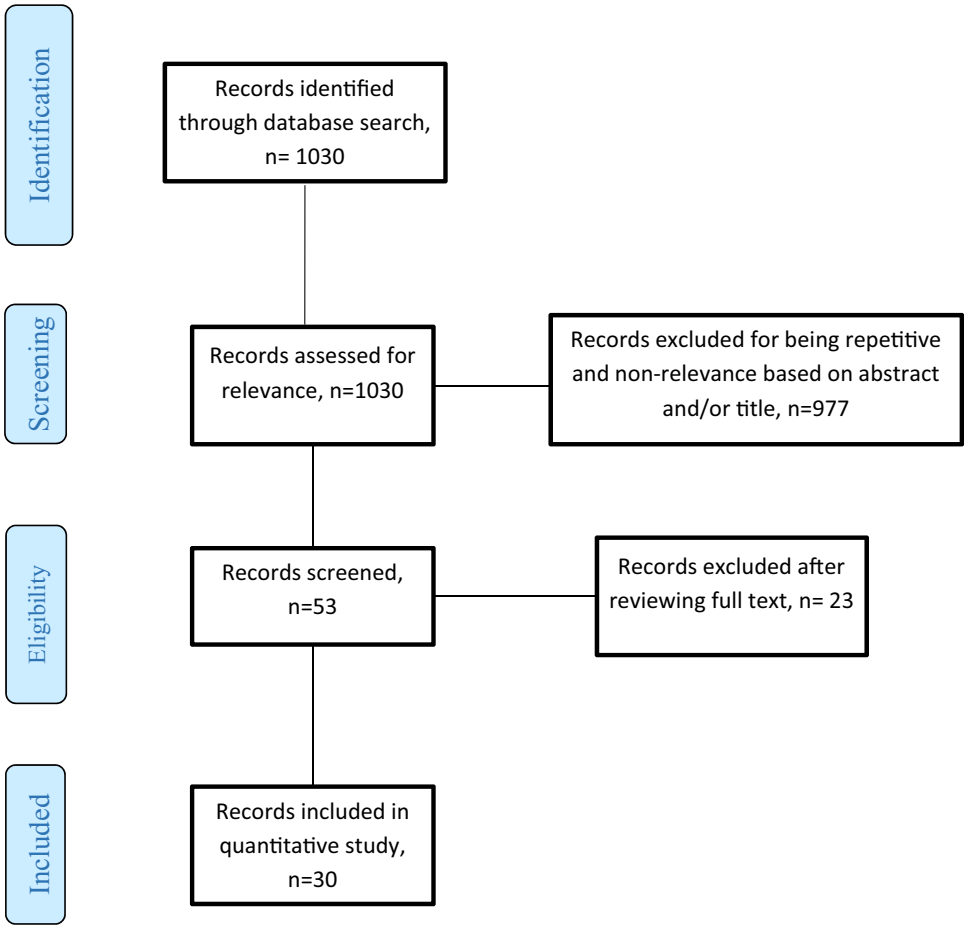

FIGURE 1. Search flowchart.

types of microspheres (TGMS and PVAMSs).[52] The remaining four were animal models; Verret *et al.* (sheep uterine and renal artery, $n = 12$) studying two types of microspheres,[47] Bilbao *et al.*, Pelage *et al.* (swine kidney, $n = 18$ and sheep uterine artery, $n = 26$, respectively) comparing microspheres with non-spherical particles[8,40] and Laurent *et al.* (sheep uterine artery, $n = 6$) comparing TGMS and PVMS.[31] In terms of the level of evidence, they were given a score of 2B.

One article (Choe *et al.*, rabbit kidney, $n = 14$) focused on two categories; infusion rate and concentration and dilution of PVA non-spherical particles. It was attributed to a level of evidence of 2B.[14] Similarly, only one article by Patel *et al.* (rabbit renal artery, $n = 2$) was found discussing the effect of flow dynamics and arterial resistance on the arterial distribution and occlusion of particles.[38] An *in vitro* study by Hidaka *et al.* was the only available model to investigate the elastic recovery and viscous relaxation of three types of microspheres. It was attributed to a level of evidence of 5.[21]

Bioresorbable particles were specifically studied in two animal models and one *in vitro* study. Weng *et al.* and Keussen *et al.* compared bioresorbable microspheres with TGMS in a rabbit kidney model ($n = 10$) and sheep uterine artery embolization ($n = 22$), respectively.[27,49] The effect of the biodegradable material in the microspheres embolization performance was investigated *in vitro* by Sommer *et al.*[44]

Experimental studies on the hemodynamics of the embolization process are also rare. The transport and distribution of embolic particles in vessels is a function of the particle's size, material, mechanical properties, concentration, the infusion rate and pressure, catheter tip, vessel anatomy, distal pressure and arterial flow distribution. *In vitro* studies by Bushi *et al.* and Caine *et al.* explored the particle distribution under different conditions in *in vitro* models of an idealized bifurcation and in a hepatic arterial system, respectively.[11,12]

DISCUSSION

As described earlier, particles remain a primary embolic staple in the field of interventional radiology. Depending on the clinical indication of a procedure, interventional radiologists should be equipped with the knowledge of the distribution properties of the particles and factors that could affect the level of arterial embolization, to choose a correct type and size of particle for an embolization procedure. Need-driven progress has been made in embolic agents in order to address deficiencies of the existing products. While several features of particle embolic require consideration, features that are subject of more clinical interest recently are particle size, type and aggregation, compressibility/deformability, carrying solution, biodegradability, and hemodynamics (Fig. 2). In this review, we evaluated the existing evidence regarding these factors and their effect on arterial distribution of embolic particles and level of embolization.

Particle Size

Choosing a particle size is of utmost clinical significance. Depending on the goal of the embolization, a certain level of the artery (with a certain diameter) needs to be occluded. For example, if the goal of the embolization is necrosis of the tumor or devascularization of hypertrophied tissue (i.e., hepatocellular carcinoma, uterine leiomyoma (uterine fibroids), or prostatic hyperplasia),[34,35,37] the particle size needs to be small so that a more distal level of the artery be blocked. On the other hand, if there is concern regarding non-target passage of the embolic beads into venous circulation (like, in arteriovenous malformations or arteriovenous fistulae) or if accidental passage of embolic material into smaller size arteries could have a devastating consequence (for example, accidental passage of embolic particles smaller than 200 micro meters may occlude spinal artery and cause permanent spinal infarction and paralysis, in patients who have bronchial artery embolization[9]), then larger size particles should be utilized for embolization. In addition, an irregular particle size distribution makes the level of embolization difficult to control; i.e. a significant number of small particles would penetrate further into the vascular bed than desirable and other larger particles would form aggregates that cause a more proximal embolization than desirable.

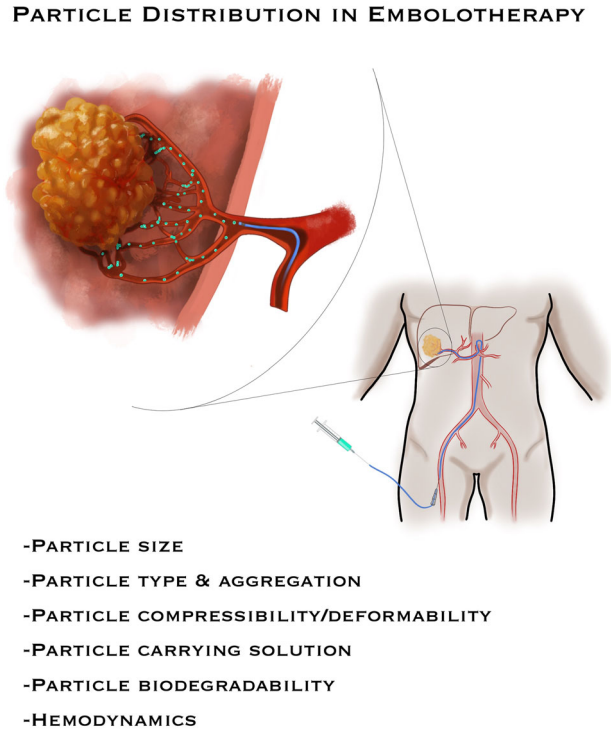

FIGURE 2. Factors affecting arterial particle distribution in embolotherapy

Several comparative animal model studies have compared the effect of the microspheres size in the arterial distribution[7,8,28,29,40,45] all pointing to the same conclusion; microspherical particles size is well correlated with the embolized vessel diameter. Thus, microspheres with smaller sizes occlude more distal vessels. Animal studies were limited because they were mainly healthy non-tumorous models and cannot be transposed to a clinical context. Another limitation is that statistical analysis for too-deep penetration compares different embolic materials, although different particle amounts were injected. It is difficult to quantify the amount of particles for each embolic agent that was injected during the procedure. Laurent *et al.*'s study offers a pathological context in a retrospective comparative study with 49 patients (suffering from nasopharyngeal angiofibromas and paragangliomas) further supporting the animal model findings.[29] Similar results were inferred from Beaujeux *et al.*, where calibrated trisacryl gelatin microspheres of different diameters were used for superselective embolization of 105 patients who had tumors or facial, spinal cord, or cerebral arteriovenous malformations (AVMs), which allowed a larger scale study of this phenomenon.[6] Unfortunately, no RCT studies were found concerning the effect of the size in particle distribution. A summary of studies considering the size is given in Table 1. A recent publication on prostate artery embolization (PAE) reported that the clinical outcomes were not significantly affected by the particle size.[46] However, there was an increased risk of adverse events with the use of smaller particles.

TABLE 1. Particle size.

Year	Type of particle studied	Author	Significant finding	Study model	Level of evidence (LOE)
2005	Trisacryl-gelatin MS	Laurent *et al.*	The size of the occluded vessels increased significantly when larger size ranges of TGMS were used. The diameter of the occluded vessels certainly depends on the caliber of injected TGMS	Retrospective comparative study reviewing of 49 patients (with NAF or PG) who were treated with embolization	2B
2008	4 different types of microspheres	Bilbao*et al.*	Particles of smaller size reach the most distal zones	Swine kidney $n = 18$	2B
2012	TGMS vs PVAMSs	Pelage et al.	Vessel diameter correlated significantly with the diameter of the measured microspheres	Sheep uterus $n = 26$	2B
1996	TGMS	Beaujeux *et al.*	Stronger correlation between the diameters of the particles and those of the occluded vessels, an advantage when it is necessary to target occlusion	105 patients who had tumors or facial, spinal cord, or cerebral arteriovenous malformations (AVMs)	2B
2009	4 types of microspheres	Stampfl *et al.*	Smaller microspheres showed more distal occlusion	Porcine kidney $n = 9$	2B
2014	Microspheres of 3 size ranges (100–300 um, 300–500 μm, 500–700 μm)	Kishimoto *et al.*.	Smaller microspheres showed more distal occlusion	Dog superior mesenteric artery ($n = 10$)	2B
2000	TGMS (150–300 μm) vs. PVA (45 to 150 μm and 150 to 250 μm)	Bendszus *et al.*	TGMS more effective in preoperative embolization of meningiomas, since they penetrate significantly more distally than PVA in either size	60 patients preoperative superselective embolization of meningiomas ($n = 30$ TGMS, $n = 15$ PVA 45–150 μm, $n = 15$ PVA 150 to 250 μm)	2B

Particle Type and Aggregation

Aggregation of the particles commonly leads to bigger particle conglomerates which results in more proximal obstruction of arteries (than intended). More proximal obstruction could cause more tissue infarction but less effective ischemia of the target treatment region and eventually less tissue necrosis.[33] This feature can be used and the level of embolization can be geared towards the desired clinical outcome that is intended. In order to achieve tumor necrosis, if ischemia to an organ is intended at the cellular level, then distal embolization is favorable and uniformly small particles are needed to achieve tissue necrosis. On the other hand, if no necrosis is intended more proximal level of embolization with larger particles and more heterogeneity in size will be utilized to occlude the blood vessel more proximally.

In terms of particle type and aggregation, six animal model studies have analyzed mainly PVA particles and calibrated microspheres. The study by Bilbao *et al.* compared 4 different microspheres.[8] As mentioned above, the animal models may not necessarily reflect the real-world clinical situation as most embolized organs were healthy. A second limitation was the restricted number of subjects (between 10 and 14) which may diminish power of these studies. A human comparative study performed by Chua *et al.* with 17 patients who had uterine artery embolization (UAE) before myomectomy, is one of the only available studies performed in a pathological context on humans.[15] They concluded that the use of microspheres is advantageous over non-spherical PVA particles since the former penetrate considerably deeper into leiomyomata in comparison with the latter, allowing a better target embolization. The major weakness of this study is the limited number of cases. Golzarian and Weng *et al.* provided an overview of the embolic agents and concluded that particle may aggregate in the catheter or in the vessels resulting in the proximal embolization of the vessels.[20] No larger studies and RCTs have confirmed these conclusions. Additional studies examining the relationship between particle type/ aggregation and the level of embolization are provided in Table 2.

Particle Compressibility/Deformability

Particles which are more compressible tend to deform more easily during embolization and this trans-

lates to a more distal embolization.[19] This is a physical characteristic which could be favorable in clinical situations when distal embolization is intended such as in prostate artery embolization, uterine artery embolization, or embolization in treatment of hepatocellular carcinoma.

Studies on particle compressibility and deformability are more common and diverse. They include four animal models comparing microspherical with non-microspherical particles[31,40,47] and a comparison of 4 different types of microspheres,[8] two *in vitro* studies,[32,39] and one double blinded RCT with 56 patients.[52] All concluded that higher deformability leads to more distal occlusion. Despite the high level of evidence of a double blinded RCT study, this particular one has certain limitations. There were a relatively small number of patients in each arms, with 27 patients in the trisacryl microsphere group and 29 in the PVA microsphere group. Secondly, using a power Doppler ultrasound for the assessment of residual perfusion for the purpose of comparison of treatment effectiveness between the two embolic agents, is not sufficiently sensitive as would have been using magnetic resonance imaging (which is the standard for such assessments). The *in vitro* study by Hidaka *et al.* showed that acrylamido polyvinyl alcohol (APVA) microspheres have a lower rigidity but a comparable viscous relaxation to TGMS.[21] They conjectured that APVA microspheres deform less than softer microspheres and hence will locate more proximally than PVA microspheres. In continuum mechanics, stress relaxation or viscous relaxation refers to the stress reduction for a given applied strain. It is a behavior of viscoelastic material that exhibits both viscous and elastic characteristics under deformation. It represents how a viscoelastic material relieves stress under constant strain over time. Embolic beads that have viscoelasticity properties will show such a behavior when deformed in vessels or microcatheters that typically have smaller sizes than the embolic particles.[21] A summary of studies considering the particle compressibility and deformability is given in Table 3.

Particle Carrying Solution

Despite being a well-known phenomenon amongst practicing interventional radiologists, very little evidence is available concerning the effect of the infusion rate, concentration/dilution (both from the same study conducted by Choe *et al.*[14]) to be able to confidently state the effects of these factors on particle distribution. One animal model comparative study was performed for each category leaving space for many possibilities of larger scale and pertinent studies. In essence, with a lower infusion rate and higher dilution, a more distal dislodgement of embolic particles could be anticipated. A summary of the study examining concentration/dilution/infusion rate is provided in Table 4. It is of utmost clinical importance to be aware that the slower rate of administration of the embolic particle will lead to a more distal arterial level embolization.[14,48] This is a physical characteristic which could be favorable in clinical situations when distal embolization is intended such as bariatric arterial embolization, prostate artery embolization, uterine artery embolization, or embolization in treatment of hepatocellular carcinoma.

Particle Biodegradability

In several clinical situations, practitioners prefer to use a bioabsorbable particle to avoid permanent occlusion of the blood vessels.[23,50] Concerning the effect of bioresorbable/biodegradable particles, Weng *et al.* (animal model) and Sommer *et al.* (*in vitro*) compared bioresorbable microspheres with TGMS and Embospheres, respectively.[44,49] Both concluded that bioresorbable agents occlude more proximally than TGMS and permanent microspheres. From a density point of view, Weng *et al.* explain that a higher cross-linking density results in a higher rigidity of the microspheres and therefore occlude slightly more proximally.[49] Sommer *et al.* showed that the biodegradable microspheres in comparison with established permanent microspheres lead to less distal occlusion immediately one week after embolization.[44] However, they would cause less post-procedure complications. Keussen *et al.* investigated the use of biodegradable microspheres in comparison with trisacryl gelatin particles and concluded that the former led to significantly more recanalization after embolization.[27] Table 5 concludes the studies evaluating the effect of bioresorbability on particle distribution.

Hemodynamics

Finally, despite the importance of understanding the hemodynamics governing the distribution of embolic particles in target embolization, very few relevant clinical studies are available. In the animal study by Patel *et al.*, it was shown that lower resistance vascular beds preferentially receive more embolic agents, a phenomenon also known as pseudoselection or flow directed selection.[38] With progression of embolization, the vascular resistance increases which leads to a change of local flow dynamics. Bushi *et al.* studied the effect of the particle size, density, and flow pulsatility in distal distribution in an idealized bifurcation model.[11] Notably they showed that the particle distribution is proportional to the flow rate division at the

TABLE 2. Particle type/aggregation.

Year	Type of particle studied	Author	Significant finding	Clinical implication	Study model	Level of Evidence (LOE)
2014	Non-spherical particles and microspheres	Golzarian and Weng	Aggregation within the catheter hub as well as within the vessel leading to more proximal occlusion within a vessel Particulate penetration, lack of hub accumulations (even at diameters larger than the minimum inner diameter), the relative ease of injection may be attributed to the lack of aggregation, the smooth and hydrophilic surface, and the deformability of the Embospheres	Aggregation of particles can result in clogging of the microcatheter and proximal occlusion of the vessels which has been shown to affect the clinical outcome	Literature review	4
1997	Polyvinyl alcohol (PVA) particles	Choe*et al.*	Slower infusion and a more diluted suspension of PVA particles diminishes aggregation	A more distal arterial occlusion, reduces the possibility of collateral reconstitution and is more effective in embolotherapy for a tumor or an arteriovenous malformation	Animal model of renal arteries of 14 rabbits	2B
2005	Non-spherical polyvinyl alcohol (PVA) vs trisacryl gelatin microspheres (TGMS)	Chua *et al.*	Lack of correlation between PVA particle size and diameter of occluded vessel due to: wide granulometric size range of the PVA particles and particle tendency to aggregate TGMS particles penetrated significantly deeper into leiomyomata compared with non-spherical PVA due to less aggregation	TGMS particles allow a better targeting and an earlier end-point to embolization. PVA particles unreliable in predicting the levels of occlusions in vessels. PVA particles produced more necrosis and cause hazardous arterial occlusion	Comparative study: 17 patients referred for UAE before myomectomy	2B
1997	Collagen-coated acrylic microspheres and polyvinyl alcohol (PVA) particles	Derdeyn *et al.*	For a given particle and vessel size MS have greater penetration	Greater penetration can lead to more effective transarterial embolization. Use of Embospheres at presence of arteriovenous shunting, such as arteriovenous malformations, cannot be recommended	Swine rete mirabile $n = 7$	2B
2003	PVA microspheres vs commercially available agents (PVA particles, gelatin spheres, gold-colored gelatin spheres)	Siskin *et al.*	Spherical agents travel distally into smaller vessels. PVA particles tend to aggregate and occlude proximally	Supports the clinical practice of using spherical agents at least one size larger than PVA particles used for similar applications	Kidney of miniature pigs $n = 11$	2B
2008	4 different types of microspheres	Bilbao *et al.*	Particle aggregation leads to more proximal occlusion		Swine kidney $n = 18$	2B
2003	TGMS vs polyvinyl alcohol (PVA) particles	Andrews and Binkert	Trisacryl-gelatin microspheres reduced renal blood flow more quickly and reliably than did PVA. The type of agent used in embolization has a greater impact on the rate of flow reduction than did particle size in the range size tested		Animal model of swine renal arteries $n = 10$	2B
2010	PVA particles and calibrated MS	Pelage*et al.*	PVA particles are associated with intense uterine necrosis and extensive arterial occlusion regardless of size. Calibrated MS, which are associated with less uterine necrosis, permit a segmental arterial occlusion correlated with size		Sheep uterus $n = 26$	2B
2009	TGMS vs PVA (non-spherical)	Laurent *et al.*	PVA particles formed large-sized aggregates that occluded proximal vessels. Microspheres occluded more distal vessels		Two groups of 10 sheep embolized in the uterine artery $n = 20$	2B

TABLE 3. Particle compressibility/deformability.

Year	Type of particle studied	Author	Significant finding	Clinical implication	Study model	Level of evidence (LOE)
2006	Embosphere, Embogold, Contour SE and Bead Block	Lewis *et al.*	Contour SE was significantly more compressible at 5 kPa. The Embosphere, Embogold and Bead Block microspheres were shown to have comparable compressibility in the range 21–27.5 kPa However, recoverability of Contour SE required several minutes in contrast to the other products	Contour SE particles are able to be compressed and move more distally in the vessel.	*In vitro*, comparative study	5
2011	Tris-acryl Microspheres vs PVA microspheres	Yu *et al.*	PVA microspheres were found to be associated with a tendency of nonelastic deformation and distal propagation	The cause of embolization failure with PVA microspheres is possibly related to the material's greater compressibility.	Double-blinded randomized controlled trial on uterine artery embolization (UAE) for uterine leiomyomas $n = 56$	1
2006	PVA microsphere vs PVA non-spherical particles	Peixoto *et al.*	PVA microspheres are physically much more compressible and deformable	Production of PVA/PVAc spherical particles that can be used to occlude blood vessels, eliminating the disadvantages of commercial PVA (non-spherical)	kidneys of New Zealand white rabbits	5
2011	Microspheres: Embozene vs Embosphere	Verret *et al.*	Increased deformation leads to more distal occlusion	These findings show that deformation of Embozene appears to determine the size (i.e. distality) of the vessel occluded as opposed to the *in vitro* granulometric particle size, which makes the level of occlusion unpredictable	Comparative animal study: Renal and uterine sheep arteries $n = 12$	2B
2008	4 different types of microspheres	Bilbao *et al.*	More distal occlusion in particles with higher Compressibility and deformation		Swine kidney $n = 18$	2B
2006	Trisacryl gelatin and polyvinyl alcohol	Laurent *et al.*	More distal vascular partition of PVAMS is likely due to the greater deformability of PVAMS in tissues		Sheep uterus $n = 6$	2B
2010	Trisacryl gelatin MS vs polyvinyl alcohol (PVA) particles	Pelage *et al.*	More distal occlusion for particles with higher deformability		Animal model of sheep uterus arteries embolization $n = 26$	2B
2011	TGMS Acrylamido polyvinyl alcohol microspheres (APVA) Polyphosphazene-coated polymethylmethacrylate microspheres	Hidaka *et al.*	APVA microspheres have a lower rigidity but a comparable viscous relaxation to TGMS		*In vitro*	5

TABLE 4. Infusion rate, concentration/dilution.

Year	Type of particle studied	Author	Significant finding	Study model	Level of Evidence (LOE)
1997	PVA non-spherical particles	Choe *et al.*	Slower infusion leads to more distal embolization. More dilution leads to more distal embolization	Rabbit kidney $n = 14$	2B

TABLE 5. Particle bioresobility.

Year	Type of particle studied	Author	Significant finding	Study model	Level of evidence (LOE)
2018	Biodegradable vs Embosphere	Sommer *et al.*	Biodegradable microspheres lead to less distal occlusion than embospheres immediately and one week after embolization, however, they would cause less post-procedure complications	*In vitro*	5
2017	Biodegradable microspheres vs TGMS	Keussen *et al.*	Biodegradable microspheres cause significantly more recanalization after embolization than TGMS	Sheep uterine artery embolization ($n = 22$)	2B
2013	Bioresorbable microspheres vs TGMS	Weng *et al.*	Altering the composition of the embolic microspheres may lead to different vascular distribution.	Rabbit kidney ($n = 10$)	2B

bifurcation. This study and certain others have suggested the prevailing opinion that the embolic beads typically follow the blood stream and distribute proportional to the flow split through ramified vascular branches. However, there has been emerging evidence from *in vitro* and numerical studies showing the limits of this intuitive assumption. In fact, the fate of particles is a function of multiple hemodynamic factors of which many relevant to the scope of this article has been addressed. For example, Kennedy *et al*., Childress and Leinstreuer *et al*. and Amili *et al*. showed how the fate of particles is strongly affected by their initial location across the vessel.[1,13,26] Along with the initial location of the particle trajectories, Aramburu *et al*. and Van den Hoven *et al*. showed the location and direction of the microcatheter tip in the injection site is crucial in the fate of particle distribution.[3,4,22] In addition, Caine *et al*. studied the distribution of glass and resin microspheres in an *in vitro* model of the hepatic arterial bed under physiologically realistic flow conditions and concluded that both types of particles follow the distributing injection solution (containing contrast agent) rather than the arterial flow distribution.[12] In another relevant study, Chung *et al*. studied the particle distribution in a realistic replica of an arterial bed and showed that the particle diameter with respect to the vessel size has an important effect on their transport beyond what is suggested by the flow division at bifurcations.[16] All these studies highlight the fact that particle behavior is a complex hemodynamic problem depending on a large number of parameters and cannot be simply estimated by assumptions such as the volumetric flow distribution at bifurcating branches. Further studies with verification and validation by clinical trials and animal models are absolutely needed to shed light on this problem.

Challenges and Recommendation (Expanding Horizons in Embolization)

Challenges primarily include non-target embolization, particle reflux, poor predictability in the particle distribution, extent of necrosis and cell death provoked by occlusion of arteries and poor control on the level of occlusion. Effects of hemodynamics, elasticity, infusion rate and concentration/dilution was also equivocal among different studies.

Our perspective on future research can include addressing challenges in the precise and sufficient transportation of embolic beads to the target vascular bed, design of desirable embolic particles and occlusion microcatheters. In our view, further *in vitro* and *in silico* studies are required to understand the fundamental underlying physics governing particle interactions with the blood stream which requires it to be fully verified against animal models and clinical trials. With ever increasing resolution of medical imaging techniques and development of more sophisticated numerical methods, we envision development of physics-informed mathematical models for a precise pre-

diction of the particle distribution as a function of the large parameter space.

CONCLUSION

Our literature review of the levels of evidence concerning factors that affect the level of distribution and arterial occlusion by embolic particles reveals the sophisticated multifactorial nature of this mechanical-physiological interactive phenomenon. So far we know of a multitude of factors that play different roles in particle distribution and possibly affect the clinical outcomes as detailed above. It has also brought to light several deficiencies. Firstly, it shows the necessity of performing further randomized controlled trials, particularly to investigate the interaction of these factors in different pathological models. Secondly, it highlights the lack of adequately powered trials to produce high quality data. Thirdly, most of the models available are not directly transposable to a clinical context. Finally, with more than 80% of studies focusing on size, aggregation and compressibility, very limited evidence is available concerning the effects of hemodynamics, elasticity, infusion rate and concentration/dilution. Each available product comes with its own set of benefits and drawbacks, all of which require careful consideration by the interventionist. Continued innovation is requisite in order to continue to evolve embolization procedures and ultimately, improve patient outcomes.

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