Biomaterials used in injectable implants (liquid embolics) for percutaneous filling of vascular spaces

Jordan, Olivier; Doelker, Eric; Ruefenacht, Daniel André

How to cite

JORDAN, Olivier, DOELKER, Eric, RUEFENACHT, Daniel André. Biomaterials used in injectable implants (liquid embolics) for percutaneous filling of vascular spaces. In: Cardiovascular and interventional radiology, 2005, vol. 28, n° 5, p. 561–569. doi: 10.1007/s00270-004-0238-7

This publication URL: https://archive-ouverte.unige.ch/unige:5498

Publication DOI: 10.1007/s00270-004-0238-7

CardioVascular and Interventional Radiology

Published Online: 30 May 2005

Cardiovasc Intervent Radiol (2005) 28:561–569
DOI: 10.1007/s00270-004-0238-7

Biomaterials Used in Injectable Implants (Liquid Embolics) for Percutaneous Filling of Vascular Spaces

Olivier Jordan,[1] Eric Doelker,[1] Daniel A. Rüfenacht[2]

[1]School of Pharmacy, University of Geneva, 30 quai Ernest-Ansermet, 1211 Geneva 4, Switzerland
[2]Department of Neuroradiology, Geneva University Hospital, 24 rue Micheli-du-Crest, 1211 Geneva 14, Switzerland

Abstract

The biomaterials currently used in injectable implants (liquid embolics) for minimally invasive image-guided treatment of vascular lesions undergo, once injected *in situ*, a phase transition based on a variety of physicochemical principles. The mechanisms leading to the formation of a solid implant include polymerization, precipitation and cross-linking through ionic or thermal process. The biomaterial characteristics have to meet the requirements of a variety of treatment conditions. The viscosity of the liquid is adapted to the access instrument, which can range from 0.2 mm to 3 mm in diameter and from a few centimeters up to 200 cm in length. Once such liquid embolics reach the vascular space, they are designed to become occlusive by inducing thrombosis or directly blocking the lesion when hardening of the embolics occurs. The safe delivery of such implants critically depends on their visibility and their hardening mechanism. Once delivered, the safety and effectiveness issues are related to implant functions such as biocompatibility, biodegradability or biomechanical properties. We review here the available and the experimental products with respect to the nature of the polymer, the mechanism of gel cast formation and the key characteristics that govern the choice of effective injectable implants.

Key words: Aneurysms—Arteriovenous malformations—Embolization—Implant—Injectable biomaterials—Interventional procedures—Tumors

Image-guided minimally invasive techniques have become widely used to treat arteriovenous malformations (AVMs), aneurysms and tumors. This evolution arises from the progress in percutaneous lesion access and performance of the deliverable implants. These implants are designed to embolize the vascular spaces once injected in a liquid form, either by directly occluding them or by inducing a secondary local thrombosis. Besides the use of coils, balloons or particles, the so-called liquid embolics have met success partly due to their ability to form a gel cast that completely fills the vascular defect. One of the key material characteristics influencing the clinical performance of a liquid embolic is its solidification mechanism. Various physicochemical properties may be involved in the *in situ* formation of an implant. Most of the embolics currently used in a clinical setting rely on either polymerization or precipitation principles. In the former, monomers or prepolymers polymerize in the presence of an initiator into a covalently cross-linked material (Fig. 1A). As for the precipitating embolics, a solution of preformed polymer in a water-miscible solvent is injected, and precipitates into a solid cast following exchange of the solvent with surrounding physiologic water (Fig. 1B). Other physicochemical principles may alternatively be used to produce implants *in situ*. Changes in the concentration of ionic species (Fig. 1C) or changes in pH may also induce the required phase transition. Finally, thermosensitive gels can solidify under temperature change, e.g., from room to body temperature.

Correspondence to: O. Jordan; *email:* olivier.jordan@pharm.unige.ch

Materials for Liquid Embolization

Liquid embolics with clinical precedents and those under experimental development are listed in Tables 1 and 2, respectively.

Polymerizing Formulations

Among the existing polymerizing embolics, cyanoacrylate (CA) glues that undergo polymerization in presence of blood were proposed in the 1970s [1]. *n*-Butyl cyanoacrylate (NBCA) (Histoacryl, Avacryl and Trufill *n*-BCA) shows a good combination of penetration and permanence. Trufill

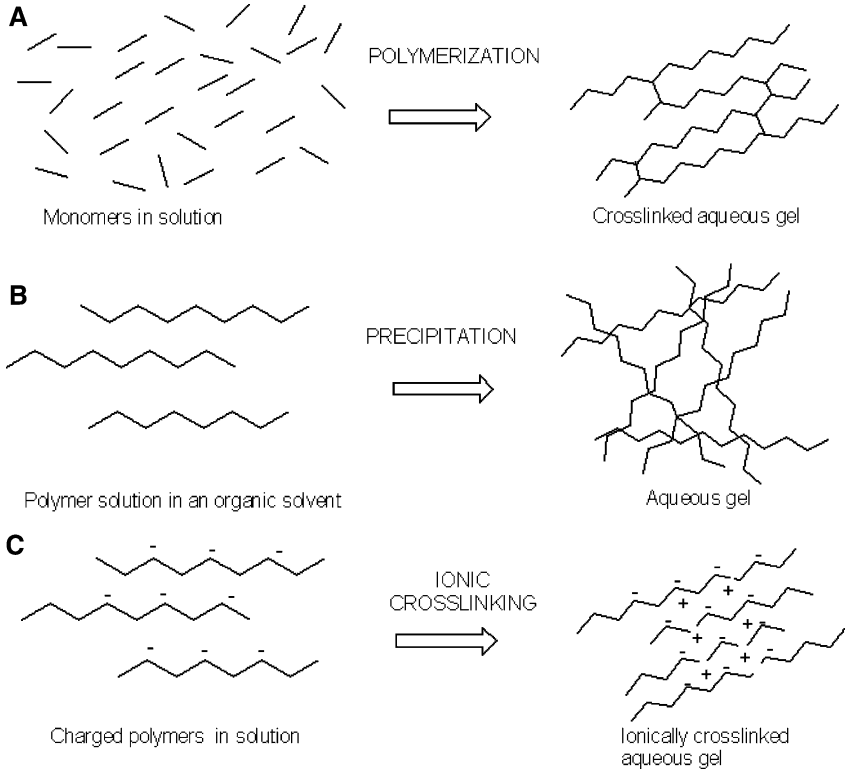

Fig. 1. Principles of injectable implant setting. Three main classes of implant formation mechanisms: (**A**) Polymerization of a monomer or prepolymer (e.g. cyanoacrylates), (**B**) precipitation in contact with bood of a performed polymer solution in an organic solvent (e.g. EVAL embolics or Onyx™) and (**C**) Ionic crosslinking of charged polymer chains in presence of counter-ion (e.g.) alginate gels).

Table 1. Liquid embolics having clinical precedents

Material	Radiopacifier	Target	Results claimed	
NBCA cyanoacrylate	Lipiodol, W	Tumors (craniofacial and skull base)	Effective for preoperative embolization	[83, 84]
NBCA cyanoacrylate	Lipiodol, W	Cerebral or spinal cord AVMs	*n*-BCA equivalent to PVA particles	[8]
EVAL	Metrizamide	Dog kidney, 3 clinical AVMs	Satisfactory occlusion	[23]
EVAL (Onyx)	Ta	Pig rete, patient AVM and tumors	12-month occlusion in pigs, 18 patient tumors, 3 AVMs	[30]
EVAL (Onyx)	Ta	AVMs	Non-adhesive embolics. AVM volume reduction of 63% (23 cases)	[32]
EVAL (Onyx)	Ta	Cerebral aneurysm Multicenter Onyx	Liquid embolics as an alternative to coil treatment. Occlusion rate superior to coils	[34]
Cellulose acetate polymer	Bi_2O_3	Cerebral AVMs	Safe AVM embolization	[39]
Cellulose acetate polymer	Bi_2O_3	Aneurysms	80–100% occlusion (8 cases)	[37, 85]
Cellulose acetate polymer and EVAL in DMSO	Ta	Rabbit kidneys and Intramuscular VX2 carcinoma	Liquid embolics outperformed PVA and Gelfoam	[28]
Fibrin glue	Iopromide	Intracranial meningiomas	Safe preoperative embolization (80 cases)	[69]
Ethibloc	Metrizamide, Lipiodol	Rat kidney and tumors	Improvement of Ethibloc radiopacity	[45]
Hydrolyzed PVAc "Embol-78" in 44% ethanol	Iopromide	51 preoperative portal vein and 6 renal artery embolizations	Safety and effectiveness of the procedures	[51, 52]
Ethanol	–	Renal artery, human	Treatment of nephrotic syndrome	[86]
Ethanol	–	Brain AVMs	Permanent embolization	[41]
Acetic acid	–	Small hepatocellular carcinoma	Acetic acid more efficient than ethanol	[63]
PMMA cement	$BaSO_4$	Vertebral bodies (vertebroplasty)	Pain relief, spine stabilization	[16]
PMMA cement	$BaSO_4$	Vertebral metastases	Pain relief	[87]

PVA, poly(vinyl alcohol); EVAL, ethylene vinyl alcohol copolymer; NBCA, *n*-butyl cyanoacrylate; DMSO, dimethyl sulfoxide; W, tungsten; Ta, tantalum

n-BCA was approved by the US Food and Drug Administration (FDA) for brain AVMs in 2000. NBCA has been used to induce complete occlusion in kidneys [2, 3] and its handling was improved by the addition of Lipiodol [4]. A high number of clinical interventions have been successfully performed to date [1, 5–8] However, adhesion to catheters and vascular walls, very rapid polymerization and the need to add radiopaque agents that interfere with the polymerization make precise control of the implant delivery difficult [9–11]. CA glues also induce a significant acute and chronic

Table 2. Liquid embolics under experimental development

Material	Radiopacifier	Animal model	Results claimed	
Ethibloc	Metrizamide, Lipiodol	Rat kidney and tumors	Improvement of Ethibloc radiopacity	[45]
NBCA cyanoacrylate	Lipiodol	Various dog arteries and kidney	Improved handling	[4]
Non-adhesive isostearyl-2-cyanoacrylate	Lipiodol	Renal artery	Improved handling, polymerization control	[13]
NBCA with radical polymerization	Lipiodol	Swine pharyngeal and renal arteries	Same occlusion rate as NBCA; lower toxicity and adhesion to vessels	[15]
Cellulose acetate polymer and EVAL in DMSO	Ta	Rabbit kidneys and intramuscular VX2 carcinoma	Liquid embolics outperforms PVA and Gelfoam	[28]
EVAL (Onyx 6% to 1%)	Ta	Rabbit VX2 carcinoma in liver	Polymer concentration controls the distal progression of the embolization	[72]
EVAL (Embolyx E)	Ta	Swine rete mirabile	Permanent occlusion, mild inflammation	[29]
Eudragit and NBCA	Ta	Rabbit external carotid	Feasibility shown	[61]
Radiopaque polyurethane	Not required	Pig liver	Effective, radiopaque, degradable material	[80]
Radiopaque cellulose	Not required	Sheep kidney	Effective and radiopaque material	[81]
Alginate hydrogel	Conray and Ta	Swine AVMs	Effective occlusion + 1-week stability	[67]
Thermosensitive polymer (*N*-isopropylacrylamide)	Iopamidol	Rabbit kidney	Feasibility, biocompatibility	[70]
PVAc latex	Iopamidol	Dog and rats renal artery + 1 patient AVM	Complete occlusion	[65]
PVAc in 50% ethanol	Metrizamide	Dog middle cerebral artery	No recanalization, enhancement after estrogen embolization	[47]
Eudragit in 50% ethanol	Iopromide	Rabbit carotid artery, dog renal artery and 1 patient AVM	Thrombogenic, nonadhesive material, but edema and necrosis observed	[60–62]
Ethanol	None	Rabbit and pig renal artery	Long-term occlusion + kidney infarction	[88]
Ethanol	Metrizamide	Dog renal artery	Ablation mechanism, influence of injection rate.	[43]
Ethanol 10–70%	None	Rat carotid artery/brain	Ethanol concentration <40% preserve media	[85]

PVAc, poly(vinyl alcohol acetate); EVAL, ethylene vinyl alcohol copolymer; NBCA, *n*-butyl cyanoacrylate; DMSO, dimethyl sulfoxide; W, tungsten; Ta, tantalum

inflammatory reaction due to toxic reaction products and the exothermic polymerization [5, 12]. In the search for non-adhesive CA, promising but still experimental products have been proposed such as derivatives with long alkyl chains [13] or 2-hexyl CA (Neuracryl) [14]. Furthermore, an alternative CA (Glubran) that solidifies through radical rather than ionic polymerization has been reported to reduce adhesion to vascular walls in animal experiments [15]. These new materials may renew the interest in CA glues.

Another type of *in situ* polymerizing implant is used for bone reinforcement in the field of vertebroplasty. The material originally proposed by Deramond et al. [16] in the mid-1980s is a cement that polymerizes into a poly(methyl methacrylate) (PMMA) cast. Vertebral body filling provides immediate bone stabilization and, with that, pain relief. In some instances, intratumoral injection allows a tumor reduction, attributed to the heat released during the polymerization reaction [17, 18]. In comparison with the above-mentioned cyanoacrylates, the cements have a much higher rigidity as indicated by their high compression modulus of 2–5 GPa [19], comparable to or higher than that of cortical bone. Despite their clinical success, the limited bone-bonding and bone-conducting ability of the acrylic cements spurred the search for new materials [20]. Cements containing exclusively a mineral phase, such as calcium phosphate cements, show osteoconductive properties, although their strength is generally lower than that of PMMA cements. They set by means of an acid–base reaction resulting in precipitated calcium salts. Composite cements including a polymerizable phase and a mineral phase may combine bone bonding with an early strength [21, 22] provided by the polymer matrix and hold promise for applications in vertebroplasty.

Precipitating Formulations

In contrast to polymerizing formulations, precipitating liquid embolics solidify not after a given time, but when in contact with physiologic fluids. This results in a specific behavior when delivering the implant: the delivery may be paused temporarily during injection to prevent leakage in a nontargeted vascular or intratumoral space.

A Japanese team initially reported the use of an ethylene-*co*-vinyl alcohol (EVAL, also abbreviated EVOH) solution for AVMs [23] and aneurysm embolization [24] that has nonadhesive properties when compared with *n*-butyl cyanoacrylates. The organic solvent used to dissolve the copolymer, dimethyl sulfoxide (DMSO), raised concerns of angiotoxicity. Although initial studies did demonstrate vasospasms following DMSO injection, subsequent reports indicated that this effect could be reduced using injection rates as low as 0.1 ml/min [25, 26]. In addition, as yet experimental solvents possessing a better hemocompatibility and reduced hemodynamic side effects could be an alternative to DMSO for precipitating embolics [27].

An EVAL solution in DMSO opacified with tantalum was commercialized by Micro Therapeutics Inc. as Embolyx and then Onyx. The latter was used for the successful embolization of rabbit kidneys [28], swine rete mirabile [29,

30], and AVMs [31, 33] and aneurysms in humans. More recently, a multicenter trial demonstrated the safety and efficacy of Onyx for the embolization of aneurysms in selected patients [34]. It received a CE mark for peripheral vascular applications (1999) and brain tumors (2000). Insufficient radiopacity and tantalum sedimentation have, however, been mentioned as drawbacks [35]. Another precipitating embolic, a cellulose acetate polymer dissolved in DMSO [36] and radiopacified with bismuth trioxide, allowed successful embolization of aneurysms [37] and AVMs [38, 39]. The team reported mild inflammatory reactions with no chronic granulomatous reaction. It was also used for embolization of kidneys [28] and spinal arteriovenous fistulae [40]. Additional precipitating embolics have been proposed, based on polyurethane or poly(acrylonitrile). Despite interesting properties, these materials have not yet proven to be safer and more efficient than the EVAL or cellulose acetate polymers.

Precipitating Sclerosing Formulations

A particular solvent for the precipitating embolics is ethanol. It can be an efficient embolization agent when used alone [41, 42] that damages the endothelium and activates the coagulation, producing complete infarction of the target organ or tumor [43]. However, the risk of injury to adjacent normal tissues is a concern, as well as cardiopulmonary collapse; some authors recommend limiting the use of ethanol to small organs such as kidneys [1]. Low ethanol concentrations ($\leq$ 40% vol ethanol in water) may be preferred in order to limit sclerosis to intimal layers and reduce damage to surrounding tissues [44].

A variety of precipitating embolics based on ethanolic solutions have been reported. The commercially available Ethibloc is an ethanolic (57% vol) emulsion based on zein, a corn protein, that is used to embolize kidney, tumors [45] and AVMs. Although efficient, the relatively high viscosity of Ethibloc may restrict its applications [46]. Poly(vinyl acetate) (PVAc) in 50% ethanol has been used following estrogen embolization to increase the embolization effect and reduce the risk of hemorrhage [47–49]. In order to increase PVAc solubility, Park et al. [50] proposed a partially hydrolyzed PVAc, ''Embol-78'', soluble in 44% ethanolic aqueous solutions. Its efficiency was demonstrated in preclinical studies for renal [51] and portal vein embolization [52]. Another promising and nonadhesive embolic is based on EVAL dissolved in 42% ethanol aqueous solutions, and has been used clinically to embolize AVMs [53, 54]. Acrylic copolymers based on hydroxyethyl methacrylate (HEMA) and methyl methacrylate (MMA) are known for their biocompatibility and hemocompatibility. HEMA-*co*-MMA dissolved in only 7% ethanol aqueous solution was thus tested on rabbit kidneys [55] and experimental aneurysms, and in humans led to efficient embolization of AVMs [56, 57]. Recently, pure HEMA dissolved in concentrated (90%) ethanol aqueous solutions led to effective embolization in pig AVM [58] and aneurysm [59] models. Finally, Eudragit, an acrylic polymer FDA-cleared for pharmaceuticals and food packaging, as a 50% aqueous ethanol solution, showed nonadhesive properties and could embolize dog renal arteries. However, a chronic reaction at 2 months [60, 61], damage to the vessel walls and brain edema necrosis raise concerns about its use for AVM embolization [62].

A sclerosing alternative to ethanol has been proposed based on aqueous acetic acid solutions. Comparative clinical studies claimed that Percutaneous Acetic acid Injection (PAI) efficiency was similar to or even superior to ethanol for primary hepatic carcinoma [63]. PAIs were also reported to be superior to ethanol for the treatment of renal cysts [64].

Alternative Aqueous Embolics

Besides the use of polymerization and precipitation to form an implant *in situ*, alternative principles of phase transition have been proposed. Although still experimental, the aqueous embolics that are based on water as a solvent may be attractive due to the absence of potentially toxic monomers, initiators or solvents. The coagulation of charged latex particles in the presence of ionic species is an example. Based on this principle, an aqueous emulsion of charged poly(vinyl acetate) particles have been assessed for the embolization of AVMs [65]. Though biocompatibility and effectiveness have been demonstrated, the aggregation remains difficult to control in a surgical setting. An ionically cross-linkable hydrogel, purified calcium alginate, demonstrated efficient renal embolization in an acute rabbit model [66] and 1-week stability in an AVM model [67]. Drawbacks of this material are the need for double-lumen catheters, concerns regarding the release of non-cross-linked potentially toxic macromolecules and the limited long-term stability of the hydrogel cast. Enzymatic cross-linking may also be used to produce hydrogels, as illustrated by fibrin glue, a biological material that mimics the coagulation cascade. Fibrin glue is a two-component material widely used and FDA-approved as a hemostatic agent (Tisseel, Hemaseel). It was shown to be safe and effective for the preoperative embolization of sinus hemangiomas [68] and intracranial meningioma [69]. Fibrin injection could reduce bleeding and induce tumor necrosis in the vascular bed. Despite its biocompatibility, the use of fibrin for AVM embolization is hindered by its fast degradation and the need for double-lumen catheterization. Another experimental strategy is the use of thermosensitive embolics, able to form a hydrogel when exposed to body temperature. For instance, gels based on *N*-isopropylacrylamide embolized mice kidneys [70] and poloxamer was used for temporary occlusion of dog arteries [71]. These different injectable water-based embolics have been demonstrated to fill in AVMs, vascular tumors and aneurysms. Despite their good biocompatibility, these formulations have not proved superior to EVAL or cyanoacrylates in terms of ease of use or efficiency for embolization. Further experimental work is required to

prevent over-rapid degradation that may hamper the clinical outcome.

Clinically Relevant Characteristics of the Injectable Implants

The criteria influencing the choice of an appropriate injectable implant are discussed below. The characteristics to be considered can be categorized according to the different clinical application steps, i.e., implant delivery, implant function and implant visibility during follow-up studies.

Implant Delivery

During implant delivery, low-viscosity preparations are preferred in order to facilitate the injection through small needles and microcatheters. The higher the viscosity, the higher the injection pressure required to deliver through narrow tubing. In the case of high-pressure injections, there exists a risk of microcatheter or connection adapter failure, which may lead to loss of implant material with the potential to produce errant implant delivery embolizing nontarget structures. Warning signs for imminent delivery failure are build-up of the injection pressure during implant delivery or changes in the diameter of the tubing when nonbraided tubing is used; finally, catheter rupture may be suspected when a sudden drop in the injection pressure occurs indicating leakage.

Once the implant has passed through the delivery system and reached the tissue, the optimal required characteristics change and include additional criteria such as setting time, setting mechanism and side effects (e.g., adhesion, toxicity).

Viscosity

Viscosity remains a criterion, with low viscosity and slow setting favored for conditions where there is a need for high implant penetration in small vascular spaces. For a given material, the viscosity of the liquid controls the distal propagation of the embolization, as shown in liver tumors [72]. If distal progression is feared, a combination of high viscosity and a fast setting time may be preferred. As additional elements to control implant delivery, techniques of local or general flow control have been described and may be used to complement implant characteristics [35, 73].

Setting Mechanisms

As outlined above, one of the fundamentally differences between polymerizing liquids and precipitating liquids is their behavior during setting. In polymerizing liquids, setting occurs in a narrow predefined time range and is initiated once the implant encounters the reaction initiator. In contrast, precipitating embolics start losing their solvents as soon as they are exposed to a miscible environment, i.e., within the body tissue, where they form a skin at the interface with water. This skin slows down the outward diffusion of the organic solvent, and therefore slows down the hardening of the deepest part of the implant. Immediately after injection, a soft material enclosed in a thin skin is thus obtained. A practical implication of this specific feature is that the injection of precipitating embolics, such as EVAL, may be paused when inadequate filling is noticed, allowing for progressive precipitation of already injected materials. This can help to build up a local plug preventing further inadequate filling and redirecting delayed continuous injections of the liquid embolic flow towards other areas of the target site.

Setting Time

For a given target, the blood flow conditions at the injection site influence the choice of the implant material. For occlusion of high-blood-flow lesions such as AVMs, fast-setting materials such as cyanoacrylates embolics may be preferable in order to avoid undue progression of the injected implant. Other methods described consist in reducing the flow by a wedge catheter, use of a calibrated balloon or by reducing the systemic blood pressure. When dealing with lesions that exhibit slow flow conditions, slow-setting compounds may be preferred to allow for better implant progression during delivery.

Side Effects: Adhesion

Once the implant has been delivered, implant adhesion to the delivery system (catheter, needle) may lead to its trapping into the embolization site with potential subsequent adverse effects; this drawback has been consistently reported for most cyanoacrylate glues. Adhesion to the catheter originates from their strong adhesive properties and their low viscosity [5]. In order to reduce this adhesion, a hydrophilic-coated catheter, nonadhesive liquid embolics such as EVAL or modified cyanoacrylates [15, 74], or a combination of a low-adhesion-risk delivery system and implant, should be used.

Side Effects: Toxicity

The local adverse effects of precipitating agents (e.g., vasospasm) are related to the presence of the organic solvent, and may be circumvented, or at least reduced, by injecting at a slow maximum rate [25], as outlined above. In contrast, polymerizing embolics may not induce vasospasms but may present side effects related to the release of toxic chemicals during polymerization.

Implant Function

Specific implant functions of interest for current minimally invasive procedures include biocompatibility, biodegradability, biomechanical properties and bioactivity.

Biocompatibility

The biocompatibility may be defined by the nature and degree of the local, chronic tissue reaction around the polymeric implant. Whether a strong, mild or no tissue reaction is required for an appropriate implant function depends on the specific application and may be controversial. For instance, a strong tissue reaction inducing angiogenesis may not be desirable in AVMs since it may support AVM recurrence in the long term. In contrast, for aneurysm embolization, a controlled tissue reaction could promote scar tissue formation [75] and facilitate the reconstruction of the parent artery.

For liquid embolics, implant biocompatibility is related to the nature of the polymer and the polymer phase change from liquid to solid. Indeed, polymerizing liquids carry a risk of chronic inflammatory reaction [5, 12] partly due to cross-linking agents, initiators and residual monomers or reaction byproducts. Less inflammation risks exist, in contrast, with precipitating nonbiodegradable embolics that contain none of these elements. Ethibloc, a precipitating embolic, is an exception, since its protein nature combined with the alcoholic solvent of the implant mixture typically induces an inflammatory reaction. Aqueous liquid embolics, such as fibrin glue or other injectable hydrogels, are likely advantageous due to their intrinsic potential of being biocompatible as a result of their high water content. Hence, if good biocompatibility is the primary required characteristic, further development of biostable aqueous embolics may be of interest.

Biodegradability

The durability of the occlusion is a further factor of relevance to the choice of an implant material. Biodegradable polymeric implants may be suitable for presurgical obliteration of highly vascularized lesions [68, 69]. Resorbable implants, such as fibrin glue, are degraded over time and, if applied in, for example, AVMs, vessel recanalization can be observed. For AVM treatment, long-lasting effect may be obtained with nondegradable polymers such as EVAL or cyanoacrylates, if material deposition occurs in the arteriovenous shunt area. With AVMs often exhibiting biologically active reactions that may be independent of the type of implant, the choice of embolic material may not be the only key to success in treating AVMs. Biodegradable implants appear attractive as a concept if they are replaced in time by biological tissue, such as might be the case when the implant would lead to lasting tissue repair in the area of an aneurysm neck before disappearing. However, the downside lies in the need to establish good biocompatibility and appropriate tissue remodeling for such materials over the degradation time.

Bioactivity

Some implants may also provide biological activity, in contrast to the conventional above-mentioned implants that are biologically mostly inert. Biological activity can be obtained through the release of a drug, as for instance in growth-factor-releasing implants [76–78]. Such implants are designed to support the tissue repair necessary for arterial wall reconstruction by stimulating the cellular elements that form a neointima in the aneurysm neck area. The implant material may also have bioactive properties per se, such as for the mineral phase in osteoconductive cements. In both cases, an acceleration of the wound healing process is targeted that, in turn, may improve the integration of the implant into the tissue. Although limited clinical evidence on their efficacy is available, recent advances in biomaterials and animal testing of bioactive implants hold promise for minimally invasive treatment.

Biomechanics

The mechanical properties of the implant should ideally match those of the target tissue in order to reduce the relative stress and eventual motion at the implant/tissue interface that occurs when the tissue is submitted to an external stress. For instance in the field of vertebroplasty, the high stiffness provided by PMMA implants leads to immediate pain relief due to mechanical stabilization. PMMA cements that exhibit a stiffness superior to normal bone lead to stiffer than normal vertebral bodies, a condition that may be considered as a factor facilitating the fractures in adjacent untreated vertebral segments that are currently increasingly observed with the use of PMMA in the treatment of osteoporotic vertebral fractures. An adaptation of the implant to match normal biomechanical values may potentially reduce this fracture risk. In contrast, preoperative embolization requires the formation of an elastic cast to facilitate subsequent surgical removal of the lesion, which is better achieved with EVAL, celluloses and hydrogels than with certain cyanoacrylates.

Implant Visibility

For safe delivery, good visibility of the implant under fluoroscopy is critical. During follow-up studies, visibility of the implant is also a key factor, although the use of MRI or CT may require less radiopacity and MR compatibility. Further, it may be of interest to allow for optimal contrast of the implant with adjacent structures without production of imaging artifacts by the implant. In consequence, one has to negotiate a radiopacity threshold with acceptable minimal density for fluoroscopy and acceptable density for CT or MRI. If very high density materials are used, such as the platinum coils used for cerebral aneurysm filling, CT becomes difficult but MR angiography can make up for this disadvantage—a concept that seems to have been well accepted within the medical community using this type of implant. Another disadvantage to consider with the delivery of very dense implants is the fact that visual control of additional implants may be hindered by the presence of the

already present implant. This problem is sometimes encountered with homogeneously radiopaque implants used in vertebroplasty procedures or AVM embolizations.

Most of the above-mentioned injectable implants are made radiopaque by the admixing of contrast agents, either in a solid form such as powders of tantalum, tungsten or barium sulfate, or in a liquid form such as Lipiodol or Ethiodol. Continuing progress in the formulation of radiopacifiers has allowed for improvement of the radiopacity (e.g., Cortoss cements as compared with earlier PMMA cements). Although the addition of a radiopacifier has proven to be efficient, its entrapment or its homogeneous mixing is not always ensured, so that phase separation, sedimentation or leaching of the radiopacifier may interfere with the clinical follow-up interpretation [79]. Leaching of radiopacifiers may potentially also lead to toxic effects. Polymers with bound radiopaque moieties have been proposed to circumvent the above-outlined problems. For this purpose, degradable radiopaque polyurethane [80], cellulose-based [81] or vinyl-based radiopaque polymers [82] have been proposed. Although still experimental, such intrinsically radiopaque polymers could provide an attractive alternative to the use of radiopaque agents.

Conclusion

Liquid polymeric formulations that may form an implant *in situ* are nowadays used for an increasing number of indications, thanks to the development of new materials, improved delivery techniques and a continuous drive to develop minimally invasive techniques in the interests of patient care. In a tailored approach, the formulation of the injectable implant should be selected to fulfill the safety and efficiency criteria related to implant delivery, implant function and implant follow-up studies. A key implant characteristic that governs this choice is the nature of the physicochemical principle used to produce *in situ* a solid or gel-like implant. Key material features are the material viscosity and setting, the radiopacity, the implant biomechanics, the biocompatibility and the biodegradability. Future developments towards application-tailored implants may open the way to clinically useful techniques in the field of minimally invasive image guided treatment.

Acknowledgments. This work was supported by the Swiss National Research Fund no 3200-057200.

References

1. Pollak JS, White RI Jr (2001) The use of cyanoacrylate adhesives in peripheral embolization. J Vasc Interv Radiol 12:907–913
2. Szmigielski W, Klamut M, Wolski T, Studnicki W, Rubaj B (1981) Urogranoic acid as a radiopaque additive to the cyanoacrylic adhesive in transcatheter obliteration of renal arteries. Invest Radiol 16:65–70
3. Günther R, Schubert U, Bohl J, Georgi M, Marberger M (1978) Transcatheter embolization of the kidney with butyl-2-cyanoacrylate: Experimental and clinical results. Cardiovasc Radiol 1:101–108
4. Stoesslein F, Ditscherlein G, Romaniuk PA (1982) Experimental studies on new liquid embolization mixtures (Histoacryl-Lipiodol, Histoacryl-Panthopaque). Cardiovasc Intervent Radiol 5:264–267
5. Kerber CW, Wong W (2000) Liquid acrylic adhesive agents in interventional neuroradiology. Neurosurg Clin North Am 11:85–99
6. Casasco A, Herbreteau D, Houdart E, George B, Tran Ba Huy P, Deffresne D, Merland JJ (1994) Devascularization of craniofacial tumors by percutaneous tumor puncture. AJNR Am J Neuroradiol 15:1233–1239
7. Paulsen RD, Steinberg GK, Norbash AM, Marcellus ML, Marks MP (1999) Embolization of basal ganglia and thalamic arteriovenous malformations. Neurosurgery 44:991–996
8. The n-BCA Trial Investigators(2002) *N*-butyl cyanoacrylate embolization of cerebral arteriovenous malformations: Results of a prospective, randomized, multi-center trial. AJNR Am J Neuroradiol 23:748–755
9. Casasco A, Houdart E, Biondi A, Jhaveri HS, Herbreteau D, Aymard A, Merland JJ (1999) Major complications of percutaneous embolization of skull-base tumors. AJNR Am J Neuroradiol 20:179–181
10. Gruber A, Mazal PR, Bavinzski G, Killer M, Budka H, Richling B (1996) Repermeation of partially embolized cerebral arteriovenous malformations: A clinical, radiologic, and histologic study. AJNR Am J Neuroradiol 17:1323–1331
11. Laurent A (1998) Materials and biomaterials for interventional radiology. Biomed Pharmacother 52:76–88
12. Vinters HV, Galil KA, Lundie MJ, Kaufmann JCE (1985) The histotoxicity of cyanoacrylates. Neuroradiology 27:279–291
13. Oowaki H, Matsuda S, Sakai N, Ohta T, Iwata H, Sadato A, Taki W, Hashimoto N, Ikada Y (2000) Non-adhesive cyanoacrylate as an embolic material for endovascular neurosurgery. Biomaterials 21:1039–1046
14. Barr JD, Hoffman EJ, Davis BR, Edgar KA, Jacobs CR (1999) Microcatheter adhesion of cyanoacrylates: comparison of normal butyl cyanoacrylate to 2-hexyl cyanoacrylate. J Vasc Interv Radiol 10:165–168
15. Levrier O, Mekkaoui C, Rolland PH, Murphy K, Cabrol P, Moulin G, Bartoli JM, Raybaud C (2003) Efficacy and low vascular toxicity of embolization with radical versus anionic polymerization of *n*-butyl-2-cyanoacrylate (NBCA). An experimental study in swine. J Neuroradiol 30:95–102
16. Deramond H, Depriester C, Galibert P, Le Gars D (1998) Percutaneous vertebroplasty with polymethylmethacrylate. Technique, indications, and results. Radiol Clin North Am 36:533–546
17. Deramond H, Wright NT, Belkoff SM (1999) Temperature elevation caused by bone cement polymerization during vertebroplasty. Bone 25:17S–21S
18. Martin JB, Wetzel SG, Seium Y, Dietrich PY, Somon T, Gailloud P, Payer M, Kelekis A, Ruefenacht DA (2003) Percutaneous vertebroplasty in metastatic disease: Transpedicular access and treatment of lysed pedicles—initial experience. Radiology 229:593–597
19. Jasper LE, Deramond H, Mathis JM, Belkoff SM (2002) Material properties of various cements for use with vertebroplasty. J Mat Sci Mat Med 13:1–5
20. Heini PF, Berlemann U (2001) Bone substitutes in vertebroplasty. Eur Spine J 10([Suppl 2]):S205–S213
21. Belkoff SM, Mathis JM, Erbe EM, Fenton DC (2000) Biomechanical evaluation of a new bone cement for use in vertebroplasty. Spine 25:1061–1064
22. Erbe EM, Clineff TD, Gualtieri G (2001) Comparison of a new bisphenol-a-glycidyl dimethacrylate-based cortical bone void filler with polymethyl methacrylate. Eur Spine J 10([Suppl 2]):S147–S152
23. Taki W, Yonekawa Y, Iwata H, Uno A, Yamashita K, Amemiya H (1990) A new liquid material for embolization of arteriovenous malformations. AJNR Am J Neuroradiol 11:163–168
24. Terada T, Nakamura Y, Nakai K, Tsuura M, Nishiguchi T, Hayashi S, Kido T, Taki W, Iwata H, Komai N (1991) Embolization of arteriovenous malformations with peripheral aneurysms using ethylene vinyl alcohol copolymer. J Neurosurg 75:655–660
25. Chaloupka JC, Huddle DC, Alderman J, Fink S, Hammond R, Vinters HV (1999) A reexamination of the angiotoxicity of superselective injection of DMSO in the swine rete embolization model. AJNR Am J Neuroradiol 20:401–410
26. Laurent A, Wassef M, Zhang HQ, Bailliard O, Houdart E, Bailly AL, Merland JJ (1997) Solutions gélifiantes pour embolisation: Etude ani-

male de la toxicité cardiovasculaire d'un constituant, le diméthylsulfoxyde. J Neuroradiol 24:314
27. Mottu F, Gailloud P, Massuelle D, Rüfenacht DA, Doelker E (2000) *In vitro* assessment of new embolic liquids prepared from preformed polymers and water-miscible solvents for aneurysm treatment. Biomaterials 21:803–811
28. Wright KC, Greff RJ, Price RE (1999) Experimental evaluation of cellulose acetate NF and ethylene-vinyl alcohol copolymer for selective arterial embolization. J Vasc Interv Radiol 10:1207–1218
29. Murayama Y, Vinuela F, Ulhoa A, Akiba Y, Duckwiler GR, Gobin YP, Vinters HV, Greff RJ (1998) Nonadhesive liquid embolic agent for cerebral arteriovenous malformations: Preliminary histopathological studies in swine rete mirabile. Neurosurgery 43:1164–1172
30. Gobin YP, Murayama Y, Milanese K, Chow K, Gonzalez NR, Duckwiler GR, Vinuela F (2001) Head and neck hypervascular lesions: Embolization with ethylene vinyl alcohol copolymer—laboratory evaluation in swine and clinical evaluation in humans. Radiology 221:309–317
31. Molyneux AJ, Coley SC (2000) Embolization of spinal cord arteriovenous malformations with an ethylene vinyl alcohol copolymer dissolved in dimethyl sulfoxide (Onyx liquid embolic system). Report of two cases. J Neurosurg 93:304–308
32. Jahan R, Murayama Y, Gobin YP, Duckwiler GR, Vinters HV, Vinuela F (2001) Embolization of arteriovenous malformations with Onyx: Clinicopathological experience in 23 patients. Neurosurgery 48:984–995
33. Duffner F, Ritz R, Bornemann A, Freudenstein D, Wiendl H, Siekmann R (2002) Combined therapy of cerebral arteriovenous malformations: Histological differences between a non-adhesive liquid embolic agent and *n*-butyl 2-cyanoacrylate (NBCA). Clin Neuropathol 21:13–17
34. Molyneux AJ, Cekirge S, Saatci I, Gal G (2004) Cerebral Aneurysm Multicenter European Onyx (CAMEO) trial: Results of a prospective observational study in 20 European centers. AJNR Am J Neuroradiol 25:39–51
35. Murayama Y, Vinuela F, Tateshima S, Akiba Y (2000) Endovascular treatment of experimental aneurysms by use of a combination of liquid embolic agents and protective devices. AJNR Am J Neuroradiol 21:1726–1735
36. Mandai S, Kinugasa K, Ohmoto T (1992) Direct thrombosis of aneurysms with cellulose acetate polymer. I. Results of thrombosis in experimental aneurysms. J Neurosurg 77:497–500
37. Kinugasa K, Mandai S, Terai Y, Kamata I, Sugiu K, Ohmoto T, Nishimoto A (1992) Direct thrombosis of aneurysms with cellulose acetate polymer. II. Preliminary clinical experience. J Neurosurg 77:501–507
38. Tokunaga K, Kinugasa K, Meguro T, Kawada S, Sugiu K, Nakashima H, Furuta T, Taguchi K, Kamata I, Mandai S, Hirotsune N, Ohmoto T (1998) Embolization of cerebral arteriovenous malformations with cellulose acetate polymer: Histological study of the resected specimens. Interv Neuroradiol 4:117–120
39. Tokunaga K, Kinugasa K, Kawada S, Nakashima H, Tamiya T, Hirotsune N, Mandai S, Ohmoto T (1999) Embolization of cerebral arteriovenous malformations with cellulose acetate polymer: A clinical, radiological, and histological study. Neurosurgery 44:981–989
40. Sugiu K, Meguro T, Nakashiama H, Ohmoto T (2001) Successful embolization of a spinal perimedullary arteriovenous fistula with cellulose acetate polymer solution: Technical case report. Neurosurgery 49:1257–1261
41. Yakes WF, Krauth L, Ecklund J, Swengle R, Dreisbach JN, Seibert CE, Baker R, Miller M, Van der Ark G, Fullagar T, Prenger E (1997) Ethanol endovascular management of brain arteriovenous malformations: initial results. Neurosurgery 40:1145–1154
42. Yakes WF, Luethke JM, Merland JJ, Rak KM, Slater DD, Hollis HW, Parker SH, Casasco A, Aymard A, Hodes J (1990) Ethanol embolization of arteriovenous fistulas: a primary mode of therapy. J Vasc Interv Radiol 1:89–96
43. Ellman BA, Parkhill BJ, Marcus PB, Curry TS, Peters PC (1984) Renal ablation with absolute ethanol. Mechanism of action. Invest Radiol 19:416–423
44. Sampei K, Hashimoto N, Tsukahara T, Kazekawa K, Iwata H, Takaichi S (1996) Histological changes in brain tissue and vasculature after intracarotid infusion of organic solvents in rats. Neuroradiology 38:291–294
45. Richter G, Rassweiler J, Kauffmann GW, Wenz W, Crawford DB (1984) Experimental study of the effectiveness of capillary embolization using contrast-enhanced Ethibloc. Invest Radiol 19:36–44
46. Matsumaru Y, Hyodo A, Nose T, Hirano T, Ohashi S (1997) Embolic materials for endovascular treatment of cerebral lesions. J Biomater Sci Polymer Ed 8:555–569
47. Su CC, Takahashi A, Yoshimoto T, Sugawara T (1991) Histopathological studies of a new liquid embolization method using estrogen-alcohol and polyvinyl acetate. Surg Neurol 36:4–11
48. Satoh K, Matsubara S, Ueda S, Matsumoto K (1996) Arteriovenous malformation treatment with embolization first. In: Taki W, Picard L, Kikuchi H (eds) Advances in interventional neuroradiology and intravascular neurosurgery. Elsevier, Amsterdam, pp 329–332
49. Sugawara T, Takahashi A, Su CC, Suga T, Yoshimoto T (1993) Experimental investigations concerning a new liquid embolization method: Combined administration of ethanol-estrogen and polyvinyl acetate. Neurol Med Chir (Tokyo) 33:71–76
50. Park S, Yoon HK, Lee N, Huh SJ, Kang GH, Lee I, Sung KB, Song HY (1999) Portal vein embolization with use of a new liquid embolic material: An experimental study. J Vasc Interv Radiol 10:339–345
51. Park SI, Lee DY, Won JY, Park S (2000) Renal artery embolization using a new liquid embolic material obtained by partial hydrolysis of polyvinyl acetate (Embol): Initial experience in six patients. Korean J Radiol 1:121–126
52. Ko G-Y, Sung K-B, Yoon H-K, Kim J-H, Weon YC, Song H-Y (2003) Preoperative portal vein embolization with a new liquid embolic agent. Radiology 227:407–413
53. Hamada J, Kai Y, Morioka M, Kazekawa K, Ishimaru Y, Iwata H, Ushio Y (2002) A nonadhesive liquid embolic agent composed of ethylene vinyl alcohol copolymer and ethanol mixture for the treatment of cerebral arteriovenous malformations: Experimental study. J Neurosurg 97:889–895
54. Hamada J, Kai Y, Morioka M, Kazekawa K, Ishimaru Y, Iwata H, Ushio Y (2002) A mixture of ethylene vinyl alcohol copolymer and ethanol yielding a nonadhesive liquid embolic agent to treat cerebral arteriovenous malformations: Initial clinical experience. J Neurosurg. 97:881–888
55. Kazekawa K, Iwata H, Shimozuru T, Sampei K, Sakaki N, Morikawa N, Matsuda S, Ikada Y (1997) Nontoxic embolic liquids for treatment of arteriovenous malformations. J Biomed Mater Res 38:79–86
56. Kazekawa K, Kawano T, Kawaguchi T, Honma T, Kaneko Y, Dosaka A, Koizumi T, Iwata H, Morikawa N, Matsuda S, Ikada Y (1998) Newly synthesized liquid embolization material for arteriovenous malformation. J Clin Neurosci 5:45–48
57. Kawaguchi T, Kawano T, Kaneko Y, Koizumi T, Tsutsumi M, Ooigawa H, Kazekawa K (2000) Transarterial embolization with HEMA-MMA of variant convexity-superior sagittal sinus dural arteriovenous fistula: Case report. Neurol Med Chir (Tokyo) 40:366–368
58. Klisch J, Yin L, Requejo F, Eissner B, Scheufler KM, Kubalek R, Buechner M, Pagenstecher A, Nagursky H, Schumacher M (2002) Liquid 2-poly-hydroxyethyl-methacrylate embolization of experimental arteriovenous malformations: Feasibility study. AJNR Am J Neuroradiol 23:422–429
59. Klisch J, Schellhammer F, Zitt J, Scheufler KM, Pagenstecher A, Nagursky H, Schumacher M (2002) Combined stent implantation and embolization with liquid 2-polyhydroxyethyl methacrylate for treatment of experimental canine wide-necked aneurysms. Neuroradiology 44:503–512
60. Yamashita K, Taki W, Iwata H, Kikuchi H (1996) A cationic polymer, Eudragit-E, as a new liquid embolic material for arteriovenous malformations. Neuroradiology 38([Suppl 1]):151–156
61. Shi Z, Huang Z, Zhang Y, Qi T, Chu M, Bao D (2002) Experimental study of Eudragit mixture as a new nonadhesive liquid embolic material. Chin Med J (Engl) 115:555–558
62. Kondo S, Kobayashi A, Nagata H, Nakahara I, Taki W, Yamashita K (1996) Subacute macroscopic and histological change of an embolized arteriovenous malformation (AVM) with Eudragit-E. In: Taki W, Picard L, Kikuchi H (eds) Advances in interventional neuroradiology and intravascular neurosurgery. Elsevier, Amsterdam, pp 31–37

63. Ohnishi K (1998) Comparison of percutaneous acetic acid injection and percutaneous ethanol injection for small hepatocellular carcinoma. Hepatogastroenterology 45([Suppl 3]):1254–1258
64. Seo TS, Oh JH, Yoon Y, Lim JW, Park SJ, Chang SG, Jeon YH (2000) Acetic acid as a sclerosing agent for renal cysts: Comparison with ethanol in follow-up results. Cardiovasc Intervent Radiol 23:177–181
65. Sadato A, Taki W, Ikada Y, Nakahara I, Yamashita K, Matsumoto K, Tanaka M, Kikuchi H, Doi Y, Noguchi T, Inada T (1994) Experimental study and clinical use of poly(vinyl acetate) emulsion as liquid embolisation material. Neuroradiology 36:634–641
66. Becker TA, Kipke DR, Brandon T (2001) Calcium alginate gel: A biocompatible and mechanically stable polymer for endovascular embolization. J Biomed Mater Res 54:76–86
67. Becker TA, Kipke DR, Preul MC, Bichard WD, McDougall CG (2002) *In vivo* assessment of calcium alginate gel for endovascular embolization of a cerebral arteriovenous malformation model using the swine rete mirabile. Neurosurgery 51:453–458
68. Kim IM, Yim MB, Lee CY, Son EI, Kim DW, Kim SP, Sohn CH (2002) Merits of intralesional fibrin glue injection in surgery for cavernous sinus cavernous hemangiomas. Technical note. J Neurosurg 97:718–721
69. Probst EN, Grzyska U, Westphal M, Zeumer H (1999) Preoperative embolization of intracranial meningiomas with a fibrin glue preparation. AJNR Am J Neuroradiol 20:1695–1702
70. Matsumaru Y, Hyodo A, Nose T, Ito S, Hirano T, Ohashi S (1996) Application of thermosensitive polymers as a new embolic material for intravascular neurosurgery. J Biomater Sci Polymer Ed 7:795–804
71. Raymond J, Metcalfe A, Salazkin I, Schwarz A (2004) Temporary vascular occlusion with poloxamer 407. Biomaterials 25:3983–3989
72. Komemushi A, Tanigawa N, Okuda Y, Kojima H, Fujii H, Shomura Y, Sougawa M, Sawada S (2002) A new liquid embolic material for liver tumors. Acta Radiol 43:186–191
73. Mawad ME, Cekirge S, Ciceri E, Saatci I (2002) Endovascular treatment of giant and large intracranial aneurysms by using a combination of stent placement and liquid polymer injection. J Neurosurg 96:474–482
74. Barr JD, Hoffman EJ, Davis BR, Edgar KA, Jacobs CR (1999) Microcatheter adhesion of cyanoacrylates: Comparison of normal butyl cyanoacrylate to 2-hexyl cyanoacrylate. J Vasc Interv Radiol 10:165–168
75. Sugiu K, Kinugasa K, Mandai S, Tokunaga K, Ohmoto T (1995) Direct thrombosis of experimental aneurysms with cellulose acetate polymer (CAP): Technical aspects, angiographic follow up, and histological study. J Neurosurg 83:531–538
76. Hatano T, Miyamoto S, Kawakami O, Yamada K, Hashimoto N, Tabata Y (2003) Acceleration of aneurysm healing by controlled release of basic fibroblast growth factor with the use of polyethylene terephthalate fiber coils coated with gelatin hydrogel. Neurosurgery 53:393–400
77. Raymond J, Metcalfe A, Desfaits AC, Ribourtout E, Salazkin I, Gilmartin K, Embry G, Boock RJ (2003) Alginate for endovascular treatment of aneurysms and local growth factor delivery. AJNR Am J Neuroradiol 24:1214–1221
78. Ohyama T, Ko IK, Miura A, Iwata H, Taki W (2004) ProNectin F-grafted-ethylene vinyl alcohol copolymer (EVAL) as a liquid type material for treating cerebral aneurysm: An *in vivo* and *in vitro* study. Biomaterials 25:3845–3852
79. Rao VR, Mandalam KR, Gupta A, Kumar S, Joseph S (1989) Dissolution of isobutyl 2-cyanoacrylate on long-term follow-up. AJNR Am J Neuroradiol 10:135–141
80. Maurer CA, Renzulli P, Baer HU, Mettler D, Uhlschmid G, Neuenschwander P, Suter UW, Triller J, Zimmermann A (2000) Hepatic artery embolisation with a novel radiopaque polymer causes extended liver necrosis in pigs due to occlusion of the concomitant portal vein. J Hepatol 32:261–268
81. Mottu F, Rüfenacht DA, Laurent A, Doelker E (2002) Iodine-containing cellulose mixed esters as radiopaque polymers for direct embolization of cerebral aneurysms and arteriovenous malformations. Biomaterials 23:121–131
82. Jordan O, Hilborn J, Levrier PH, Rüfenacht DA, Doelker E (2004). Novel radiopaque polymer for interventional radiology. Transactions of the 7th World Biomaterials Congress, Sydney, Australia, p 706
83. Casasco A, Herbreteau D, Houdart E, George B, Tran Ba Huy P, Deffresne D, Merland JJ (1994) Devascularization of craniofacial tumors by percutaneous tumor puncture. AJNR Am J Neuroradiol 15:1233–1239
84. Gruber A, Bavinzski G, Killer M, Richling B (2000) Preoperative embolization of hypervascular skull base tumors. Minim Invasive Neurosurg 43:62–71
85. Kinugasa K, Mandai S, Tsuchida S, Sugiu K, Kamata I, Tokunaga K, Ohmoto T, Taguchi K (1994) Cellulose acetate polymer thrombosis for the emergency treatment of aneurysms: Angiographic findings, clinical experience, and histopathological study. Neurosurgery 34:694–701
86. Tikkakoski T, Leppanen M, Turunen J, Anderson S, Sodervik H (2001) Percutaneous transcatheter renal embolization with absolute ethanol for uncontrolled nephrotic syndrome. Case reports. Acta Radiol 42:80–83
87. Martin JB, Wetzel SG, Seium Y, Dietrich PY, Somon T, Gailloud P, Payer M, Kelekis A, Ruefenacht DA (2003) Percutaneous vertebroplasty in metastatic disease: Transpedicular access and treatment of lysed pedicles—initial experience. Radiology 229:593–597
88. Ekelund L, Jonsson N, Treugut H (1981) Transcatheter obliteration of the renal artery by ethanol injection: Experimental results. Cardiovasc Intervent Radiol 4:1–7
89. Sampei K, Gotoh S, Nakano J, Shibata I, Terao H, Kaneko I, Kazekawa K (1996) Usefulness of a combined therapy for AVM: Embolization and stereotactic radiosurgery. In: Taki W, Picard L, Kikuchi H (eds) Advances in interventional neuroradiology and intravascular neurosurgery. Elsevier, Amsterdam, pp 293–296