



In vitro evaluation of radiopacity of contrast-loaded superabsorbent polymer microspheres (SAP-MS) with static imaging and flow model

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Abstract

Purpose To evaluate the radiopacity of contrast-loaded superabsorbent polymer microspheres (SAP-MS) under X-ray imaging.

Materials and methods SAP-MS were suspended in contrast material (iodixanol) and the diameter change was assessed. The diameter of contrast-loaded SAP-MS in saline was measured sequentially. Radiography of the contrast-loaded SAP-MS was evaluated as radiopacity by contrast-to-noise ratio and visibility by multiple reader scoring. Under digital subtraction angiography, contrast-loaded SAP-MS were injected into a flow model. The flow speed was 1–10 cm/s, and images were acquired at 1–7.5 frames per second using a pulse width of 10–85 ms. Images were assessed by multiple reader scoring.

Results The diameter of SAP-MS increased to 4.0–5.0 times its original size for approximately 15 min. The diameter of contrast-loaded SAP-MS in saline further increased by 10–30% within several minutes and returned to the previous size. Radiopacity and visibility of contrast-loaded SAP-MS decreased in 30 min after mixing with saline. Visibility was better with slow flow speed and narrow pulse width.

Conclusion For effective observation, contrast-loaded SAP-MS should be kept in non-diluted contrast material until use. The conditions of slower flow and use of a narrow pulse width are recommended.

Keywords Embolization · Microspheres · Radiopacity · Radiopaque beads

Introduction

Microspheres have been used in transarterial embolization. Theoretically, as microspheres are calibrated by size, it would be possible to embolize only the target vessels by using the optimal size of microspheres [1]. In clinical situations, however, insufficient embolization caused by subsequent redistribution and non-target embolization caused by overflow or shunts have been reported [2–4]. Since

microspheres are radiolucent, they are suspended in iodine contrast material and injected under fluoroscopic monitoring during the procedure. Though it is not clear whether the radiolucent nature of the microspheres contributes to the potential complications, use of directly visible radiopaque microspheres would likely facilitate safe and optimal embolization therapy. Therefore, radiopaque microspheres have been developed and some studies reported that radiopaque microspheres are visible under X-ray imaging [5–8]. However, there are only a few radiopaque microspheres commercially available in the limited countries.

Superabsorbent polymer microspheres (SAP-MS) swell by absorbing fluids. It is reported that contrast-loaded SAP-MS are visible under X-ray imaging [9, 10]. However, the radiopacity and visibility of SAP-MS under various conditions and modes of imaging have not yet been addressed. The purpose of this in vitro study was to evaluate the radiopacity and visibility of contrast-loaded SAP-MS with static imaging and flow model.

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Materials and methods

Microscopic evaluation

Diameter change of SAP-MS with contrast material

We used three sizes of SAP-MS (HepaSphere; Biosphere Medical, Rockland, MA, USA), 50–100, 100–150, and 150–200 μm . SAP-MS (25 mg per vial) were suspended in 10 mL of non-ionic iso-osmolar contrast material (iodixanol: Visipaque 270, Daiichi Sankyo, Tokyo, Japan). Changes in the size of SAP-MS were measured using a stereomicroscope (SZX 16-3111, Olympus, Tokyo, Japan). The diameter was measured at 0, 2, 5, 10, 15, 25, 30, 45, 60, 120, 180, 240, and 300 min. The measurements were made for 20 particles each and the mean value was determined.

Diameter change of contrast-loaded SAP-MS with saline

The suspension of contrast material including contrast-loaded SAP-MS was mixed with saline at volume ratios of 1:1 (50%), 1:3 (25%), 1:7 (12.5%), and 1:9 (10%). The diameter was measured at 0.5, 2, 5, 10, 15, 25, and 30 min after mixing. Measurements were made for 20 particles each and the mean value was determined. Three sizes of SAP-MS, 50–100, 100–150, and 150–200 μm were evaluated.

Static imaging

Digital radiography of the contrast-loaded SAP-MS was obtained using an angiographic equipment (Artis zee floor; Siemens Healthineers, Munich, Germany). A plastic dish with the diameter of 9 cm (Johnson and Johnson Plaza, New Brunswick, NJ, USA) containing the contrast-loaded SAP-MS was placed on the patient table, and digital radiographs were taken. The source-to-image distance was set at 100 cm, the source-to-table distance was set at 70 cm, and a field of view of 11 cm was used. The number of image pixels was 512×512 and the size of a pixel was 0.154 mm. Automatic exposure control (AEC) of the system defined the parameters including X-ray tube voltage, tube current, and the settings of additional filters. We evaluated only two sizes of SAP-MS with 100–150 and 150–200 μm because the size of SAP-MS with 50–100 μm was not visible in a pre-study.

Assessment by contrast-to-noise ratio (CNR)

Digital radiography of the suspension of contrast material including contrast-loaded SAP-MS mixed with saline at the volume ratio of 1:1 (50%), 1:3 (25%), 1:7 (12.5%), and 1:9 (10%) was obtained sequentially at intervals of 0.5–5 min.

The plastic dish was placed in the air at 15 cm above the patient table using a triangular prism object made of sheet of cardboard to evaluate the radiopacity of contrast-loaded SAP-MS themselves. The radiopacity of the contrast-loaded SAP-MS was assessed quantitatively using CNR with software installed in the equipment. CNR was calculated as follows [11].

$$\text{CNR} = \left| \text{Signal (ROI)}_{\text{Object}} - \text{Signal (ROI)}_{\text{Background}} \right| / \text{SD}_{\text{Background}}$$

where $\text{Signal (ROI)}_{\text{Object}}$ is the mean X-ray attenuation value of the SAP-MS in the region of interest (ROI). $\text{Signal (ROI)}_{\text{Background}}$ is the mean X-ray attenuation value in the background ROI. $\text{SD}_{\text{Background}}$ is the standard deviation of the attenuation value in the background ROI. A round ROI was drawn on the radiography of 10 particles each and 3 backgrounds each. ROI of each particle included 21 pixels for 100–150 μm and 61 pixels for 150–200 μm . ROI of each background included 5000–10,000 pixels. Time-to-CNR curves were drawn, and the maximum CNR and area under the curve (AUC) were evaluated.

Visual assessment

The plastic dish containing the contrast-loaded SAP-MS was placed on a water equivalent phantom (Tough Water Phantom PH-40, 30×30 cm, Kyoto Kagaku Co. Ltd, Kyoto, Japan) with the thickness of 15 cm. This is because we assumed the use for vascular malformations or tumors of the extremities, head and neck. Digital radiography was obtained at the same intervals as in the previous study. The visibility was scored as four grades (4: excellent; well-defined and countable, 3: good; ill-defined but countable, 2: fair; visible but uncountable, 1: poor; invisible) by four interventional radiologists with 2–10 years' experience, and the mean value was recorded as the visual score (Fig. 1).

Imaging with flow model

A flow model was assembled with a mechanical injector (Zone Master, SHEEN MAN CO. Ltd, Osaka, Japan) and a silicon tubing with a 3-mm inner diameter (Fig. 2). A 2.0-French microcatheter (Progreat Alpha, Terumo, Tokyo, Japan) was inserted into the flow model through a Y connector. The flow model was placed on the water equivalent phantom with the thickness of 15 cm and infused with saline at the speed of 1–10 cm/s by the injector. Under imaging by digital subtraction angiography (DSA), 0.05 mL of the suspension of contrast material including contrast-loaded SAP-MS was manually injected through the microcatheter into the saline flow using 1 mL syringe for 3 s. Two sizes of SAP-MS, 100–150 and 150–200 μm were evaluated. DSA images were acquired at 1–7.5 frames per second. Visibility was

Fig. 1 Radiography of contrast-loaded SAP-MS with diluted contrast material. Contrast-loaded SAP-MS were visualized by digital radiography. The visibility was scored as four grades, score 4: excellent (**a**), score 3: good (**b**), score 2: fair (**c**), and score 1: poor (**d**)

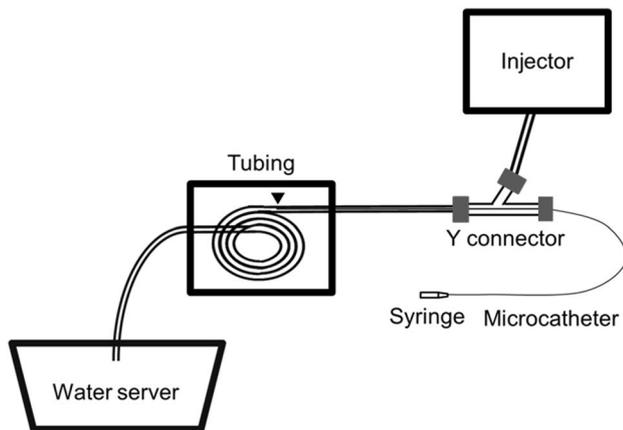
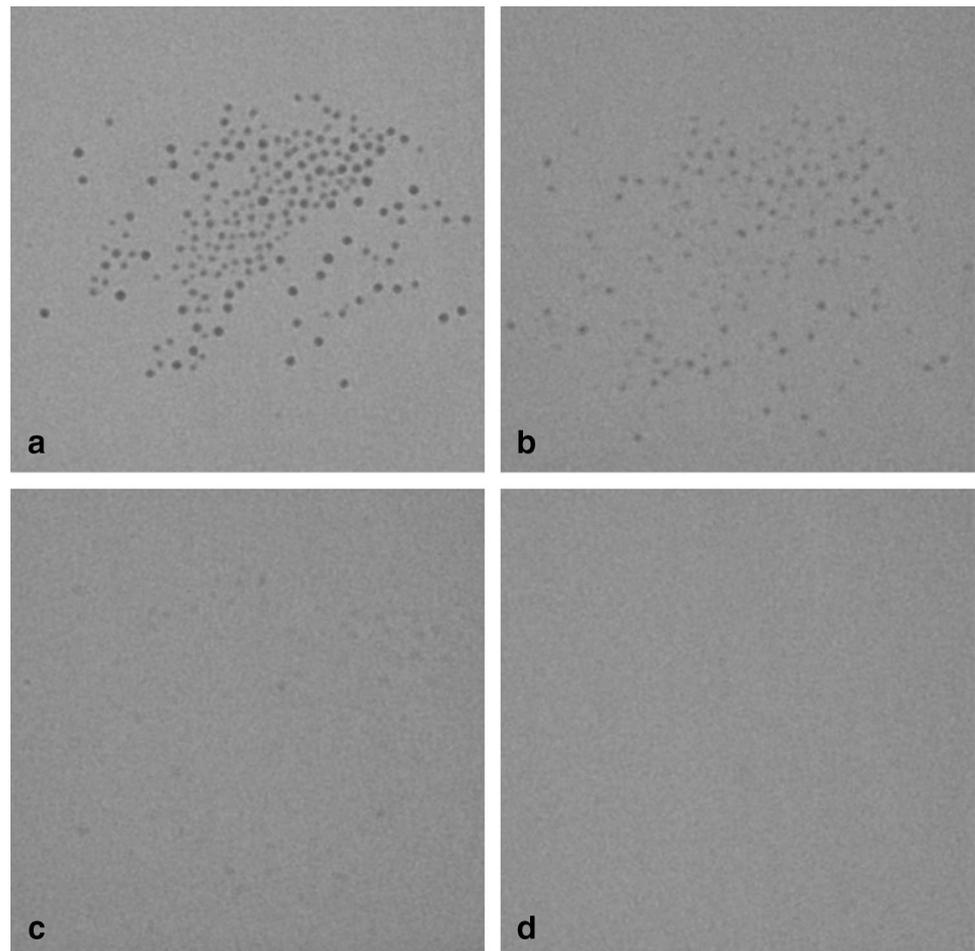


Fig. 2 Schematic diagram of the flow model. Arrow head indicates the location of tip of microcatheter

scored as four grades (4: excellent; well-defined and round, 3: good; ill-defined and oval, 2: fair; unclear but seemed like SAP-MS, 1: poor; invisible) by the same four interventional radiologists based on the criteria (Fig. 3). The most visibility

of contrast-loaded SAP-MS in the DSA images was adopted as the score.

Statistical analysis

For static imaging, the statistical association between the ratio of saline, CNR, and visual score was evaluated by regression analysis. Visual scores with the flow model were analyzed with three-way analysis of variance. Statistical analysis was performed with SAS 9.4 (SAS Institute Inc., Cary, NC, USA). The level of significance was set as 0.05.

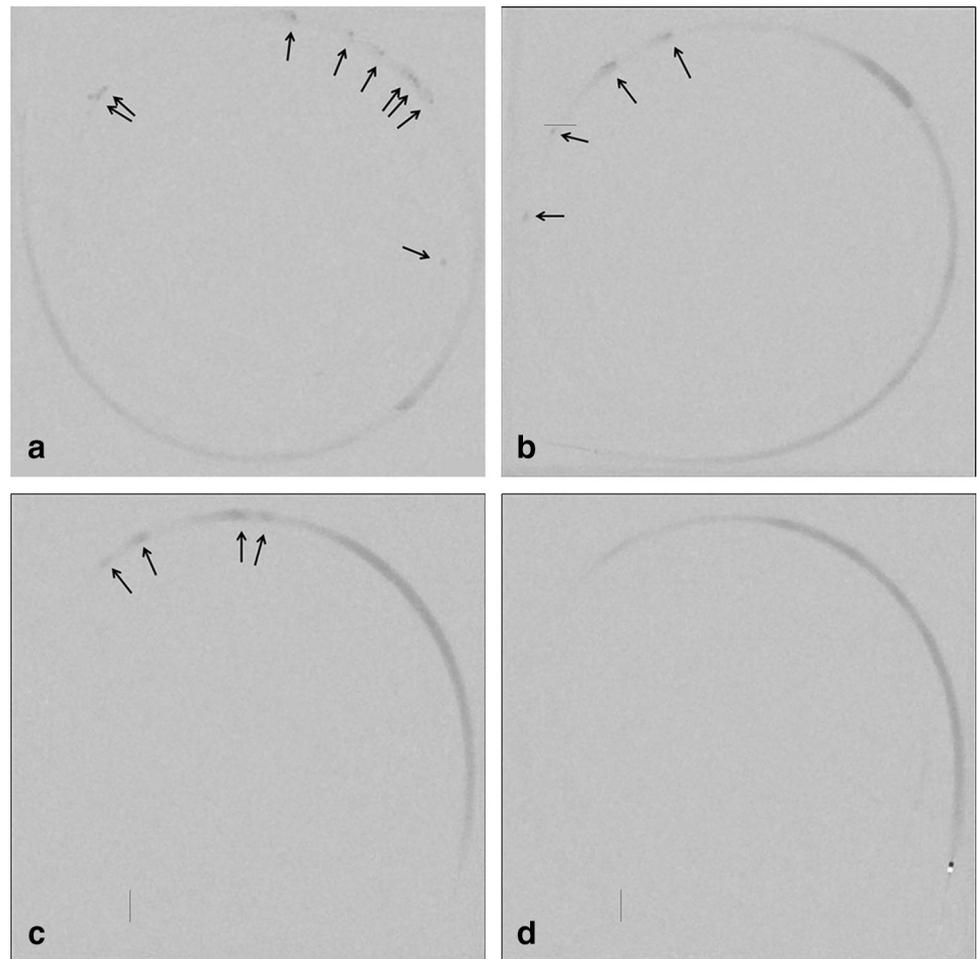
Results

Microscopic evaluation

Diameter change of SAP-MS with contrast material

The diameter of SAP-MS increased in approximately 15 min and then reached equilibrium (Fig. 4a). Finally, the diameter

Fig. 3 DSA images of contrast-loaded SAP-MS using a flow model. Contrast-loaded SAP-MS were visible under DSA (arrow). The visibility was scored as four grades, score 4: excellent (**a**), score 3: good (**b**), score 2: fair (**c**), and score 1: poor (**d**)



was 4.0–5.0 times greater than its original size. More rapid swelling was observed in the SAP-MS with smaller sizes.

Diameter change of contrast-loaded SAP-MS with saline

Mixed with saline, the diameter of contrast-loaded SAP-MS increased further by 10–30% in a few minutes, and then returned to the previous size in approximately 20 min. Figure 4b shows the ratio of diameter change for SAP-MS of 150–200 μm . The change in the diameter was more obvious when the volume ratio of saline was larger. A similar change was observed for the smaller sizes of SAP-MS with 50–100 and 100–150 μm (not shown).

Static imaging

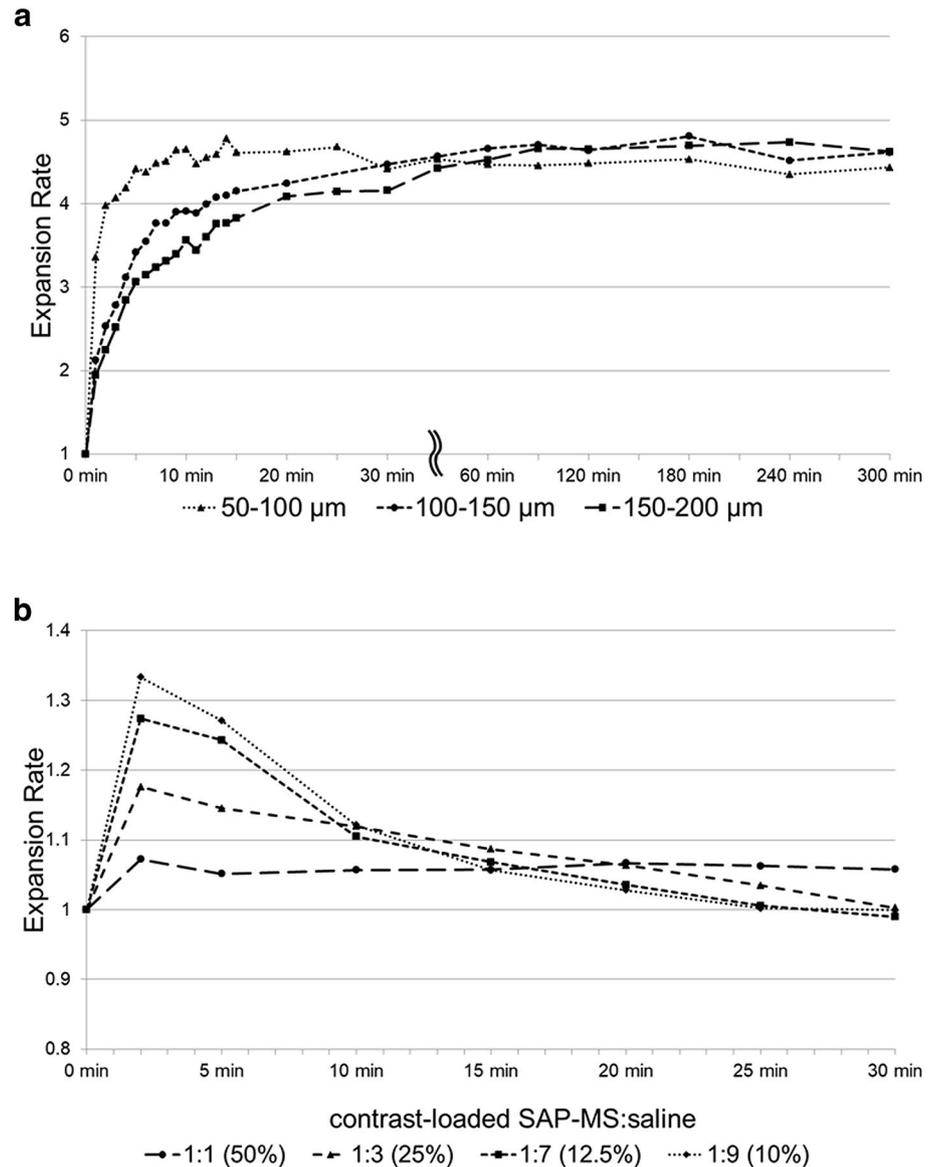
Contrast-loaded SAP-MS were visualized by digital radiography (Fig. 1). The tube voltage varied from 63 to 70 kV and the tube current from 181 to 456 mA. After mixing with saline, both CNR and visual scores gradually decreased (Fig. 5), and finally SAP-MS became invisible in 10 min (100–150 μm) and in 30 min (150–200 μm).

The average visual scores were higher than 2.5 (fair to good) within 5 min for 100–150 μm and within 20 min for 150–200 μm (Fig. 5c, d). Statistical analysis showed that the CNRs were significantly higher when the volume ratio of saline was larger. Visual scores were significantly higher when the volume ratio of saline was larger for 100–150 μm .

Imaging with flow model

In the flow model, contrast-loaded SAP-MS were visible under DSA when the suspension outside the contrast-loaded SAP-MS was diluted (Fig. 3). The AEC defined the following parameters: pulse width 10–85 ms, tube voltage 63–80 kV, and tube current 249–442 mA. The average visual score was 3 (good) or better with the slower flow speed (1 cm/s and 2 cm/s). With the faster flow speed (5 cm/s and 10 cm/s), the score was 3 or better with the narrow pulse width (10–15 ms) and was worse with the wider pulse width. Higher frame rates were associated with the better score in the faster flow speed. With the slower flow speed, even using lower frame rates, the visibility was kept at 3 or better

Fig. 4 a Diameter change of SAP-MS with contrast material. **b** Diameter change of contrast-loaded SAP-MS in saline (150–200 μm). A similar change was observed for the smaller sizes of SAP-MS with 50–100 and 100–150 μm (not shown)



(Table 1). Statistical analysis showed that the visual score was significantly related to the flow speed, pulse width, and combination of the two (Table 2).

Discussion

Conventional microspheres themselves are invisible under X-ray imaging. Complications associated with embolization therapy for hepatocellular carcinoma using conventional microspheres have been reported including pancreatitis due to reflux of microspheres [2], fatal hepatic abscesses after additional embolization [3], and fatal pulmonary embolism caused by passage of microspheres through arteriovenous shunts [2, 4]. An *in vitro* study demonstrated that proximal embolization occurred when a high infusion rate and high

concentration were used [12]. It is considered that the use of radiopaque microspheres may contribute to the safety and effectiveness of the embolization procedure.

SAP-MS swell after absorbing fluid following exposure to aqueous-based media [9, 10]. In general, the absorbency of superabsorbent materials is defined by properties of the material and the fluid including ionic osmotic pressure, hydrophilic property, and crosslink density [13]. In this study, the diameter of contrast-loaded SAP-MS was 4.0–5.0 times greater than its original size, and more rapid swelling was observed in SAP-MS with smaller sizes. The speed of fluid absorption is considered to be dependent on the ratio of surface area to volume.

In clinical situations, contrast-loaded SAP-MS are often used when mixed with saline or diluted contrast material. Our study demonstrated that, after mixing with saline, the

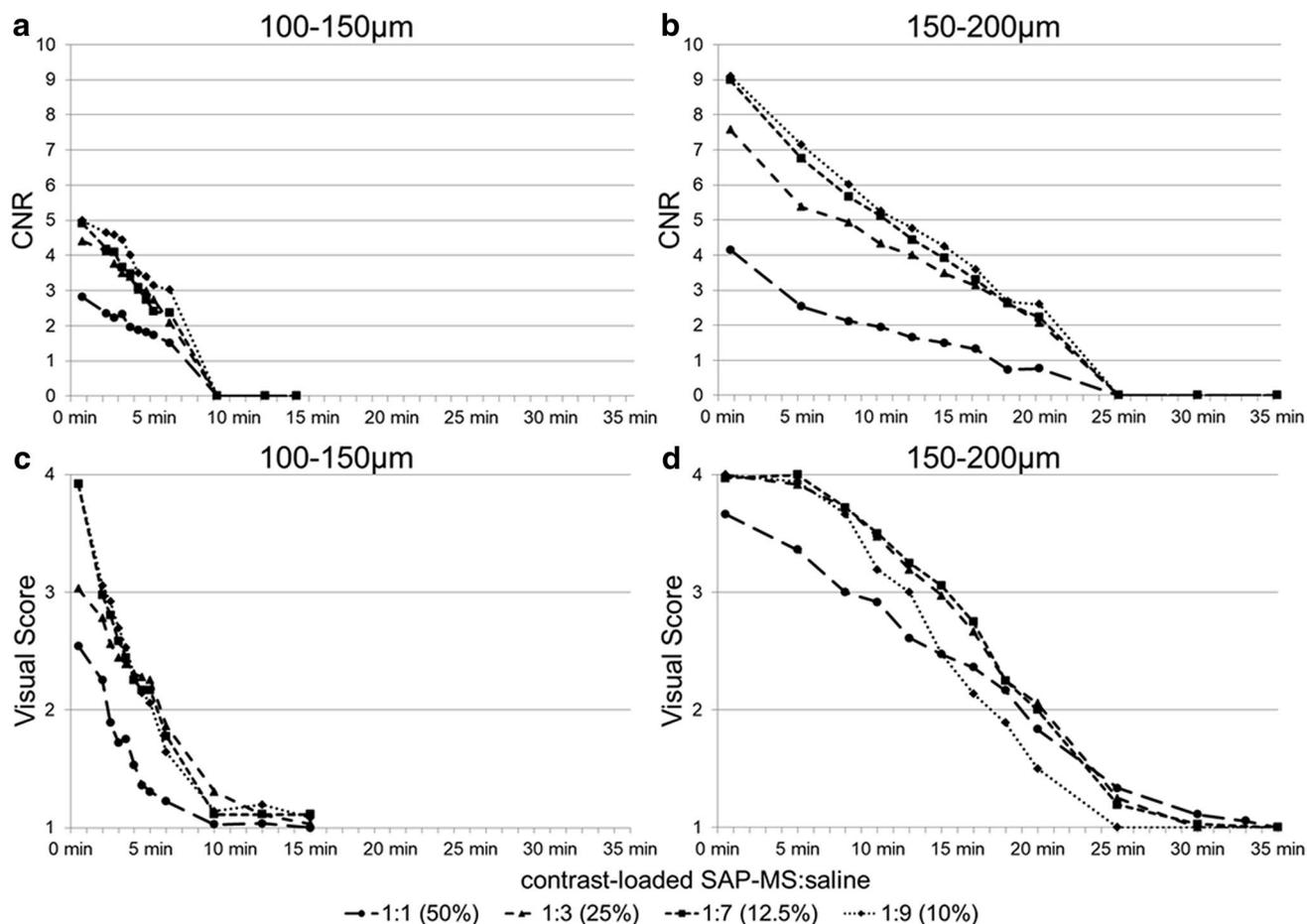


Fig. 5 Change of contrast-loaded SAP-MS CNR and visual score with saline. Both CNR (a, b) and visual scores (c, d) gradually decreased. CNR contrast-to-noise ratio

diameter of contrast-loaded SAP-MS further increased by 10–30%, and then returned to the previous size. Tanimoto et al. reported that diameters of SAP-MS suspended in iodixanol and saline were not different and no change was observed at 10 min after injection into the rabbit artery, indicating that the final expansion rates of SAP-MS in saline, iodixanol, and blood are similar [14]. Our findings may raise some concern that the size change of contrast-loaded SAP-MS might promote further undesirable movement in the vessels, such as proximal aggregation and distal redistribution of the particles.

The important purpose of use of radiopaque microspheres is to recognize the movement of radiopaque microspheres just after injection in real time and to find out the endpoint. Our study demonstrated that radiopacity of contrast-loaded SAP-MS gradually decreased after mixing with saline. In clinical situations, the possible recognition time of the contrast-loaded SAP-MS would be expected to be as long as possible. Therefore, it is suggested that contrast-loaded SAP-MS should be kept in non-diluted contrast material until use,

and mixing with saline (if necessary) should be done just before the injection for effective observation. However, the better visibility was kept only within 5 min for 100–150 μm. The possible recognition time of the contrast-loaded SAP-MS might be short and it is potential for the effect on the safety and effectiveness of the embolization procedure. Further studies are needed to visualize contrast-loaded SAP-MS for a long time.

The mechanism underlying the changes in radiopacity and diameter of SAP-MS is considered as follows (Fig. 6):

1. Just after mixing with saline, there are concentration gradients of ions and molecules, notably water and contrast material, between inside and outside the contrast-loaded SAP-MS (Fig. 6c).
2. The concentration gradients cause movement of water absorbed into SAP-MS and of contrast material released from SAP-MS. It is considered that the speed of movement of water is faster than that of contrast material due to the differences in concentration gradient, molecular

Table 1 Average value of visual score of contrast-loaded SAP-MS

A 100–150 μm						B 150–200 μm					
Flow speed (cm/s)	Frame rate (fps)	Pulse width				Flow speed (cm/s)	Frame rate (fps)	Pulse width			
		10–15 ms	20–30 ms	35–50 ms	65–85 ms			10–15 ms	20–30 ms	35–50 ms	65–85 ms
1	1	A	A	A	N/A	1	1	A	A	A	A
	2	A	A	A	N/A		2	A	A	A	A
	4	A	A	A	N/A		4	A	A	A	A
2	1	A	A	A	A	2	1	A	A	A	A
	2	A	A	A	A		2	A	A	A	A
	4	A	A	A	A		4	A	A	A	A
5	1	A	A	B	B	5	1	A	A	A	B
	2	A	A	A	B		2	A	A	B	B
	4	A	A	A	B		4	A	A	A	B
	7.5	A	A	N/A	N/A		7.5	A	A	N/A	N/A
10	1	A	B	C	N/A	10	1	A	B	C	C
	2	A	B	C	N/A		2	A	B	C	C
	4	A	B	C	N/A		4	A	B	C	C
	7.5	A	B	N/A	N/A		7.5	A	A	N/A	N/A

A: Score ≥ 3 B: 3 > Score ≥ 2 C: 2 > Score

N/A not available, *fps* frames per second

Table 2 Visual scores of contrast-loaded SAP-MS with analysis of variance

A 100–150 μm				B 150–200 μm			
Factor	DF	F value	P value	Factor	DF	F value	P value
Pulse width	3	115.25	< 0.0001	Pulse width	3	127.38	< 0.0001
Flow speed	3	317.59	< 0.0001	Flow speed	3	386.55	< 0.0001
Pulse width*flow speed	7	78.19	< 0.0001	Pulse width*flow speed	9	48.32	< 0.0001
Frame rate	3	7.04	0.0001	Frame rate	3	0.07	0.9752
Pulse width*frame rate	7	1.53	0.1537	Pulse width*frame rate	7	0.82	0.5671
Flow speed*frame rate	7	4.18	0.0002	Flow speed*frame rate	7	0.8	0.5897
Pulse width*flow speed*frame rate	15	2.52	0.0013	Pulse width*flow speed*frame rate	19	1.61	0.0483

DF degree of freedom

*: Combination

weight, and viscosity. First, the volume of water moving into SAP-MS is larger than that of contrast material released from SAP-MS, causing a further increase in diameter and decrease in radiopacity (Fig. 6d).

- Then the release of contrast material is continued while the movement of water becomes slower, resulting in a decrease in the diameter of SAP-MS and radiopacity (Fig. 6e).
- Finally, the composition of the solutions between inside and outside SAP-MS becomes the same, with SAP-MS thereby becoming invisible. The final diameter returns to the same size as shown in Fig. 6b (Fig. 6f).

In this study, using the flow model, the conditions of slower flow and use of a narrower pulse width resulted in better visibility. DSA image quality is related to movement of the object (flow speed) and pulse width. When flow speed is slow, the distance SAP-MS moves during irradiation is short, and so the object is clear even when a wide pulse width is used. With the faster speed, use of a narrower pulse width caused the object to become clear because the distance SAP-MS moves during irradiation is shorter. Comparable results have been reported in an experimental study simulating cardiac imaging [15]. However, actual blood flow may be much faster than this experimental flow. Under such

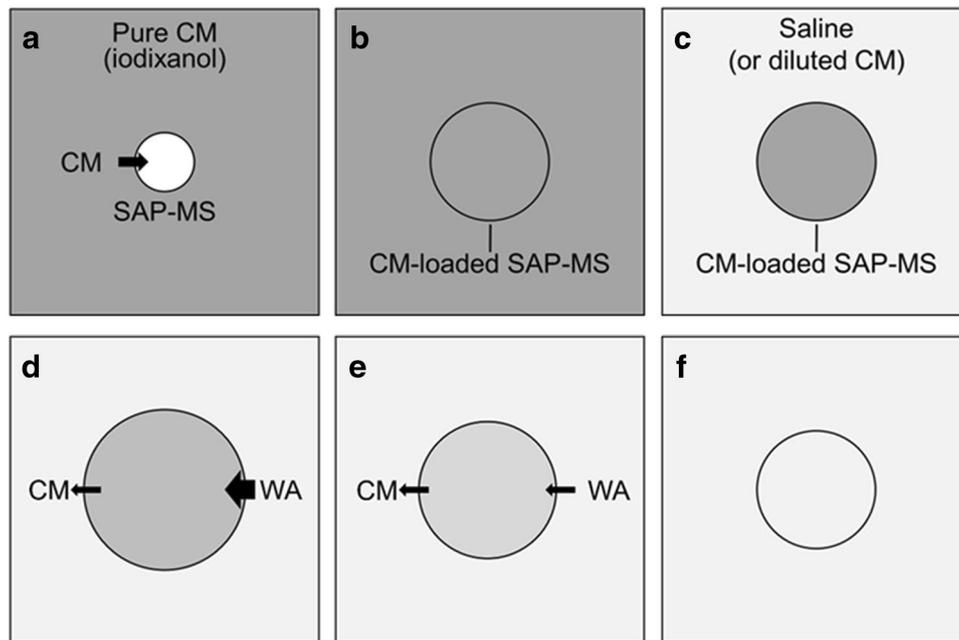


Fig. 6 Mechanism of change of contrast-loaded SAP-MS. **a** When suspended in pure CM (iodixanol, 270 mgI/mL), SAP-MS start to absorb it. **b** Contrast-loaded SAP-MS swell, and their diameter becomes 4–5 times greater than the original size. **c** When mixed with saline or diluted CM, concentration gradients between inside and outside contrast-loaded SAP-MS cause movement of water and of CM. **d** First, the volume of water moving into SAP-MS is larger than that

of CM released from SAP-MS, causing a further increase in diameter and decrease in radiopacity. **e** Release of CM is continued while the movement of water becomes slower, resulting in a decrease in the diameter of SAP-MS and radiopacity. **f** Finally, the composition of solutions between inside and outside SAP-MS becomes the same, with SAP-MS thereby becoming invisible. The final diameter returns to that seen in **b**. CM contrast material, WA water

situations, it would be difficult to recognize contrast-loaded SAP-MS. In this study, under slow flow speed, the visibility was also kept good even when using low frame rates. Use of lower frame rates will contribute to reducing radiation exposure.

There are only a few radiopaque microspheres commercially available. LC bead LUMI™ (BTG plc, London, UK) has been approved by the Food and Drug Administration of the United States for the treatment of hypervascular tumors and arteriovenous malformations. It is reported that LC bead LUMI™ is visualized under fluoroscopy and DSA with slower flow speed during the embolization procedure, and remains visible on computed tomography (CT) after embolization over the 90 days even if the size is small [7, 8]. Therefore, LC bead LUMI™ might have an advantage over contrast-loaded SAP-MS at the point of identifying exact location after the embolization. However, the comparison of contrast-loaded SAP-MS and LC bead LUMI™ has not yet been reported and further consideration is needed.

Our study has several limitations. First, iodixanol was the only contrast material evaluated because we assumed it would be used for vascular malformations or tumors of the extremities, head and neck. Iodixanol is a standard iodine contrast for angiography of these sites because of its iso-osmolar property and the minimum sense of heat developing

after injection. The parameters including diameter, radiopacity, and visibility might be different when other aqueous-based media such as contrast materials or antineoplastic agents with various iodine content, osmotic pressure, and hydrophilic property were used.

Second, we evaluated the radiopacity and visibility of only two sizes of SAP-MS with 100–150 and 150–200 μm because, in a pre-study, SAP-MS with 50–100 μm was considered to be too small to evaluate the visibility with our equipment.

Third, measurement of CNR on radiography may be subjected to some errors because the diameter of SAP-MS was very small. To measure this as precisely as possible, we digitally enlarged the images, measured 20 particles and calculated the average.

Finally, the visibility of contrast-loaded SAP-MS was evaluated using a phantom with a height of 15 cm. The visibility of contrast-loaded SAP-MS would be influenced depending on the thickness of the phantom.

In conclusion, SAP-MS should be suspended in contrast material for more than 15 min for iodine loading. For effective observation, contrast-loaded SAP-MS should be kept in non-diluted contrast material until use. The conditions of slower flow and use of a narrow pulse width are useful for better observation of contrast-loaded SAP-MS.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical statement This article does not contain any studies with human participants or animals performed by any of the authors.

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