

# Safety and Utility of Uterine Artery Embolization with CO<sub>2</sub> and a Gadolinium-based Contrast Medium

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The authors evaluated the safety and clinical outcomes of uterine artery embolization (UAE) without the use of conventional iodinated contrast media for symptomatic uterine leiomyomata. Patients underwent UAE with use of CO<sub>2</sub> gas and a gadolinium-based contrast medium. The safety and feasibility of the technique were assessed. Patients were followed up at 24 hours, 1 month, and 6 months after UAE and yearly thereafter. UAE without iodinated contrast medium was attempted in eight patients (mean age, 42.7 years  $\pm$  4.1), and bilateral UAE was successful in all patients. The mean fluoroscopy time was 14.9 minutes. The mean amount of gadolinium-based contrast medium used was 30.6 mL or 0.181 mmol/kg. No major complications were noted. The mean improvement in the symptom severity score was 53.8. The mean reduction in leiomyoma volume was 42%. To date, no repeat interventions have been performed. UAE with CO<sub>2</sub> and a gadolinium-based contrast medium is a viable treatment option for patients with a severe allergy to iodinated contrast media or renal insufficiency.

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Abbreviations: GFR = glomerular filtration rate, NSF = nephrogenic systemic fibrosis, UAE = uterine artery embolization

UTERINE artery embolization (UAE) has been proved to be an effective minimally invasive treatment for symptomatic uterine leiomyomata, with low complication rates (1–3). UAE, however, carries the identical contraindications as other endovascular interventions, including allergic reactions to iodinated contrast media and iodinated contrast media–induced renal insufficiency. The use of iodinated contrast media has been associated with an adverse reaction risk in 0.6%–8% of patients, with 90% of adverse events classified as being allergic

in nature (4). Although most reactions are mild or moderate, the use of iodinated contrast media carries a small but significant risk of severe, life-threatening reaction (4). Recently, CO<sub>2</sub> gas has emerged as a useful alternative to conventional iodinated contrast dyes and has found applications in a variety of interventional techniques. The purpose of this study was to evaluate the safety and clinical outcomes of UAE without the use of conventional iodinated contrast media.

## MATERIALS AND METHODS

### Patient Group

A study was conducted among all patients treated with UAE for symptomatic uterine leiomyomata between 2002 and 2005 at our institution. Consecutive patients with contraindications to the use of conventional iodinated contrast media who underwent UAE with tris-acryl gelatin microspheres (Embosphere; BioSphere Medical, Rockland, Mass) as the embolization agent and CO<sub>2</sub> and the gadolinium-based

contrast medium gadodiamide (Omniscan; GE Healthcare, Princeton, NJ) as the angiographic contrast medium were included in the study. Contraindication to iodinated contrast media was defined as a documented history of anaphylactic reaction to iodinated contrast media or documented moderate (glomerular filtration rates [GFR], <60 mL/min per 1.73 m<sup>2</sup>) to severe (GFR, <15 mL/min per 1.73 m<sup>2</sup>) renal insufficiency.

The institutional review board approved the study and granted authorization to collect data prospectively. All patients underwent thorough clinical evaluation before UAE, including the determination of symptom severity scores as a part of the uterine fibroid symptom and quality of life assessment (5). Patients were also evaluated with magnetic resonance (MR) imaging with intravenous gadolinium-based contrast medium. Benefits and possible risks were discussed with patients before obtaining informed consent. The fluoroscopy time during UAE, volume of embolic materials used during UAE, amount of any

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contrast medium used during UAE, leiomyoma and uterine volumes before and after UAE, symptom severity scores, and any repeat interventions after the initial UAE were recorded prospectively and analyzed.

### Embolization Technique

Before undergoing UAE, patients received 12.5 mg of dolasetron mesylate (Anzemet; Aventis Pharmaceuticals, Kansas City, Mo) for possible nausea symptoms and 1 g of cefazolin (Baxter Healthcare, Deerfield, Ill) as a prophylactic antibiotic. Intraoperatively, patients received intravenous midazolam (Bedford Labs, Bedford, Ohio) and fentanyl (Baxter Healthcare, Deerfield, Ill) for moderate sedation and 60 mg of intravenous ketorolac (Abbott, North Chicago, Ill) to counteract inflammation and cramping.

UAE was performed by means of a single right common femoral artery access. After the initial aortogram (Fig 1a, 1b) was obtained with a 5-F catheter (Omni Flush; Angiodynamics, Queensbury, NY) with CO<sub>2</sub> gas by using the Angioflush III system (Angiodynamics), the left internal iliac artery was selected with a 5-F glide Bentson-Hanafee-Wilson JB-1 or hockey-stick catheter (Terumo Medical, Somerset, NJ), and an angiogram of the left internal iliac was obtained with use of CO<sub>2</sub>. The left uterine artery was selected with the glide catheter (Fig 1c), and the ascending portion of the uterine artery was subselected with a 3-F microcatheter (Renegade Hi-Flo; Boston Scientific, Natick, Mass). A subselective uterine artery angiogram was obtained by using CO<sub>2</sub> gas with use of the 3-F microcatheter (Fig 1d).

Uterine leiomyomata were embolized with 500–700- $\mu$ m trisacryl gelatin microspheres (Embosphere). The microspheres were mixed with the gadolinium-based contrast medium to assist in visualization during embolization (Fig 1e). To keep the dose of the gadolinium-based contrast medium low, we wasted as much pre-instilled saline from the microsphere vial as we could without losing embolic materials before it was mixed with approximately 5 mL of the gadolinium-based contrast medium. The use of such a technique enabled us to keep the dose of the gadolinium-based contrast medium to less than 0.3 mmol/kg per

bilateral UAE while the concentrated gadolinium-based contrast medium enabled visualization of the embolic mixture during embolization. The endpoints of embolization with microspheres were occlusion of the perileiomyoma plexus of known leiomyomata, stasis of the flow in the distal part of the uterine artery, and reduction of flow in the proximal part of the main uterine artery on studies obtained with the gadolinium-based contrast medium during embolization. Subsequently, a Waltman loop was formed with the JB-1 catheter and the right uterine artery selected. The artery was subselected with a 3-F microcatheter, and an angiogram was obtained with CO<sub>2</sub> gas. Uterine arteriography and embolization were performed with the same technique as that used for the left uterine artery. Follow-up aortography was performed with CO<sub>2</sub> gas (Fig 1f).

After UAE, patients were admitted to the interventional radiology service for a 24-hour hospital stay. Patients were followed up clinically, including the assessment of symptom severity scores at 1 and 6 months after UAE and yearly thereafter. MR imaging was performed 6 months after UAE.

### Study Endpoints

The primary study endpoints were the feasibility of UAE without the use of an iodinated contrast medium and the safety during and after the procedures. Successful treatment was defined as the completion of the bilateral UAE with achievement of the endpoints of embolization without the use of iodinated contrast medium. Minor complications were defined as temporary and self-limiting symptoms that did not necessitate therapy or normal therapy without any clinical sequelae, and major complications were defined as those necessitating further intervention and/or hospitalization or those producing permanent sequelae (6).

The secondary study endpoints were symptomatic and imaging improvements without repeat intervention after primary treatment with UAE. Patients who required repeat intervention for residual symptoms after the primary treatment with UAE were recorded. The repeat interventions were defined as therapeutic dilatation and curettage, myomectomy, hyster-

ectomy, and repeat UAE for symptomatic leiomyoma after the initial UAE treatment.

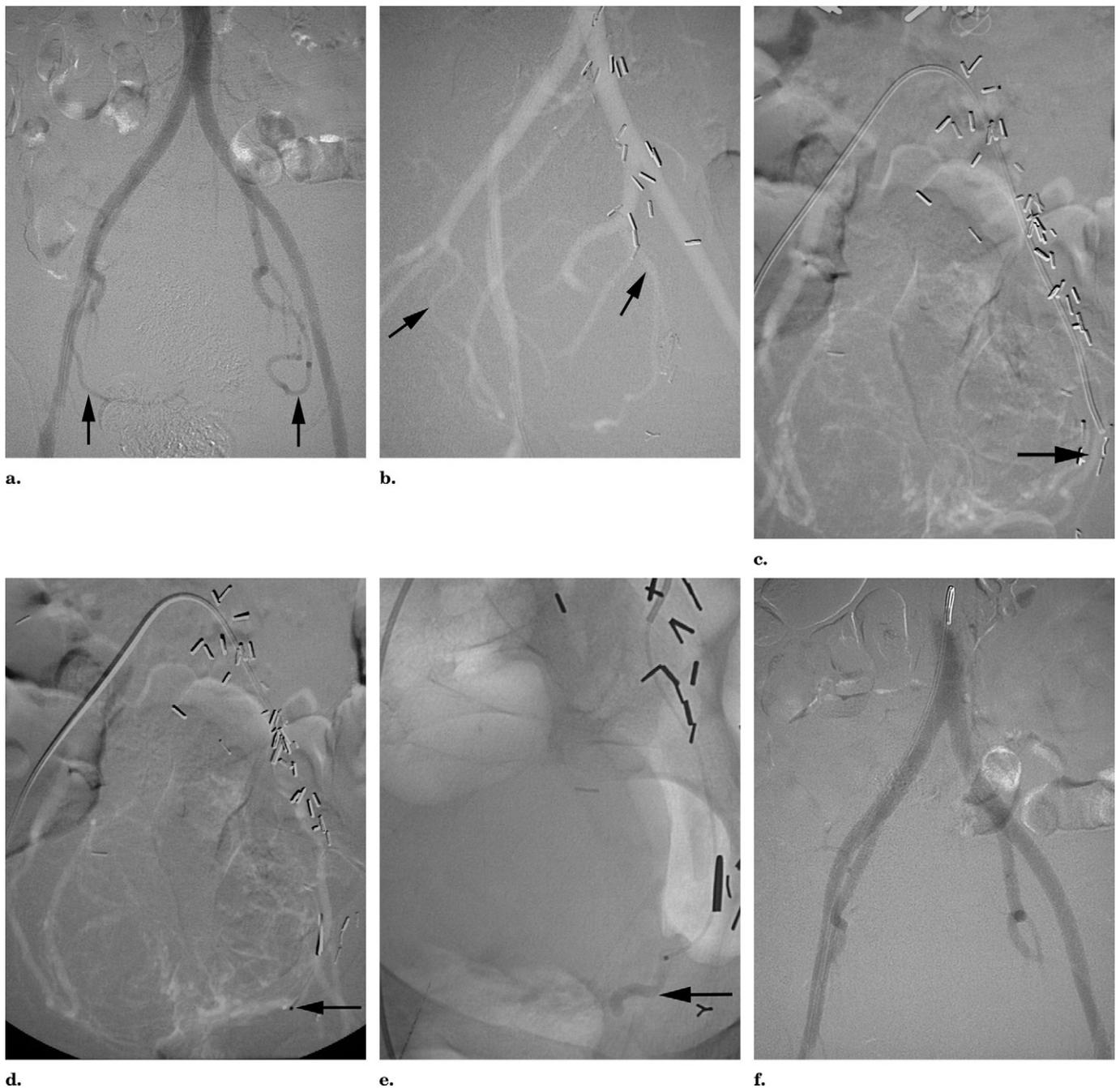
Symptoms were quantitatively assessed by means of the symptom severity score as a part of the uterine fibroid symptom and quality of life assessment, which was validated (5) for its effectiveness in symptomatic uterine leiomyomata. In the questionnaire, symptoms of bleeding, clotting, fluctuations in menstrual duration and length, pain, frequent daytime and nighttime urination, and fatigue were rated on a scale of 1 to 5. Raw scores were converted to a transformed score by using the following equation: transformed score = (raw score – 8)/32  $\times$  100. The transformed scores in the range of 0–100, with 100 being the most severely symptomatic, were calculated and compared before and after UAE.

The volumes of the uterus and the most dominant leiomyoma were measured as a prolate ellipsoid shape by using the following equation: volume = 0.5233  $\times$  D1  $\times$  D2  $\times$  D3, where D1 is the longitudinal dimension, D2 the anterior-posterior dimension, and D3 the transverse dimension. (7). All three measurements were obtained in their greatest dimensions with use of MR images.

### RESULTS

Eight women with a mean age ( $\pm$  standard deviation) of 42.7 years  $\pm$  4.1 (range, 35–49 years) were included in the study. Two patients were white, five patients were black, and one patient was Asian. Each patient had a contraindication to the use of iodinated contrast media: two had renal insufficiency and six had reported severe allergies or documented histories of anaphylactic reaction to iodinated contrast media.

UAE without the use of iodinated contrast media was attempted in eight patients, and all patients successfully completed UAE with CO<sub>2</sub> gas and a gadolinium-based contrast medium. The mean fluoroscopy time was 14.9 minutes (range, 5–21.8 minutes). The mean amount of gadolinium-based contrast medium used was 30.6 mL  $\pm$  16.1 or 0.181 mmol/kg  $\pm$  0.079 (range, 0.071–0.275 mmol/kg). An iodinated contrast medium was not used. For the two patients with impaired renal

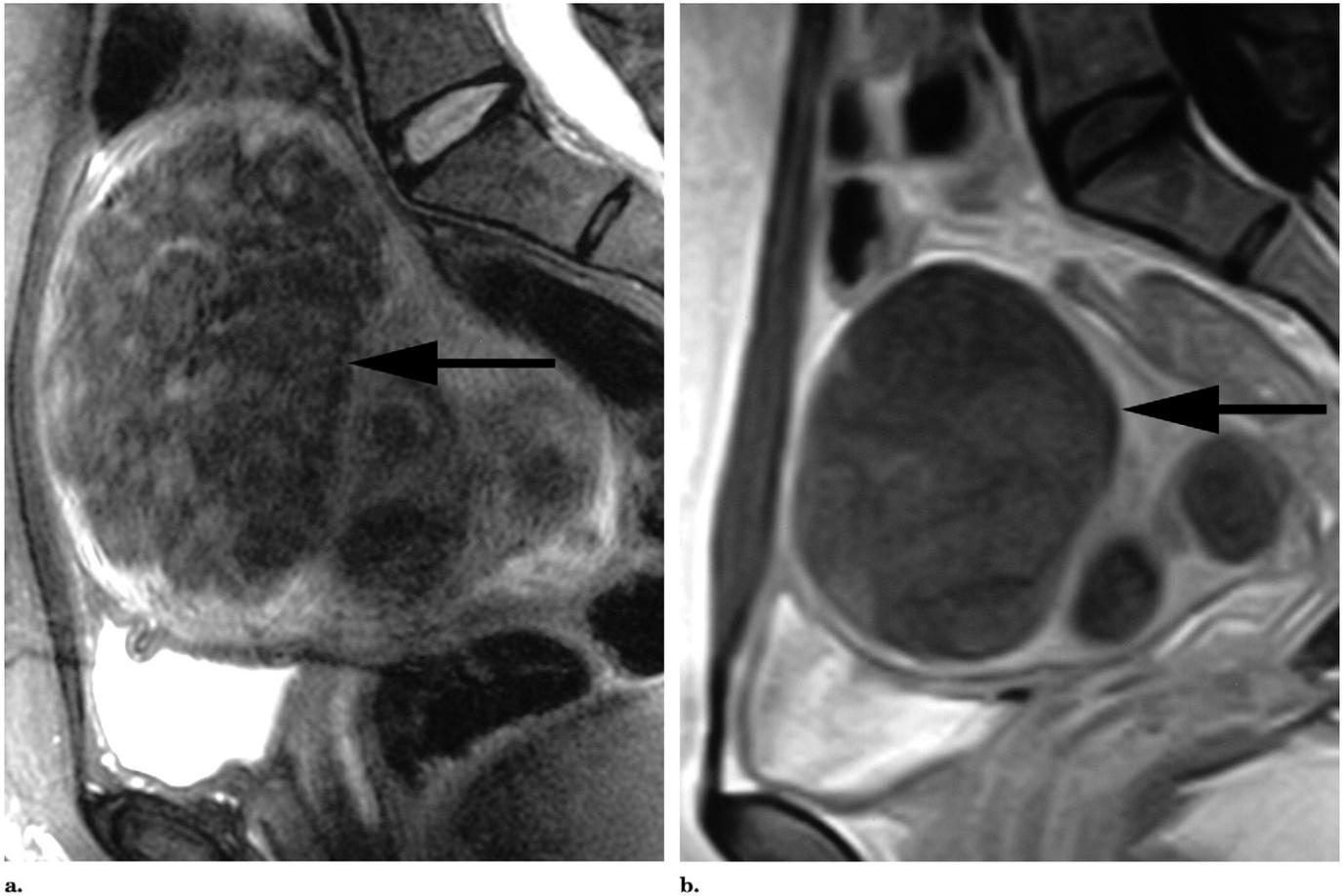


**Figure 1.** (a) Digital subtraction angiogram of the pelvis obtained with CO<sub>2</sub> gas shows prompt visualization of the bilateral uterine arteries (arrows). Uterine arteries with uterine leiomyoma are promptly filled with CO<sub>2</sub> gas because of the hypervascularity of the arteries and anterior locations. (b) Digital subtraction angiogram of the pelvis obtained in an oblique projection shows the origin of the uterine arteries (arrows). (c, d) Digital subtraction angiograms of the left uterine artery obtained with CO<sub>2</sub> gas by using a 5-F catheter (c) and a 3-F microcatheter (d) show prompt filling of the uterine artery (arrow) and perileiomyomata arteries. Note cross-filling of the right uterine artery and iliac arteries. (e) Spot fluoroscopic obtained with a gadolinium-based contrast medium during embolization with a 3-F microcatheter shows the left uterine artery (arrow) and uterine arterial branches. (f) Digital subtraction angiogram of the pelvis obtained with CO<sub>2</sub> gas after UAE shows that the bilateral uterine arteries are no longer visualized.

function, the serum creatinine levels and GFR remained stable or improved; the GFR in these two patients was 29 mL/min per 1.73 m<sup>2</sup> and 45 mL/min

per 1.73 m<sup>2</sup>, respectively, before UAE and 30 mL/min per 1.73 m<sup>2</sup> and 77 mL/min per 1.73 m<sup>2</sup> after UAE. All eight patients were discharged the following

day without complications. No symptoms related to inadvertent distant embolization or misembolization were noted. Specifically, none of the patients



**Figure 2.** (a) Sagittal T2-weighted MR image obtained before UAE shows a substantially enlarged leiomyoma (arrow) with effacement on the rectus abdominus muscle. (b) Sagittal contrast-enhanced T1-weighted MR image obtained after UAE shows a substantial reduction in the size of the treated leiomyoma (arrow) and the lack of enhancement. Note the flattening of the rectus abdominus muscle after UAE.

developed leg or buttock symptoms suggestive of distant embolization or any sciatic or neurologic symptoms during hospitalization. No postembolization syndrome necessitating repeat admission was noted.

The mean dominant leiomyoma volume at baseline was estimated to be 237.9 cm<sup>3</sup> (range, 31.8–943.2 cm<sup>3</sup>). The mean uterus volume at baseline was estimated to be 926.1 cm<sup>3</sup> (range, 397.4–2,811.3 cm<sup>3</sup>). The mean dominant leiomyoma volume at MR imaging performed 6 months after UAE was estimated to be 171.8 cm<sup>3</sup> (range, 9.8–652.5 cm<sup>3</sup>), a mean decrease of 42% (Fig 2). The mean uterus volume at 6-month follow-up was estimated to be 511.2 cm<sup>3</sup> (range, 116.5–1,564.8 cm<sup>3</sup>), a mean decrease of 55%. No extrauterine organ damage or extrapelvic fluid or hemorrhage was noted at follow-up MR imaging.

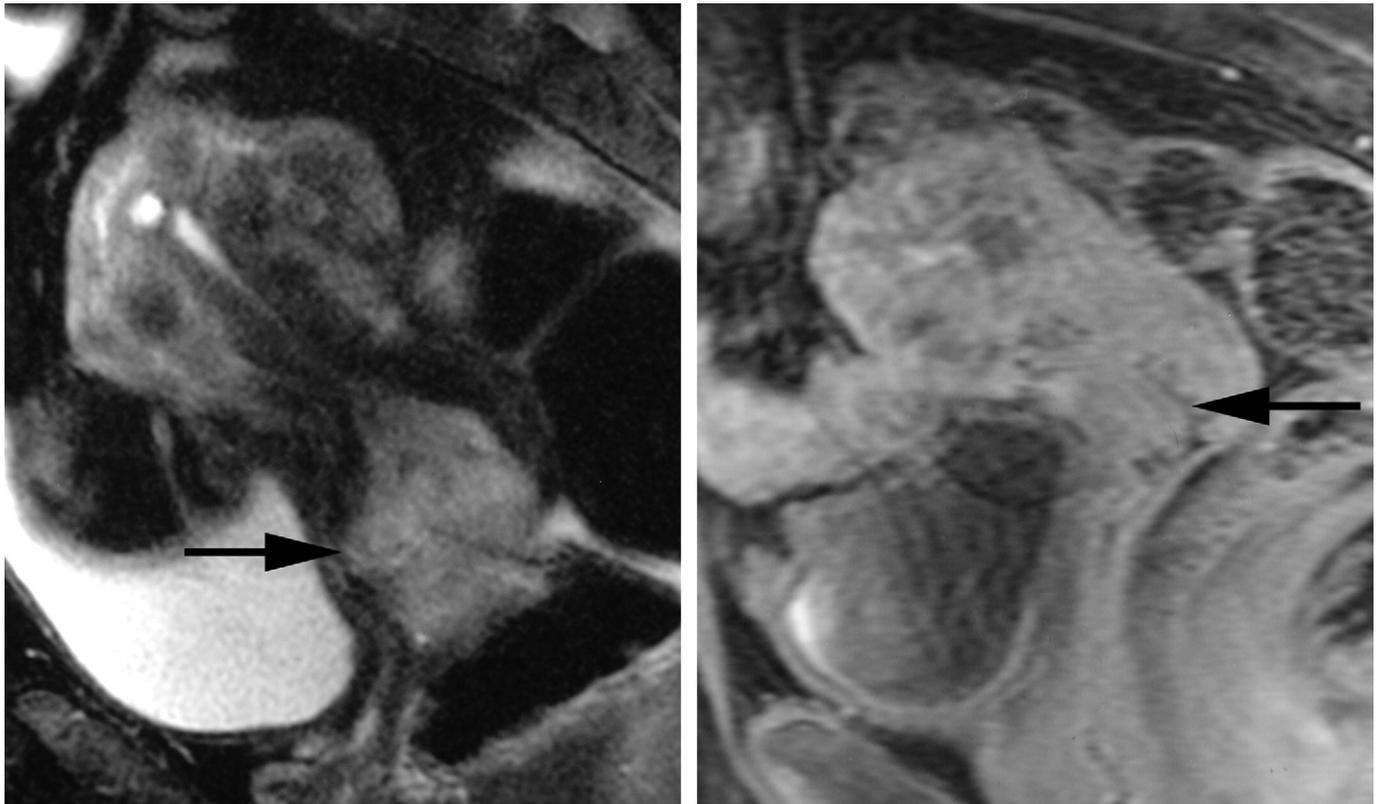
All patients had symptomatic im-

provement at a mean clinical follow-up of 18.3 months  $\pm$  10.7. The mean transformed symptom severity score at baseline was 64.7  $\pm$  10.6. The mean transformed symptom severity score after UAE was 13.8  $\pm$  4.2, resulting in an improvement of 53.8  $\pm$  10.7. No major complications were noted at follow-up. There was one minor complication: A patient developed uncomplicated spontaneous leiomyoma evacuation that did not necessitate a gynecologic procedure or further intervention (Fig 3). No repeat hospital admission was required. None of the patients underwent repeat intervention for residual or recurrent symptoms from leiomyomata during the follow-up period.

## DISCUSSION

As we demonstrated in our study, the combined use of alternative con-

trast media of CO<sub>2</sub> gas and a gadolinium-based contrast medium in UAE was feasible and safe. Unlike iodinated contrast media, which mix with and opacify blood, CO<sub>2</sub> displaces blood when injected, creating a radiolucent image that can be digitally reversed and/or enhanced. Because CO<sub>2</sub> is more than 20 times more soluble than oxygen in blood, it clears rapidly. In addition, injected gas is quickly absorbed into the bloodstream (8). CO<sub>2</sub> is then readily eliminated at the lungs by means of normal ventilation, limiting recirculation within the vascular system (8). CO<sub>2</sub> is an inexpensive gas that is non-allergenic, making it well-suited for use in patients with a documented history of severe allergic reaction to standard contrast reagents. CO<sub>2</sub> angiography has been shown to be well-tolerated in patients undergoing a variety of endovascular proce-



**Figure 3.** (a) Sagittal T2-weighted MR image obtained through the endocervical canal before UAE shows a large endocervical leiomyoma (arrow) with high T2 signal. (b) Sagittal contrast-enhanced T1-weighted MR image obtained through the mid-sagittal level after UAE shows normal restoration of the endocervix (arrow) after complete spontaneous evacuation of the endocervical leiomyoma.

dures (9). The advances in technology—including the improvement of digital subtraction angiography with stacking software programs, injection devices, and techniques—have made CO<sub>2</sub> contrast angiography more practical and readily available (10). Because CO<sub>2</sub> does not induce allergic reactions, CO<sub>2</sub> angiography can enable patients with documented severe allergies to benefit from UAE procedures.

Another advantage of CO<sub>2</sub> is its lack of nephrotoxicity (11). In a recent prospective randomized study of patients undergoing renovascular imaging (12), patients who received CO<sub>2</sub> with a small amount of ioxaglate contrast medium had a significantly lower risk of developing renal failure compared to those who received a higher amount of ioxaglate contrast medium. CO<sub>2</sub> has been successfully for guiding renal angioplasty and stent placement for renal artery stenosis (13). CO<sub>2</sub> arteriography has also been demonstrated to be safe and effective in pa-

tients with chronic renal failure (14). In comparison, iodinated contrast media have been shown to induce nephropathy in approximately 10% of patients with preexisting renal insufficiency (15).

Our study adds further evidence of the safety and feasibility of UAE without the use of iodinated contrast media to that presented in a case report describing the use of CO<sub>2</sub> gas to guide UAE (16). As a gas, CO<sub>2</sub> is 400 times less viscous than standard iodinated contrast media, making it especially well-suited for use with small-caliber catheters in the visualization of small vessels. In our experience, CO<sub>2</sub> gas was adequate for visualization and guidance of subselective catheterization of uterine arteries before embolization. Subselective uterine artery CO<sub>2</sub> angiography via a 3-F microcatheter demonstrated adequate visualization of the perileiomyoma plexus so that embolization could be planned. All eight procedures in this study were successfully completed without perio-

or postprocedural complications, and all patients were discharged without an adverse event. None of the patients were re-admitted or needed further interventions for leiomyomata during the follow-up period.

The mean fluoroscopic time of 14.9 minutes for completing bilateral UAE in our study is compatible to that previously reported during UAE with iodinated contrast media (17,18). Thus, UAE with CO<sub>2</sub> gas and a gadolinium-based contrast medium does not add a substantially higher radiation dose to patients than does the conventional technique.

With use of the concentrated gadolinium and microsphere mixture technique as described, we were able to visualize the embolic material flow and staining in target leiomyomata during embolization. Such a technique enabled us to limit our total gadolinium dose to less than 0.3 mmol/kg for each patient to complete bilateral UAE without having to place a coil, as was the case in the earlier report (16). As

the use of gadolinium-based contrast medium enhanced the imaging quality of CO<sub>2</sub> arteriography (19), the addition of a gadolinium-based contrast medium to the microspheres helps us reach satisfying embolization endpoints and avoid over- or nontarget embolization.

Case reports of a rare yet important potential complication when using a gadolinium-based contrast medium for intraarterial use in patients with renal insufficiency—nephrogenic systemic fibrosis (NSF)—have been reported. NSF was first identified in 1997 and was reported in 2000 by Cowper et al (20). NSF, which was once thought to be a dermatologic disease, is a systemic disease that may affect the skin, lungs, skeletal muscles, heart, and other organs (21). Symptoms of NSF may resemble those of scleroderma and may begin 2 days to 18 months after contrast medium exposure and may contribute to death by restricting ventilation or mobility, leading to falls (22). To date, about 215 patients with NSF have been reported worldwide; 75 of those patients have been reviewed in detail. All patients received a high dose of a gadolinium-based contrast medium—with some receiving only one dose—for MR imaging or MR angiography (23). According to the U.S. Food and Drug Administration, reported cases of NSF were associated with open-chain compounds, gadodiamide, gadopentetate dimeglumine (Magnevist; Berlex Imaging, Montville, NJ) and gadoversetamide (OptiMARK; Mallinckrodt, St Louis, Mo) but not with cyclic compounds (including gadoteridol [ProHance; Bracco Diagnostics, Princeton, NJ] and gadobenate dimeglumine [MultiHance; Bracco Diagnostics]) (21, 23). NSF caused by a gadolinium-based contrast medium is the focus of active research, and published data warrant caution in the use of the contrast medium in patients with renal insufficiency. We agree with the recommendations by the Food and Drug Administration that gadolinium-based contrast media should be used with caution in patients with moderate (GFR, <60 mL/min per 1.73 m<sup>2</sup>) to severe (GFR, <15 mL/min per 1.73 m<sup>2</sup>) renal insufficiency and that the lowest amount of contrast medium should be given (23).

Limitations of our study include a

relatively small number of patients for whom this technique was used, and a report of outcomes from the technique applied by an experienced interventional radiologist specialized in UAE treatments with high volume. We used this technique only in patients with absolute contraindications to iodinated contrast media, and this is reflected on a small number of patients in this study. We believe that the technique can be effectively used by well-trained interventional radiologists, and further studies are warranted. There are few patient characteristics that may limit the use of this technique: uterine artery cannulation may be difficult in women with very small uterine arteries or those who are receiving Lupron (TPA Pharmaceuticals, Lake Forest, Ill). A large dose of gadolinium-based contrast medium may be needed in women with gigantic leiomyomata who may require a large quantity of embolic particles; thus, the technique may not be appropriate. Finally, women who are morbidly obese may be difficult to evaluate with fluoroscopy without the use of iodinated contrast media.

Nevertheless, our study shows that UAE with CO<sub>2</sub> and a gadolinium-based contrast medium can be safe and effective in the treatment of symptomatic uterine leiomyomata in patients with contraindications to conventional iodinated contrast media. The use of these alternative agents expands the possibilities of treatments for patients with symptomatic leiomyomata who had previously not been able to benefit from endovascular intervention.

In conclusion, UAE with CO<sub>2</sub> and a gadolinium-based contrast medium as alternative agents should be considered a viable treatment in patients with symptomatic uterine leiomyomata and severe allergies to conventional iodinated contrast media or renal impairment.

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