Suitability of Patients with Autosomal Dominant Polycystic Kidney Disease for Renal Transcatheter Arterial Embolization

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ABSTRACT

In patients with autosomal dominant polycystic kidney disease (ADPKD), massive renal enlargement is a serious problem. Renal transcatheter arterial embolization (TAE) can reduce renal volume (RV), but effectiveness varies widely, and the reasons remain unclear. We investigated factors affecting renal volume reduction rate (RVRR) after renal TAE in all 449 patients with ADPKD who received renal TAE at Toranomon Hospital from January of 2006 to July of 2013, including 228 men and 221 women (mean age =57.0±9.1 years old). One year after renal TAE, the RVRR ranged from 3.9% to 84.8%, and the least squares mean RVRR calculated using a linear mixed model was 45.5% (95% confidence interval [95% CI], 44.2% to 46.8%). Multivariate analysis using the linear mixed model revealed that RVRR was affected by the presence of large cysts with wall thickening (regression coefficient [RC], −6.10; 95% CI, −9.04 to −3.16; P<0.001), age (RC, −0.82; 95% CI, −1.03 to −0.60; P<0.001), dialysis duration (RC, −0.10; 95% CI, −0.18 to −0.03; P<0.01), systolic BP (RC, 0.39; 95% CI, 0.19 to 0.59; P<0.001), and the number of microcoils used for renal TAE (RC, 1.35; 95% CI, 0.83 to 1.86; P<0.001). Significantly more microcoils were needed to achieve renal TAE in patients with younger age and shorter dialysis duration. In conclusion, cyst wall thickening had an important effect on cyst volume reduction. Renal TAE was more effective in patients who were younger, had shorter dialysis duration, or had hypertension, parameters that might associate with cyst wall stiffness and renal artery blood flow.


Autosomal dominant polycystic kidney disease (ADPKD) is a common hereditary disorder that occurs in approximately one in every 400–1000 live births. Almost one half of patients with ADPKD develop ESRD by age 60 years old, and it is the fourth leading cause of ESRD in adults worldwide. Deterioration of renal function is usually proportional to the increase in kidney size, and many patients with ADPKD and renal dysfunction have massive kidneys. They develop various symptoms related to abdominal distension that impair their quality of life, and there can also be an adverse influence on the prognosis. Methods for reducing the size of enlarged kidneys include aspiration and injection of sclerosant into renal cysts, surgical and laparoscopic cyst fenestration, and laparoscopic nephrectomy. However, serious complications can occur, and the outcome is frequently suboptimal; therefore, management of massive kidneys in patients with ADPKD is controversial. We previously reported that renal transcatheter arterial embolization (TAE) is effective for reducing renal

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volume (RV). As of December of 2014, we have performed renal TAE in 891 patients with ADPKD and symptomatic renal enlargement, and we have found that there is usually a marked reduction of RV after about 1 year (Supplemental Figure 1). We have also reported that renal TAE might prolong the survival of patients with ADPKD. Renal TAE is currently performed worldwide, and various embolic agents are reported to be effective. Renal TAE is also done before renal transplantation to obtain sufficient volume reduction for graft implantation, because pretransplantation nephrectomy is associated with significant complications in patients with ADPKD, including hernia, infection, bleeding, and bowel perforation. In a study of 73 patients with ADPKD, renal TAE was found to be a safe and effective alternative to nephrectomy before renal transplantation. It has also been suggested that nephrectomy and renal TAE before transplantation should be compared in a randomized multicenter trial. Because no severe adverse events related to renal TAE have been reported, it seems to be a safe method for reducing RV. However, its effect varies widely among patients for reasons that are currently unknown.

We performed this study to identify factors influencing volume reduction by renal TAE to achieve more appropriate selection of patients for this procedure and improve its timing.

RESULTS

In total, 458 patients on dialysis received renal TAE for symptomatic renomegaly from January of 2006 to July of 2013. Among them, six patients were excluded, because they underwent partial TAE for cyst hemorrhage, and three patients were excluded because of prior renal TAE (Figure 1). The remaining 449 patients were enrolled, including 228 men and 221 women, with a mean age of 57.0 ± 9.1 years old (Table 1, Supplemental Table 1). Unilateral renal TAE was done in 14 patients (because of prior nephrectomy in eight patients, because the catheter could not enter the other renal artery because of severe stenosis in four patients, and to preserve residual kidney function in two patients).

Fifteen patients died within 1 year of renal TAE (Table 2). The 1-year death rate was 3.34%, which was not significantly different from that of Japanese patients with ADPKD ages 55–60 years old on dialysis (2.59% in 2012 and 2.94% in 2013) (Supplemental Table 2). The mortality rate was better after renal TAE than after bilateral open nephrectomy (3% operative mortality rate and 7% 1-year death rate). Laparoscopic nephrectomy has been reported to have fewer complications and improved feasibility and safety for patients with ADPKD. However, mortality after laparoscopic nephrectomy has been unclear in patients with ADPKD. In our study, the 1-year overall survival rate after renal TAE was similar to that of patients without ADPKD and with stage 4 CKD undergoing radical nephrectomy for unilateral sporadic benign renal tumors.

Five patients underwent nephrectomy (four for renal cell carcinoma and one for severe renal cyst infection), two patients

### Table 1. Clinical characteristics of all enrolled patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (men/women)</td>
<td>449 (228/221)</td>
</tr>
<tr>
<td>Age (yr), mean ± SD</td>
<td>57.0 ± 9.1</td>
</tr>
<tr>
<td>Dialysis duration (mo), median (IQR)</td>
<td>50 (19–97)</td>
</tr>
<tr>
<td>Body mass index, mean ± SD</td>
<td>21.9 ± 2.6</td>
</tr>
<tr>
<td>Total kidney volume (cm³), median (IQR)</td>
<td>4511 (3117–6418)</td>
</tr>
<tr>
<td>Right RV (cm³), median (IQR)</td>
<td>2267 (1575–3239)</td>
</tr>
<tr>
<td>Left RV (cm³), median (IQR)</td>
<td>2321 (1598–3230)</td>
</tr>
<tr>
<td>sBP (mmHg), mean ± SD</td>
<td>134.3 ± 18.3</td>
</tr>
<tr>
<td>Medications, %</td>
<td></td>
</tr>
<tr>
<td>Antihypertensive agents</td>
<td>79.5</td>
</tr>
<tr>
<td>Diuretics</td>
<td>35.0</td>
</tr>
<tr>
<td>No. of microcoils, mean ± SD</td>
<td>41.6 ± 13.3</td>
</tr>
<tr>
<td>ACI (%), median (IQR)</td>
<td>18.3 (3.3–40.0)</td>
</tr>
<tr>
<td>No. of additional renal arteries</td>
<td>One additional renal artery, 69 patients; two, 18 patients; three, one patient; four, one patient</td>
</tr>
<tr>
<td>Large cyst (&gt; 5 cm), % (no.)</td>
<td></td>
</tr>
<tr>
<td>Large cyst with wall thickening</td>
<td>2.7 (12)</td>
</tr>
<tr>
<td>Large cyst with acute hemorrhage</td>
<td>5.9 (26)</td>
</tr>
<tr>
<td>Normal large cyst</td>
<td>22.5 (101)</td>
</tr>
<tr>
<td>Other complicated large cyst</td>
<td>19.4 (87)</td>
</tr>
<tr>
<td>Large cyst unclassified</td>
<td>3.3 (15)</td>
</tr>
<tr>
<td>Laboratory data</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dl), mean ± SD</td>
<td>10.2 ± 1.4</td>
</tr>
<tr>
<td>Albumin (g/dl), mean ± SD</td>
<td>3.08 ± 0.34</td>
</tr>
<tr>
<td>CRP (mg/dl), median (IQR)</td>
<td>0.2 (0.1–0.6)</td>
</tr>
<tr>
<td>Uric acid (mg/dl), mean ± SD</td>
<td>7.3 ± 1.4</td>
</tr>
<tr>
<td>Corrected calcium (mg/dl), mean ± SD</td>
<td>9.9 ± 0.8</td>
</tr>
<tr>
<td>Phosphorus (mg/dl), mean ± SD</td>
<td>5.3 ± 1.3</td>
</tr>
</tbody>
</table>

IQR, interquartile range (25%–75%); ACI, aortic calcification index.
received renal transplantation, and five patients had repeat TAE within 1 year for abdominal pain and hematuria associated with cyst bleeding or RV re–enlargement (two patients initially received unilateral renal TAE and subsequently underwent TAE on the other side). Twenty-two patients were lost to follow-up within 1 year after renal TAE for unknown reasons, including seven patients who continued to attend our hospital but did not receive follow-up computed tomography (CT). Dry weight (DW) decreased until 3 months after TAE and then, began to increase as food intake improved (Figure 2A). Systolic BP (sBP) decreased significantly after TAE (Figure 2B).

Complications of Renal TAE
Most of the patients had severe flank pain for about 3 days, and high fever (>38°C) with elevation of inflammatory markers, such as serum C–reactive protein (CRP), continued for about 1 week (the maximum least squares mean serum CRP level was 16.4 mg/dl). Epidural anesthesia was provided for pain relief in most patients. Most patients became anuric after slight macroscopic dark hematuria had continued for about 6 months. Three deaths were thought to be associated with renal TAE. One patient died of severe arrhythmia and acute heart failure on the third day after TAE, which might have been related to inflammation and rapid accumulation of fluid. The blood level of a renally excreted antiarrhythmic agent also increased rapidly after TAE, which might have contributed to death. The second patient developed features of tumor lysis syndrome and died on the eighth day after renal TAE. He had a history of bladder cancer with complete resection, but there might have been renal metastasis. Severe constipation was common for about 5 days after renal TAE. Two patients developed intestinal perforation within 5 days after renal TAE. One of them died 2 months later without recovering, which was the third death associated with renal TAE. One patient required right nephrectomy for severe renal cyst infection.32 There were also two sudden deaths within 1 month after renal TAE for unknown reasons, although death might have been associated with severe inflammation and/or rapid

Table 2. Outcome of all enrolled patients

<table>
<thead>
<tr>
<th>Follow-Up Time</th>
<th>No. of Patients</th>
<th>No. of Dropouts</th>
<th>Reason for Dropout, n</th>
<th>Cause of Death, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 mo</td>
<td>449</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>1 mo</td>
<td>442</td>
<td>7</td>
<td>Death, 4; nephrectomy, 3</td>
<td>Sudden death, 2; arrhythmia, 1; tumor lysis, 1</td>
</tr>
<tr>
<td>3 mo</td>
<td>431</td>
<td>11</td>
<td>Death, 3; renal transplantation, 1; second renal TAE, 2; nephrectomy, 2; unknown, 4 (1)</td>
<td>Intestinal perforation, 2; liver cyst infection, 1</td>
</tr>
<tr>
<td>6 mo</td>
<td>425</td>
<td>6</td>
<td>Death, 4; unknown, 2</td>
<td>Liver failure, 3; liver cyst infection, 1</td>
</tr>
<tr>
<td>12 mo</td>
<td>400</td>
<td>25</td>
<td>Death, 4; second renal TAE, 3; renal transplantation, 1; unknown, 16 (6)</td>
<td>Cerebral hemorrhage, 2; liver failure, 1; multiple organ failure, 1</td>
</tr>
<tr>
<td>Total</td>
<td>400</td>
<td>49</td>
<td>Death, 15; nephrectomy, 5; second renal TAE, 5; renal transplantation, 2; unknown, 22 (including seven who did not receive follow-up CT)</td>
<td>Liver failure, 4; cerebral hemorrhage, 2; liver cyst infection, 2; intestinal perforation, 2; sudden death, 2; multiple organ failure, 1; arrhythmia, 1; tumor lysis, 1</td>
</tr>
</tbody>
</table>

Numbers in parentheses indicate patients who continued to attend our hospital but did not receive follow-up CT. NA, not applicable.

Figure 2. Changes of DW and sBP. (A) Least squares mean (95% CI) of DW at each time point using a linear mixed model. DW decreased significantly until 3 months after renal TAE and then began to increase. * P value < 0.001 compared with DW before renal TAE. (B) Least squares mean (95% CI) of sBP at each time point using a linear mixed model. sBP decreased significantly from 3 months after renal TAE. * P value < 0.01 compared with sBP before renal TAE; ** P value < 0.001 compared with sBP before renal TAE.
accumulation of fluid. Severe gastrointestinal bleeding occurred in some patients using nonsteroidal anti-inflammatory agents for analgesia after renal TAE. Pseudoaneurysm developed at the femoral artery puncture site in three patients, and severe hematoma occurred in some patients, which can be expected after catheter intervention, but distal cholesterol crystal embolization did not occur.

Embolization of Additional Renal Arteries
At least one additional renal artery was embolized in 89 patients (19.8% of all patients enrolled), corresponding to a previous report that 18.5% of Asians have additional arteries.33 TAE of one additional renal artery was done in 69 patients, two additional arteries were embolized in 18 patients, and three or four additional arteries were embolized in one patient each (Table 1).

Changes of the RV Reduction Rate
Changes of the renal volume reduction rate (RVRR) after renal TAE are shown in Figure 3B. At 1 year after TAE, the RVRR ranged from 3.9% to 84.8%, and its least squares mean value was 45.5% (95% confidence interval [95% CI], 44.2% to 46.8%). Multivariate linear mixed model analysis using stepwise elimination revealed that the presence of large cysts with wall thickening and other complicated large cysts, age, dialysis duration, sBP, antihypertensive therapy, serum uric acid, and the number of microcoils used for renal TAE had a significant influence on the RVRR (Figure 4, Table 3, Supplemental Table 3). In patients <50 years old, the RVRR was 17.6% higher than in patients ages ≥65 years old at 1 year after TAE (Figure 5A). In patients with a dialysis duration <20 months, the RVRR was 11.4% higher than in patients whose dialysis duration was ≥100 months (Figure 5B). Furthermore, the RVRR was 4.8% higher in patients whose sBP was ≥148 mmHg than in patients whose sBP was ≤120 mmHg (Figure 5C).

Large Cysts (Minor Axis >5 cm)
Among all large cysts, the presence of cysts with wall thickening was the factor most significantly associated with a smaller RVRR (Table 3). Cysts with acute hemorrhage were associated with an increased RVRR according to univariate analysis, but the association was not significant on multivariate analysis. Normal cysts were also associated with a decrease of the RVRR, but the association was weaker than for cysts with wall thickening. Other complicated cysts were significantly associated with an increase of RVRR, but this association was weaker than for cysts with acute hemorrhage. The volume of large cysts with wall thickening showed no significant change after 1 year, although the volume of the rest of the kidney decreased significantly (Figure 6, Supplemental Figure 2).

**DISCUSSION**
Severe complications can occur after renal TAE, but complications may be reduced by attending to the following points. On the basis of the sequential changes of DW in our patients (Figure 2A), appropriate adjustment of DW is very important after renal TAE to avoid complications like congestive heart failure, although frequent dialysis was not required in most patients. In addition, the blood levels of renally excreted drugs can increase rapidly after renal TAE because of the onset of anuria, and therefore, it is necessary to monitor such drugs carefully. It was reported that performing renal TAE before nephrectomy reduces surgical complications.34 Although it is possible to perform renal TAE in patients with renal cell carcinoma, TAE can induce tumor lysis syndrome in patients with metastatic renal cancer, and therefore, suspected renal metastasis is a contraindication. Renal cyst infection can progress rapidly after renal TAE, and it should not be performed in patients with active cyst infection, although we previously reported that the incidence of renal cyst infection decreases if adequate RV reduction is achieved by renal TAE.35 A proton pump inhibitor should be administered after renal TAE to prevent gastrointestinal bleeding,
and food intake should be restricted for several days to prevent intestinal perforation.

In this study, RV was calculated with the equation for an ellipsoid. It was reported that total kidney volume calculated using the ellipsoid equation (TKVe) is strongly correlated with total kidney volume measured by stereology (TKVs) without systematic underestimation or overestimation. It was also reported that the difference between TKVe and TKVs exceeded 10% in 30% of their patients and exceeded 20% in 6%. TKVe might be less accurate in patients with large cysts than in patients without large cysts, but the difference between TKVe and TKVs did not exceed 15% in our 12 patients who had large cysts with wall thickening.

In this study, large cysts with wall thickening had the greatest independent influence on RVRR, whereas other large cysts did not influence RVRR as strongly. We also found that renal TAE is not effective for reducing the volume of large cysts with wall thickening. Although there were only 12 patients with large cysts and wall thickening in this series, their data suggest that cyst wall thickening (stiffness) may have

Figure 4. Influence of various factors on the RVRR. The changes (95% CIs) of slope coefficients of RVRR curves stratified by predictive variables. Large cyst with wall thickening was associated with the greatest decrease of RVRR. Hb, hemoglobin; TKV, total kidney volume.

Table 3. The changes (95% CIs) of slope coefficients of RVRR curves by predictive variables in univariate and multivariable linear mixed model analyses

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regression Coefficient</td>
<td>Lower 95% CI</td>
</tr>
<tr>
<td>Sex, men</td>
<td>-0.10</td>
<td>-0.83</td>
</tr>
<tr>
<td>Age per 5 yr</td>
<td>-1.14</td>
<td>-1.33</td>
</tr>
<tr>
<td>Dialysis duration per 12 mo</td>
<td>-0.24</td>
<td>-0.32</td>
</tr>
<tr>
<td>Body mass index</td>
<td>-0.08</td>
<td>-0.23</td>
</tr>
<tr>
<td>sBP per 10 mmHg</td>
<td>0.37</td>
<td>0.16</td>
</tr>
<tr>
<td>Antihypertensive therapy</td>
<td>0.49</td>
<td>0.24</td>
</tr>
<tr>
<td>Diuretics</td>
<td>0.93</td>
<td>0.17</td>
</tr>
<tr>
<td>No. of coils per 10 coils</td>
<td>-0.23</td>
<td>-0.38</td>
</tr>
<tr>
<td>Second operator</td>
<td>2.26</td>
<td>1.78</td>
</tr>
<tr>
<td>Large cyst with wall thickening</td>
<td>-6.40</td>
<td>-9.66</td>
</tr>
<tr>
<td>Large cyst with acute hemorrhage</td>
<td>5.33</td>
<td>3.30</td>
</tr>
<tr>
<td>Normal large cyst</td>
<td>-1.29</td>
<td>-2.35</td>
</tr>
<tr>
<td>Other complicated large cyst</td>
<td>2.36</td>
<td>1.23</td>
</tr>
<tr>
<td>Large cyst unclassified</td>
<td>1.53</td>
<td>-1.16</td>
</tr>
<tr>
<td>Log10 (RV before renal TAE)</td>
<td>3.24</td>
<td>1.63</td>
</tr>
<tr>
<td>Hemoglobin, g/dl</td>
<td>-0.34</td>
<td>-0.62</td>
</tr>
<tr>
<td>Albumin, g/dl</td>
<td>0.77</td>
<td>-0.33</td>
</tr>
<tr>
<td>Log10 CRP, mg/dl</td>
<td>0.60</td>
<td>-0.14</td>
</tr>
<tr>
<td>Uric acid, mg/dl</td>
<td>-0.59</td>
<td>-0.86</td>
</tr>
<tr>
<td>Corrected calcium, mg/dl</td>
<td>-0.03</td>
<td>-0.52</td>
</tr>
<tr>
<td>Phosphorus, mg/dl</td>
<td>0.17</td>
<td>-0.13</td>
</tr>
</tbody>
</table>

*These variables were selected by stepwise elimination using a linear mixed model.
more influence than cyst size on RV reduction after TAE. Large cysts with wall thickening might arise from repeated infection and/or intracystic bleeding, because their intracystic pattern was complicated on magnetic resonance imaging (MRI), and wall thickening is often seen in infected cysts. Chronic inflammation generally induces wall thickening and rigidity with fibrosis. In chronic cystitis and chronic cholecystitis, mural inflammation is characterized by infiltration of mononuclear cells, leading to irreversible tissue destruction with fibrosis, reduced compliance, and wall thickening. Severe inflammation can cause dystrophic calcification. Similar chronic inflammation might occur in renal cysts with repeated infection and/or bleeding, leading to fibrosis, poor compliance, wall thickening, and calcification. This concept is consistent with the report that renal cyst calcification is frequent in patients with ADPKD and might result from cyst hemorrhage.

Age had the biggest independent influence on RVRR after a large complicated cyst, but the aortic calcification index (ACI) was not a significant determinant according to multivariate analysis (Table 3), suggesting that age–related cyst wall changes unrelated to calcification might influence RVRR. In patients with CKD, progressive scarring or fibrosis of the renal parenchyma is common, and parenchymal fibrosis and renal tubular atrophy progress with aging. In patients with ADPKD, the severity of interstitial fibrosis shows the strongest association with rapid progression to ESRD. Mural degeneration and fibrosis may occur after sufficient expansion and aging of a cyst, causing cyst solidification that influences the RVRR after renal TAE, but histologic examination would be needed to confirm.

The duration of dialysis was another factor that influenced the RVRR. This might have been related to ectopic calcification, including renal cyst walls, because dialysis duration is the main factor associated with vascular calcification in patients with CKD. In fact, the ACI was correlated with dialysis duration in this study (Pearson correlation coefficient; r=0.2194; P<0.001). Thus, renal cyst calcification might also be correlated with dialysis duration and influence the RVRR after renal TAE, consistent with the report that renal cyst calcification is more frequent in patients with larger kidneys and worse renal function.

This study also revealed that hypertension had an independent influence on RVRR. The majority of adult patients with ADPKD has hypertension, and its onset is younger in ADPKD (30–34 years old) than in essential hypertension. Onset of hypertension before age 35 years old was reported to be significantly correlated with renal failure and kidney enlargement, and therefore, hypertension may be related to progressive increase of RV and rapid cyst growth. Accordingly, the larger RVRR after renal TAE in patients who are hypertensive could be related to more rapid growth of their cysts.

The number of microcoils was the other factor with an independent influence on RVRR. As shown in Supplemental Tables 4 and 5, significantly more microcoils were needed for complete renal artery occlusion in younger patients than in elderly patients and in patients with a shorter dialysis duration than in patients with a longer duration, implying that the luminal area was larger in younger patients with a shorter dialysis duration and that renal artery narrowing occurs with
insufficient, and renal enlargement might slow spontaneously. It has been reported that 10.5% of patients undergoing pretransplant renal TAE did not achieve sufficient renal volume reduction for graft implantation.\textsuperscript{25} Selection of suitable candidates for pretransplant renal TAE might be possible on the basis of our findings.

Microcoils are not a perfect embolic material for renal TAE, especially with regard to convenience and cost. It is necessary to develop new embolic materials to improve the safety, effectiveness, convenience, and cost of renal TAE.

A limitation of this study is possible variation in the completeness of arterial embolization, although we performed the same renal TAE procedure in all patients. In addition, arterial recanalization may have occurred in some patients, which might have affected the RVRR. Cyst hemorrhage or kidney re-enlargement might be noted if renal TAE is inadequate or recanalization occurs, and five of our patients required a second TAE procedure for these reasons.

**CONCISE METHODS**

This was a retrospective single–center cohort study designed to investigate the effectiveness of renal TAE for patients with ADPKD. Use of renal TAE for enlarged kidneys in patients with ADPKD was initially approved by the ethics committee of Toranomon Hospital in 1996.

**Patients**

All patients with ADPKD who received renal TAE at Toranomon Hospital from January of 2006 to July of 2013 were enrolled in this study. These patients were identified from the database of the Toranomon Hospital Department of Nephrology (Kawasaki, Japan), which was updated by a research assistant each time that renal TAE was performed. We confirmed all of the patients who received renal TAE from the medical records of Toranomon Hospital (Tokyo and Kawasaki, Japan). All patients were adults (ages ≥20 years old)
who met the criteria for diagnosis of ADPKD defined by Pei et al.\textsuperscript{58} and Progressive Renal Disease Research from the Ministry of Health, Labor and Welfare of Japan (Supplemental Appendix). Candidates for renal TAE were patients who were on maintenance dialysis and had compression symptoms related to enlarged polycystic kidneys, including dysphagia, gastroesophageal reflux, early satiety, severe changes of bowel habits, dyspnea, and orthopnea. They all received renal TAE of their own free will and gave written consent after being fully informed about the procedure, including complications, such as fever, pain, and anuria. We essentially performed renal TAE in all patients referred to us, but we consulted specialists and considered their eligibility carefully if they had severe medical complications. Because patients eventually become anuric after renal TAE, it was not usually performed before the urine volume decreased to <500 ml/d and the patient had oliguria or anuria. We excluded patients who received partial renal TAE for renal cyst bleeding and patients who underwent repeat renal TAE.

**Clinical and Laboratory Assessments**

Patients who received renal TAE were usually required to attend our hospital regularly for at least 1 year afterward to evaluate the clinical outcome and adjust the DW. Clinical features, including height and weight, past medical history, and smoking history, were recorded before performing renal TAE. Weight and BP were also recorded at 1, 3, 6, and 12 months after renal TAE. DW was used as the body weight of patients on dialysis. BP was measured with an automatic device in the sitting position, and the average of three sBP readings measured in the morning on a nondialysis day was used for analysis. Body mass index was calculated as the weight in kilograms divided by the square of the height in meters. Laboratory tests were done before renal TAE as well as 1, 3, 6, and 12 months after TAE. Blood tests were performed at the start of dialysis in patients on hemodialysis. All laboratory tests were done by automated standardized methods at our hospital within 24 hours of collecting the blood samples.

**Imaging Studies**

Abdominal CT was routinely performed in all patients before renal TAE and at 1, 3, 6, and 12 months after TAE with a 16- MDCT Scanner (Aquilion 16; Toshiba). In general, contrast-enhanced CT was only performed before renal TAE, excluding 37 patients with heart pacemakers, claustrophobia, and other contraindications. MRI was performed by the method reported previously\textsuperscript{37} (Supplemental Appendix).

RV was calculated from CT scans using the equation for an ellipsoid: \[ V = \frac{4}{3} \pi a \cdot b \cdot c \], where \( a \) is the maximum length of the kidney, and \( b \) and \( c \) are the maximum widths in the two transverse dimensions. The volume was determined before renal TAE and at 1, 3, 6, and 12 months after TAE.

We compared the volume of large cysts with wall thickening before renal TAE and at 1 year after TAE, and we also compared the volume of the rest of the kidney at these times. To calculate the volume of the large cysts and that of the rest of the kidney, CT scans obtained at a slice interval of 1 cm were analyzed using Synapse software (Fujifilm Company, Tokyo, Japan) to measure the respective areas on each slice, and the cyst and kidney volumes were calculated as the sum of the respective areas.

The ACI was evaluated as reported previously.\textsuperscript{59,60} In brief, ten CT slices were obtained at 1-cm intervals above the bifurcation of the common iliac vessels, the cross-section of the abdominal aorta on each slice was divided into 12 sectors, and the number of calcified sectors was counted. Then, the ACI was obtained with the following formula:

\[ \text{ACI} (\%) = \frac{\text{(number of sectors with calcification)} \times 100}{\text{(number of sectors evaluated)}} \]

The ACI was determined by three observers independently, and the mean of three measurements was used for analysis.

**Renal TAE Procedure**

The procedure for renal TAE has changed over time since 1996,\textsuperscript{15} but it has not been altered since January of 2006 (including the microcoils used). After the femoral artery was cannulated, aortography was performed using a pig tail catheter (Beacon; Cook Medical Inc.) (Supplemental Figure 2), and selective renal artery angiography was performed using a shepherd hook catheter (Cathex Co., Tokyo, Japan). A microcatheter (Renegade; Boston Scientific Co.) was inserted into the peripheral branches of the renal artery by using a guide wire. Then, platinum microcoils were advanced with a pusher (Trupush; Codman Neuro; Johnson & Johnson). We used two kinds of platinum microcoils (C-Stopper 18 cm [Piolax Medical Devices Inc., Yokohama, Japan] and Tornado 14.2 cm [Cook Medical Inc.]), with the C-Stopper coil generally being used to obstruct peripheral branches and the Tornado being used for the proximal renal artery. Microcoils are covered by health insurance for arterial embolization in Japan, and we are familiar with performing renal TAE by using microcoils as the embolic material. To avoid recanalization, coils were inserted as perripherally as possible into small renal artery branches, and both peripheral and proximal renal artery occlusions were performed as completely as possible on both sides simultaneously (Supplemental Figure 7).

Figure 7. Comparison of CT findings for large cysts with wall thickening or acute hemorrhage. (A) CT scan of a large cyst with wall thickening (arrow). A large cyst with wall thickening was defined as a cyst with minor axis \( >5 \) cm, marked thickening of its walls \( \geq 4 \) mm thick, and mural calcification. (B) CT scan of a large cyst with acute hemorrhage (arrow). A large cyst with acute hemorrhage was defined as a cyst with minor axis \( >5 \) cm and acute intracystic hemorrhage.

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\( a \times b \times c \times \pi / 6 \)
Figure 3). It is desirable to embolize as many branches of the vessels supplying both kidneys as feasible, including additional renal arteries and capsular arteries, because high blood flow in any remaining arteries increases the risk of hemorrhage secondary to volume overload.

Definitions
We classified all large cysts (minor axis >5 cm) into five groups according to the presence/absence of wall thickening, acute intracystic hemorrhage on CT, and isointensity of the cyst contents with water on MRI. A large cyst with wall thickening was defined as a cyst with marked thickening of its walls (≥4-mm thick) and mural calcification (Figure 7A). These cysts were distinguished from cysts with both slight wall thickening (<3.5 mm) and acute intracystic hemorrhage. A large cyst with acute hemorrhage was defined as a cyst containing a poorly demarcated mass with a high CT density (50–80 Hounsfield Unit) (Figure 7B). A normal large cyst was defined as a cyst that had contents showing isointensity with water on MRI (low intensity on T1-weighted images/diffusion-weighted images and high intensity on T2-weighted images). Other complicated large cysts were defined as cysts with a different intensity to water on MRI that had no wall thickening or acute hemorrhage. Unclassified cysts had no wall thickening or acute hemorrhage on CT, but MRI was not performed. These five kinds of cysts were investigated to determine whether there was any influence on the RVRR.

We defined an additional renal artery, other than the main renal artery, as an artery arising from the aorta and terminating in the kidney (Table 1).

Sudden death meant that a patient who was not known to have a serious condition died suddenly at night, and the death was not witnessed. Cardiovascular disease or cerebrovascular disease was suspected in patients with sudden death, but the actual cause was uncertain.

Statistical Analyses
We calculated the RVRR as follows: RVRR (%) = (1 – RV at each time after renal TAE/RV before renal TAE) × 100. RVRR was calculated for each kidney. Normally distributed baseline variables were summarized as the means±SDs, and non-normally distributed numeric baseline variables were summarized as medians and interquartile ranges. To estimate the mean values of RV, RVRR, DW, sBP, and serum CRP at each time point, the least squares means (95% CIs) were calculated using a linear mixed model. The regression coefficient (95% CI) for the relation between the RVRR and each of the variables tested was determined by using univariate linear mixed models. Predictive variables for the multivariable analysis were selected by the stepwise elimination method with linear mixed models. In these models, RVRR was a response variable, and time was a continuous variable as a fixed effect. Predictive variables, such as age, sex, duration of dialysis, body mass index, sBP, RV, past medical history (cardiovascular disease, heart failure, diabetes mellitus, and cancer), history of smoking, use of antihypertensive agents, use of diuretics, ACI, number of microcoils used for renal TAE, large cysts with wall thickening, large cysts with acute hemorrhage, normal large cysts, other complicated large cysts, unclassified large cysts, hemoglobin, serum albumin, CRP, cholinesterase, alkaline phosphatase, γ-glutamyltranspeptidase, uric acid, LDL-cholesterol, HDL-cholesterol, triglycerides, corrected Ca, phosphorus, ferritin, and iron, were fixed effects. Interaction predictive variables and time were fixed effects, and a patient was a random effect. To evaluate the influence of the operator on RVRR, we used the second operator as a predictive variable in the model, because the first operator was the same for all patients. To graphically evaluate the effects of predictive variables on the change of RVRR, quartiles of age, dialysis duration, and sBP were used, and the least squares mean (95% CI) of the RVRR at each time point was estimated using linear mixed models. Logarithmically transformed values of RV before renal TAE, CRP, alkaline phosphatase, γ-glutamyltranspeptidase, triglycerides, and ferritin were used for mixed model analysis.

Differences between before and after values of continuous variables with a normal distribution were assessed by the paired r test. All analyses were performed with SAS software, version 9.3 (SAS Institute Inc., Cary, NC), and P<0.05 was considered to indicate significance.

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DISCLOSURES
None.

REFERENCES

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