Prevalence of Renal Artery Stenosis in Autopsy Patients With Stroke

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Background and Purpose—Atherosclerotic renal artery stenosis commonly exists as one manifestation of more generalized atherosclerosis. It is a progressive but potentially curable disorder. Thus, information on renal artery involvement in atherosclerotic diseases could be important. We investigated the prevalence of renal artery stenosis in autopsied patients with stroke over 40 years of age.

Methods—From 2167 consecutive autopsy patients who died between 1980 and 1997, we studied 346 cases of mean age of 69±11 years with clinical evidence of stroke.

Results—Atherosclerotic renal artery stenosis (≥75% luminal area narrowing) was found in 36 patients (10.4%). Patients with renal artery stenosis were older and had worse renal function. Renal artery stenosis was found in 14.7%, 28.6%, and 23.9% of patients with hypertension, renal insufficiency, and aortic aneurysm, respectively. Extracranial carotid artery stenosis (>50% luminal area narrowing) was found in 101 patients (29.2%). Of the 346 stroke patients, 256 had a history of brain infarction. In patients with brain infarction, renal artery stenosis was found in 31 (12.1%) and carotid stenosis was found in 81 (33.6%). Patients with carotid artery stenosis were more likely to have renal artery stenosis than patients without carotid artery stenosis (24.4% versus 5.9%, \(P<0.0001\)). Multiple logistic regression analysis identified renal insufficiency, hypertension, female gender, and presence of carotid artery stenosis as independent predictors of renal artery stenosis in patients with brain infarction.

Conclusions—These data reveal that atherosclerotic renal artery stenosis is common in patients with stroke, especially in those with brain infarction. (Stroke. 2000;31:61-65.)

Key Words: autopsy ■ hypertension ■ carotid stenosis ■ renal artery ■ stroke

Atherosclerotic renal artery stenosis is an important cause of hypertension and renal insufficiency. Early autopsy studies confirm that mainly elderly patients are affected.\(^1,2\) Several angiographic studies have shown that renal atherosclerosis usually exists as one manifestation of more generalized atherosclerosis,\(^2\) including symptomatic peripheral vascular disease, aortic aneurysm,\(^3\) and ischemic heart disease.\(^4\) Renal artery stenosis is progressive\(^5,6\) and potentially leads to end-stage renal disease.\(^2\) It may account for between 10% and 20% of patients on dialysis in some surveys.\(^7,8\) The increased mortality was observed in patients with renal artery stenosis, because they have comorbid cardiovascular disease and greater age.\(^5,7,9\) Revascularization procedures of the renal artery are frequently clinically useful.\(^2,10–13\) Thus, information on renal artery involvement in atherosclerotic disease could be important in the overall treatment of the patients, as well as in the clinical outcome.

We have recently reported, on the basis of autopsy study, that renal artery stenosis is common in patients with myocar-

dial infarction.\(^14\) Stroke is another important atherosclerotic disease, but the prevalence of renal artery stenosis has not been reported. The prevalence is probably high, because stroke event rate has been closely related to carotid atherosclerosis,\(^15,16\) and extracranial vascular atherosclerosis is increasing in Japanese patients with brain ischemia.\(^17\) The aim of this study is to determine the prevalence of atherosclerotic renal artery stenosis in stroke patients on the basis of autopsy study. In addition, we tried to analyze the predictive factors of high-risk patients with atherosclerotic renal artery stenosis.

Methods

Patients

During the 17-year period between 1980 and 1997, 2167 patients were autopsied at National Cardiovascular Center Hospital in Osaka, Japan. To examine atherosclerotic renal artery stenosis in elderly patients, we studied retrospectively all the autopsy cases for patients aged ≥40 years who had a history of stroke. Patients with nephrectomy (n=8), horseshoe kidney (n=2), renal cell carcinoma (n=5), or

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dissecting aneurysm of the aorta involving the renal artery (n = 2) or carotid artery (n = 4) were excluded from this study. We also excluded patients without precise information on the renal artery (n = 12) and carotid artery (n = 13). Two patients who had received endarterectomy of carotid artery because of severe atherosclerotic stenosis were included. A total of 346 patients remained for analysis.

Hypertension was diagnosed when blood pressure was ≥140 and/or 90 mmHg on at least 2 different visits to the hospital, or if the patient was taking antihypertensive agents. Diabetes mellitus was defined as a patient’s use of oral hypoglycemic agents or insulin, and/or having a fasting blood glucose level ≥7.8 mmol/L (140 mg/dL) or random nonfasting blood glucose level ≥11.1 mmol/L (200 mg/dL). Hypercholesterolemia was defined as a patient’s taking lipid-lowering agents and/or having a serum cholesterol level ≥5.7 mmol/L (220 mg/dL). Proteinuria was diagnosed as urinary protein level >1(+) by the dye-impregnated paper strip method and renal insufficiency as a serum creatinine level ≥133 μmol/L (1.5 mg/dL). Laboratory data, including serum creatinine, cholesterol, glucose, and urinalysis, were collected within 1 year before the fatal event that led to death (ie, sepsis and multiple organ failure). The types of stroke were classified from the clinical history, neurological examination, and findings of CT and/or MRI scans, according to the National Institute of Neurological Disorders and Stroke Classification of Cerebrovascular Disease III. We did not categorize the infarct into subtypes such as atherothrombotic, cardioembolic, and lacunar infarction. The cases with asymptomatic cerebrovascular disease and transient ischemic attack were not included in this study.

Autopsy Study
According to the regulations of our pathology department, the thoracoabdominal aorta, brachiocephalic artery, extracranial carotid arteries, renal arteries, and kidneys were removed on block. Bilateral extracranial carotid arteries (including common carotid and internal carotid arteries) and renal arteries were dissected. Macroscopically apparent stenosis of ≥75% luminal area narrowing was defined as renal artery stenosis. Carotid artery stenosis was defined as >50% luminal area narrowing. All carotid arteries and renal arteries were reviewed by 2 pathologists (N.N. and C.Y.) under blinded conditions for clinical information. The specimen of these arteries were reviewed by them together, and the final decision was made through a consensus meeting after discussion. Known or suspected aortic aneurysm and coronary artery disease were confirmed by autopsy protocols of 392 patients with a clinical history of endarterectomy of carotid artery because of severe atherosclerotic stenosis. A total of 346 patients remained for analysis.

Statistical Analysis
Significance of the differences between the 2 groups was analyzed by the Student t test, χ2 analysis, or Fisher exact test on an appropriate basis. Multiple logistic regression analysis was performed with use of a maximum likelihood function to identify predictors and risk factors of significant renal artery stenosis. Independent variables were age, sex, presence of hypertension, diabetes mellitus, hypercholesterolemia, proteinuria, renal insufficiency, smoking history, coronary artery disease, aortic aneurysm, and carotid artery stenosis. Data were expressed as the mean±SD.

Results
Among 2167 autopsy cases between 1980 and 1997, the autopsy protocols of 392 patients with a clinical history of stroke and age ≥40 years were referred for possible enrollment; 346 were finally included. Types of stroke were the following: brain infarction (n = 219), subarachnoid hemorrhage (n = 36), brain hemorrhage (n = 51), brain infarction plus subarachnoid hemorrhage (n = 8), brain infarction plus hemorrhage (n = 29), and subarachnoid plus brain hemorrhages (n = 3).

The clinical characteristics of the studied cases are summarized in Table 1. The mean age of the patients was 69±11 years. Hypertension was recognized in 63.4% of patients and proteinuria in 35.5%. Renal insufficiency was noted in 22.4%. The mean serum creatinine concentration was 302±240 μmol/L (3.4±2.7 mg/dL) in patients with renal insufficiency, while it was 89±24 μmol/L (1.0±0.3 mg/dL) in those without it.

Of the 346 patients, 36 patients (10.4%) had atherosclerotic renal artery stenosis. Twenty-six (7.5%) had unilateral disease (16 stenosis and 10 occlusion), while 10 (2.9%) had bilateral disease (2 bilateral occlusion, 4 with occlusion and stenosis, and 4 bilateral stenosis). Renal artery occlusion was, therefore, present in 4.6% of patients. Only 8 of the 36 cases (22.2%) had the established diagnosis of renal artery stenosis before autopsy.

Location and volume of the clinically relevant brain infarction or hemorrhage, illustrated by CT and/or MRI, was not different between patients with and without renal artery stenosis. Patients with renal artery stenosis were older than those without (mean age 73 versus 69 years, respectively; P = 0.02) and had worse renal function (mean creatinine 221 versus 124 μmol/L, respectively; P < 0.001). Prevalence of the atherosclerotic renal artery stenosis increased with age: 0% and 2% in the age groups 40 to 49 and 50 to 59 years, respectively, and 11%, 13%, and 14% in the age groups 60 to 69, 70 to 79, and ≥80 years, respectively (Figure).

As shown in Table 2, of 346 stroke patients, 68 (19.7%) had ≥75% stenosis in at least 1 of the extracranial carotid arteries (45 unilateral and 23 bilateral), and 23 (6.6%) were

<table>
<thead>
<tr>
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The prevalence of renal artery stenosis and age in autopsy patients with stroke. The number of patients with renal artery stenosis and the total number of patients are the numerator and denominator, respectively, within each column.

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The prevalence of renal artery stenosis and age in autopsy patients with stroke. The number of patients with renal artery stenosis and the total number of patients are the numerator and denominator, respectively, within each column.
carotid artery occlusion (4 bilateral and 19 unilateral). Stenosis of $\geq 50\%$ was detected in 101 patients (29.2%; 68 unilateral and 33 bilateral). Of 101 patients, 23 (22.8%) with carotid artery stenosis had renal artery stenosis, the prevalence of which was significantly higher than in stroke patients without carotid stenosis (13 of 245, 5.3%; $P$, 0.0001).

Of 346 stroke patients, 256 had history of brain infarction (219 with brain infarction, 29 with brain infarction plus hemorrhage, 8 with brain infarction plus subarachnoid hemorrhage). The mean age was 71 $\pm$ 10 years, including 164 men (64%) and 92 women (36%). Carotid artery stenosis was more common in men than in women (34.8% versus 19.8%, $P$, 0.01 in all strokes, and 40.2% versus 21.7%, $P$, 0.01 in brain infarction). In patients with brain infarction, the prevalence of renal artery stenosis was higher than in those without brain infarction (12.1 versus 5.6%, $P$, 0.08). The prevalence of extracranial carotid artery stenosis was also higher in patients with brain infarction than without brain infarction ($\geq 50\%$ carotid artery stenosis: 33.6% versus 16.7%, $P$, 0.08; $\geq 75\%$ stenosis: 24.6% versus 5.6%, $P$, 0.0001).

Considering that carotid atherosclerosis is frequently associated with ischemic stroke events, we examined the relationship between renal artery and extracranial carotid artery stenosis in patients with brain infarction. Renal artery stenosis was observed in 21 patients (24.4%) with carotid artery stenosis ($\geq 50\%$) and in 10 patients (5.9%) without carotid artery stenosis ($P$, 0.0001). Conversely, 67.7% of patients with renal artery stenosis had carotid artery stenosis.

Table 3 shows the predictors and risk factors of renal artery stenosis in cases with all strokes and brain infarction. The prevalence of renal artery stenosis in all strokes was significantly higher in patients with hypertension, renal insufficiency and aortic aneurysm than in those without the respective factors. Renal artery stenosis was found in 14.7%, 28.6%, and 23.9% of stroke patients with hypertension, renal insuf-

### Table 2. Prevalence of Renal Artery Stenosis and Extracranial Carotid Artery Stenosis in Autopsy Patients With Stroke

<table>
<thead>
<tr>
<th>Renal Artery Stenosis (≥75%)</th>
<th>Carotid Artery Stenosis (≥75%)</th>
<th>Carotid Artery Stenosis (≥50%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All strokes (n=346)</td>
<td>36 (10.4%)</td>
<td>68 (19.7%)</td>
</tr>
<tr>
<td>History of brain infarction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n=256)</td>
<td>31 (12.1%)†</td>
<td>63 (24.6%)*</td>
</tr>
<tr>
<td>No (n=90)</td>
<td>5 (5.6%)</td>
<td>5 (5.6%)</td>
</tr>
</tbody>
</table>

* $P$, 0.0001, † $P$, 0.08 vs without history of brain infarction.

### Table 3. Association of Clinical Characteristics With Renal Artery Stenosis in Autopsied Cases With Stroke or Brain Infarction

<table>
<thead>
<tr>
<th>Clinical Characteristic</th>
<th>Prevalence of Renal Artery Stenosis</th>
<th>All Strokes</th>
<th>Brain Infarction</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=346 (%)</td>
<td>n=256 (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>23/215 (10.7)</td>
<td>20/164 (12.2)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Female</td>
<td>13/131 (9.9)</td>
<td>11/92 (12.0)</td>
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</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>4/126 (3.2)</td>
<td>3/93 (3.2)</td>
<td>$&lt;0.001$</td>
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</tr>
<tr>
<td>Yes</td>
<td>32/218 (14.7)</td>
<td>28/162 (17.3)</td>
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<td></td>
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<tr>
<td>Diabetes mellitus</td>
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<td></td>
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<tr>
<td>No</td>
<td>26/262 (9.9)</td>
<td>22/190 (11.6)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10/80 (12.5)</td>
<td>9/64 (14.1)</td>
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<tr>
<td>Hypercholesterolemia</td>
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<tr>
<td>No</td>
<td>21/219 (9.6)</td>
<td>18/164 (11.0)</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>Yes</td>
<td>15/116 (12.9)</td>
<td>13/89 (14.6)</td>
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<tr>
<td>Smoking</td>
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<tr>
<td>No</td>
<td>10/144 (6.9)</td>
<td>8/105 (7.6)</td>
<td>0.08</td>
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<tr>
<td>Yes</td>
<td>25/196 (12.8)</td>
<td>22/148 (14.9)</td>
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<tr>
<td>Proteinuria</td>
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<tr>
<td>No</td>
<td>18/209 (8.6)</td>
<td>14/160 (8.8)</td>
<td>0.09</td>
<td></td>
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<tr>
<td>Yes</td>
<td>17/115 (14.8)</td>
<td>16/90 (17.8)</td>
<td></td>
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<tr>
<td>Renal insufficiency</td>
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<td></td>
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<tr>
<td>No</td>
<td>14/267 (5.2)</td>
<td>13/202 (6.4)</td>
<td>$&lt;0.0001$</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>22/277 (28.6)</td>
<td>18/52 (34.6)</td>
<td></td>
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<tr>
<td>Coronary artery disease</td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>19/232 (8.2)</td>
<td>15/156 (9.6)</td>
<td>NS</td>
<td></td>
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<tr>
<td>Yes</td>
<td>17/114 (14.9)</td>
<td>16/100 (16.0)</td>
<td></td>
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</tr>
<tr>
<td>Aortic aneurysm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>25/300 (8.3)</td>
<td>20/216 (9.3)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11/46 (23.9)</td>
<td>11/40 (27.5)</td>
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</tbody>
</table>
This study identified predictors and risk factors for athero-
scerotic renal artery stenosis in autopsied patients aged ≥40
years who had clinical history of stroke. In patients with renal
insufficiency, hypertension, aortic aneurysm, or extracranial
carotid artery stenosis, the prevalence of renal artery stenosis
was higher than in those without the respective factors.
Increasing age was also an important risk factor for renal
artery atherosclerosis. Multiple logistic regression analysis
showed that presence of renal insufficiency, carotid artery
stenosis, and hypertension increased the prevalence of renal
artery stenosis by 6.6-, 4.8-, and 4.1-fold in patients with
age ≥50 years who had clinical history of stroke. In patients
with renal insufficiency, hypertension, and male gender, may
not influence the prevalence of renal artery stenosis, being
consistent with other reports in atherosclerotic population.4,7,14,18 In addition,
female gender was an independent predictor of significant
renal artery stenosis in patients with brain infarction, although
the prevalence of renal artery stenosis was not different between
males and females by χ² analysis. Some investigators showed
female gender as one of the predictor of significant renovas-
ation elsewhere. Predictors of renal artery stenosis in pa-
cient renal artery stenosis as ≥75% luminal area narrowing.
The degree of renal artery stenosis, as we defined in this
study, was almost the same as that of previous angiographic
studies that defined significant renal artery stenosis as 50% or
greater diameter narrowing.4,18

There have been no population-based studies providing
accurate data regarding the prevalence of renal artery steno-
sis. Several studies7,8,19 have suggested that renal artery
stenosis may be responsible for 1% to 5% in unsel ected
patients with hypertension, and 5% to 22% in patients aged
≥50 years with end-stage renal disease. In early autopsy
studies,1,2 prevalence of renal artery atherosclerosis was
reported to be increased in aged patients. Several angiog-
graphic studies reported that the prevalence of renal artery
atherosclerosis ranges from 11% to 42% in patients with
generalized arterial disease2–4 and 34% in elderly patients
with congestive cardiac failure.20 Our data were at the very
low end of that range, at least in part because not all of the
strokes were directly associated with atherosclerosis. In this
study, cases with subarachnoid hemorrhage and cerebral
hemorrhage were included as stroke patients, and cardioem-
bolic infarction and lacunar infarction, both of which would
occur in patients without atherosclerotic disease, were
included as brain infarction. Hans et al21 reported that the
prevalence of renal artery stenosis was 7.2% in patients who
received carotid arteriography, including 14% of stroke, 44%
of carotid stenosis, and 42% of transient ischemic attack
patients. This rate was lower than ours. One possible expla-
nation for the difference is that patients with renal insuffi-
ciency may be excluded from their angiographic study to
avoid acute renal failure due to radiocontrast-induced
nephropathy.

Clinical suspicion of atheromatous renal artery stenosis
was usually based on the higher age of patients who show an
abrupt onset of hypertension, pulmonary edema with accel-
erated hypertension, progressive renal failure, presence of
other atherosclerotic disease, and acute impairment in renal
function during treatment with an angiotensin converting
enzyme (ACE) inhibitor. Some reports demonstrated that
hypercholesterolemia, smoking history,22 diabetes mellitus,
and male gender also predicted renal artery stenosis in
hypertensive patients among the atherosclerotic population.
However, in this study, hypercholesterolemia, diabetes mel-
litus, and smoking history were not independent predictors,
probably because these risk factors contributed to stroke
independently of renal artery stenosis, being consistent with
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female gender was an independent predictor of renal artery
stenosis in patients with brain infarction, although the prev-
ance of renal artery stenosis was not different between
to 50% of the above factors,

$\text{Variable} \quad \text{Odds Ratio} \quad 95\% \text{ CI} \quad P$

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal insufficiency</td>
<td>6.6</td>
<td>2.3–18.8</td>
<td>0.0003</td>
</tr>
<tr>
<td>Carotid artery stenosis (&gt;50%)</td>
<td>4.8</td>
<td>1.9–12.4</td>
<td>0.0008</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4.1</td>
<td>1.0–15.8</td>
<td>0.024</td>
</tr>
<tr>
<td>Female</td>
<td>3.4</td>
<td>1.1–11.0</td>
<td>0.035</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>6.3</td>
<td>2.3–17.5</td>
<td>0.0003</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3.7</td>
<td>1.0–13.7</td>
<td>0.033</td>
</tr>
<tr>
<td>Female</td>
<td>2.9</td>
<td>0.9–8.8</td>
<td>0.067</td>
</tr>
<tr>
<td>Carotid artery stenosis (=75%)</td>
<td>2.2</td>
<td>0.9–5.7</td>
<td>0.095</td>
</tr>
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Discussion

This study identified predictors and risk factors for athero-
sclerotic renal artery stenosis in autopsied patients aged ≥40
years who had clinical history of stroke. In patients with renal
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Of 346 stroke patients, 36 patients (10.4%) had significant
renal artery stenosis; of these, 4.6% had renal artery occlusion
and 2.9% had bilateral disease. In patients with brain infarc-
tion, the prevalence rate became 12.1%. We defined signifi-
cant renal artery stenosis as ≥75% luminal area narrowing.
The degree of renal artery stenosis, as we defined in this
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males and females by χ² analysis. Some investigators showed
female gender as one of the predictor of significant renovas-
ation elsewhere. Predictors of renal artery stenosis in pa-
tients with stroke may be different from those of general population. Proteinuria, which was frequently detected in patients with renal artery stenosis, was associated with the prevalence of renal artery stenosis in patients with brain infarction.14

It has been reported that patients with stenotic extracranial carotid arteries were more likely to have renal artery stenosis. The association between renal artery and extracranial carotid artery atherosclerosis has been studied on the basis of angiography or ultrasonography. The 45% to 100% of patients with renal artery stenosis had comorbid carotid artery stenosis,11,23–25 and carotid stenosis was considered an independent predictor of renal artery stenosis in patients with aortoiliac disease.36 These findings were very close to our results. Even in patients with brain infarction, extracranial carotid artery stenosis was an independent predictor of renal artery stenosis.

Some studies have indicated that the survival rate of patients with renal artery stenosis is low, and major causes of death are cardiovascular or cerebrovascular diseases rather than renal failure.6–7,9 High production of angiotensin II was suggested to be associated with this increased mortality. Thus, early and successful surgery or angioplasty could attenuate acceleration of atherosclerosis, in addition to stabilizing renal function and controlling blood pressure. We should consider the possibility of both renal function recovery and risk associated with revascularization procedures due to comorbid atherosclerotic diseases such as ischemic heart disease and stroke. In addition, stroke patients are commonly treated with an ACE inhibitor, because this drug has been reported to have a favorable effect on cerebral blood flow autoregulation. Therefore, patients with stroke require careful monitoring of renal function when an ACE inhibitor is administered, since they may have bilateral renal artery stenosis.

In conclusion, the current autopsy study showed that the prevalence of atherosclerotic renal artery stenosis was 10.4% in patients aged ≥40 years with stroke and 12.1% in such patients with brain infarction. Patients with extracranial carotid artery stenosis were more likely to have renal artery stenosis. Renal insufficiency, presence of carotid artery stenosis, and hypertension were independent predictors of renal artery stenosis among autopsied patients with brain infarction.

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References

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