Original Article

Angiotensin-Converting Enzyme Inhibitor Usage in Patients with Incidental Atherosclerotic Renal Artery Stenosis

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The efficacy of angiotensin converting enzyme (ACE) inhibitors in treatment of renovascular disease has been controversial. It has been reported that patients with incidental atherosclerotic renal artery stenosis (ARAS) are sometimes treated with ACE inhibitors before being considered for renal revascularization. This study was designed to describe the frequency and the characteristics of patients with incidental ARAS, and to examine the frequency of ACE inhibitor usage in such patients. We studied a cohort of consecutive patients undergoing abdominal aortography at the time of cardiac catheterization. Patients were stratified and compared based on the presence and severity of ARAS. ARAS ($\geq 50\%$) was present in 146 (17.0%) of 859 evaluable patients. Factors independently related to the presence of ARAS were age (odds ratio (OR) = 1.07, $p < 0.001$), severity of coronary artery disease (OR = 2.13, $p < 0.001$) and peripheral vascular disease (OR = 1.79, $p = 0.021$). Among all patients with ARAS, the percentage of ACE inhibitor usage was 74.7% (109/146). Among patients with severe ARAS, moderate ARAS, mild ARAS, insignificant ARAS and normal renal arteries, the percentage of ACE inhibitor usage was 85.7% (95% confidence interval (CI): 69–100%), 82.9% (95% CI: 71–95%), 68.5% (95% CI: 59–78%), 68.6% (95% CI: 55–82%) and 53.9% (95% CI: 50–58%), respectively (contingency coefficient = 0.17, $p < 0.001$). In patients with severe ARAS, ACE inhibitor use, calcium channel blocker use and diuretic use were shown to correlate significantly with serum creatinine levels after controlling for potential confounding factors. In this study, ACE inhibitors were used commonly in patients with incidental ARAS; the frequency of ACE inhibitor use correlated with the severity of ARAS.

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Key Words: renovascular disease, angiotensin-converting enzyme inhibitor, cardiac catheterization

Introduction

Atherosclerotic renal artery stenosis (ARAS) is a recognized cause of renal impairment (1, 2) and secondary hypertension (3) and is becoming more common due to the prevalence of atherosclerosis in an increasingly aging population. Multiple noninvasive modalities are available to detect ARAS, though the decision to screen for ARAS is contingent on clinical

suspicion. Many patients with renovascular disease now go undetected because their blood pressure and renal function are well controlled and stable upon medical treatment (4). However, when treated with angiotensin converting enzyme (ACE) inhibitors, 6% to 38% of patients with severe renovascular disease may develop acute renal failure (5, 6). The broadening indication for ACE inhibitor therapy perhaps makes it more important to screen for ARAS. We sought to demonstrate the prevalence of incidental ARAS in a selected

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population undergoing routine cardiac catheterization, and the frequency of ACE inhibitor usage in patients with varying degrees of ARAS.

Methods

A total of 859 patients who were referred to the Cardiovascular Center of Tongren Hospital in Beijing from March 2000 to October 2002 for cardiac catheterization because of suspected coronary artery disease were invited to participate in this study. Referrals for coronary angiography were made by clinical cardiologists who were not involved with this study. Patients with a serum creatinine level greater than 2.5 mg/dl were excluded from consideration because of safety concerns about contrast volume administration. The study was approved by the Ethical Committee of the Heart Institute, Capital University of Medical Sciences. Written informed consent was obtained from all participants.

Before patients had cardiac catheterization, demographic data, medical history, physical findings, and blood chemistries were obtained. Patients were considered to have hypertension if they had a history of the disease or were receiving antihypertensive medication. Blood pressure was measured in the supine position. Duration of hypertension and medication, especially ACE inhibitor treatment, was recorded. Only patients with well controlled blood pressure (<140/90 mmHg) were included.

Peripheral vascular disease was defined as a history of claudication, a history of stroke, or abdominal aortic aneurysm (7). Symptoms of congestive heart failure were recorded and classified in accordance with the New York Heart Association (NYHA) criteria. Hyperlipidemia was defined as a cholesterol level above 200 mg/dl or low-density lipoprotein >120 mg/dl, or a history of hyperlipidemia and treatment with lipid-lowering medications. Coronary angiography was performed following puncture of the femoral artery using the modified Seldinger technique. After the cardiac diagnostic procedure, abdominal aortography was performed with a 6F pigtail catheter positioned at the level of the renal arteries to screen for the presence of anatomical renal artery stenosis. Abdominal aortography was done in a 10° LAO projection with 30 ml of Omnipaque 350 at a rate of 20 ml s⁻¹ acquired at 30 frames per second. Selective renal artery injections were done to look for more distal renal artery stenosis, or when overlapping vessels made interpretation of the aortogram difficult. If appropriate, percutaneous coronary intervention was performed at the discretion of the patient's clinical cardiologist.

The presence and severity of coronary atherosclerotic lesions were determined as follows: significant stenosis was defined as a narrowing of the coronary artery diameter of 50% or more, in comparison with a proximal reference segment. Single-, double-, and triple-vessel disease were defined as a significant lesion in 1, 2, or 3 major epicardial vessels, respectively.

The aortogram was independently interpreted by two experienced angiographers blinded to the patient information. The severity of renal artery stenosis was expressed by a patency index, which was calculated as the sum of the patent portion of both renal arteries, with 2.0 representing normal appearance and 0 representing complete occlusion of the renal arteries in both kidneys. For example, in the case of unilateral renal artery occlusion (contralateral normal) or 50% bilateral RAS, the patency index = 1.0; for unilateral renal artery occlusion with contralateral 60% RAS, or bilateral 80% RAS, the patency index = 0.4. Patients were grouped as follows: patency index less than 0.5, severe ARAS; patency index 0.5 to 1.0, moderate ARAS; patency index 1.1 to 1.5, mild ARAS; patency index 1.5 to 1.9, insignificant ARAS; patency index = 2.0, normal (8).

The distribution and prevalence of ARAS were determined in the study population. Stepwise univariate and multiple logistic regression was used to evaluate the independent association of individual covariates with renal artery stenosis. The variables that were significant in the univariate model were then entered into a stepwise logistic regression model to identify the best set of independent predictors of ARAS. Multiple group comparisons were done by one-way ANOVA. A Spearman's correlation study was used to test the relationship between renal function and the residual lumen patency subgroup. Categorical variables were analyzed by contingency of χ^2 tests. Multiple regression was used to determine the association between drug usage and serum creatinine levels after controlling for potential confounding factors, including diabetes, age, hypertension and congestive heart failure. Unless otherwise indicated, continuous variables are presented as the mean $\pm$ SD and discrete variables are presented as a percentage. A statistical difference was considered significant at a *p* value of less than 0.05.

Results

A total of 859 patients were studied, 274 (31.9%) females and 585 (68.1%) males. The clinical and demographic characteristics of these patients are shown in Table 1. The mean age of the cohort was 60.5 $\pm$ 10.8 years.

Six hundred and twenty (72.2%) patients had hypertension. A large proportion of patients were taking an ACE inhibitor (58.4%) and/or a β -blocker (74.7%).

A total of 301 patients (35%) had no disease of the epicardial coronary arteries. One hundred and fifty (17.5%) had 1-vessel disease, 125 (14.6%) had 2-vessel coronary artery disease, and 283 (32.9%) had 3-vessel coronary disease. Fifty-five patients (6.4%) had left main lesion.

Significant ARAS ($\geq$ 50% luminal narrowing of at least one renal artery) was present in 146 patients (17.0%). Insignificant ARAS (<50%) of one or two renal arteries was found in 57 (6.6%) patients. Severe ARAS, moderate ARAS, mild ARAS, insignificant ARAS and normal renal arteries were present in 21 (2.4%), 41 (4.7%), 89 (10.4%), 51 (5.9%)

Table 1. Clinical and Demographic Characteristics of 859 Patients Undergoing Abdominal Aortography

Characteristics	Values
Age (year)	60.5 ± 10.8
Male (%)	577 (67.4)
Height (m)	1.67 ± 0.07
Weight (kg)	71.46 ± 11.23
Body mass index (kg/m ²)	25.56 ± 3.49
Previous myocardial infarction (%)	245 (28.5)
Smoker (current and former) (%)	112 (13.0)
Diabetes mellitus (%)	186 (21.8)
Ejection fraction (%)	65.12 ± 10.05
Peripheral vascular disease (%)	112 (13.0)
Creatinine (mg/dl)	1.01 ± 0.35
Serum creatinine >1.3 mg/dl (%)	101 (11.8)
Hypertension (%)	620 (72.2)
Blood pressure (mmHg)	
Systolic	125 ± 15
Diastolic	71 ± 9
NYHA score	1.74 ± 0.80
Hyperlipidemia (%)	388 (45.2)
Drug	
Mean No. of antihypertensive drugs	1.69 ± 0.95
ACE inhibitor (%)	502 (58.4)
β-Blocker (%)	642 (74.7)
Diuretics (%)	87 (10.1)
Calcium channel blocker (%)	206 (24.0)
Angiotensin receptor blocker (%)	14 (1.63)
Severity of coronary artery disease	
Coronary stenosis per patient	1.45 ± 1.27
Normal	301 (35.0)
1 vessel	150 (17.5)
2 vessel	125 (14.6)
3 vessel	283 (32.9)
Left main	55 (6.4)

NYHA, New York Heart Association; ACE, angiotension-converting enzyme.

those with ARAS < 50% or those with normal renal arteries, and were more likely to have diabetes mellitus, peripheral vascular disease, and previous myocardial infarction. Serum creatinine was higher in the ARAS group. Significantly more stenotic coronary segments were diagnosed in the ARAS group. Multivariate logistic regression of all variables revealed that three risk factors were independently predictive of renal artery disease. The most important risk factors were age (odds ratio (OR)) = 1.07, 95% confidence interval (CI): 1.05–1.11, $p < 0.001$), severity of coronary artery disease (OR = 2.13, 95% CI: 1.76–2.95, $p < 0.001$) and peripheral vascular disease (OR = 1.79, 95% CI: 1.09–2.95, $p = 0.021$) (Table 4).

Serum creatinine and the medications taken by the patients in the different groups are listed in Table 5. There was a significant correlation between the serum creatinine level and residual lumen patency (Spearman's $\rho = -0.194$, $p < 0.001$). Among the patients on ACE inhibitors, 4.2% (21/502) had severe ARAS. Patients with increasing severity of ARAS were older and on more antihypertensive drugs. The percentages of patients taking an ACE inhibitor in the severe ARAS, moderate ARAS, mild ARAS, insignificant ARAS, and normal artery groups were 85.7% (95% CI: 69–100%), 82.9% (95% CI: 71–95%), 68.5% (95% CI: 59–78%), 68.6% (95% CI: 55–82%) and 53.9% (95% CI: 50–58%), respectively (contingency coefficient = 0.17, $p < 0.001$).

Among patients with ARAS, serum creatinine levels were higher in those who were taking ACE inhibitors than in those who were not (1.21 ± 0.51 mg/dl vs. 0.97 ± 0.28 mg/dl, $p = 0.001$). Table 6 shows the results of a multiple regression analysis of the association between drug usage and serum creatinine level after stratification by the severity of ARAS. In patients with severe ARAS, ACE inhibitors, calcium channel blockers and diuretics were shown to correlate significantly with serum creatinine levels after controlling for potential confounding factors.

Discussion

In the present cohort of patients undergoing routine cardiac catheterization, abdominal aortography identified an overall prevalence of ARAS of 17%, which is higher than the previously reported 7% prevalence in Japanese (9), but similar to the prevalences of 15% reported using patient cohorts (7, 10) and 19.2% reported in a cohort of hypertensive patients (11). Our study demonstrated that most patients with incidental ARAS were being treated with ACE inhibitors, and that the patients with severe ARAS had the greatest probability of ACE inhibitor use.

A decade ago, approximately 30% of patients with ARAS were taking an ACE inhibitor as part of their medical regimen at the time of diagnosis (12, 13). In our study, more than 80% of patients with severe or moderate ARAS were taking ACE inhibitors, but only 53.9% of patients without

Table 2. ARAS According to Side and Extent of Stenosis

% Stenosis of right renal artery	% Stenosis of left renal artery			
	0	1–49	50–69	≥ 70
0	656	25	17	17
1–49	22	10	7	2
50–69	19	6	15	10
≥ 70	22	4	8	19

and 657 (76.5%) patients, respectively (Table 2).

As shown in Table 3, there were no differences in gender, NYHA scores, smoking, hypertension, or hyperlipidemia between patients with and those without ARAS. However, patients with ARAS of 50% or more tended to be older than

Table 3. Comparison of the Non-ARAS and ARAS Group

	Without ARAS (n = 713)	With ARAS (n = 146)	p value
Sex (male) (%)	478 (67.0)	99 (67.8)	0.91
Age (year)	59.17 ± 10.64	67.25 ± 8.66	<0.001
Body mass index (kg/m ²)	25.65 ± 3.40	24.92 ± 3.21	0.017
Hypertension (%)	506 (71.0)	114 (78.1)	0.082
Diabetes mellitus (%)	136 (19.1)	50 (34.2)	0.046
Peripheral vascular disease (%)	77 (10.8)	35 (23.9)	0.04
Smoke (%)	271 (38.0)	68 (46.6)	0.054
Previous myocardial infarction (%)	191 (26.8)	54 (37.0)	0.013
Hyperlipidemia (%)	320 (44.9)	68 (46.6)	0.708
Systolic blood pressure (mmHg)	120 ± 15	126 ± 15	0.016
Diastolic blood pressure (mmHg)	70 ± 8	72 ± 9	0.47
Ejection fraction (%)	65.59 ± 10.09	63.38 ± 9.80	0.105
Serum creatinine (mg/dl)	0.98 ± 0.30	1.18 ± 0.50	<0.001
Serum creatinine >1.3 mg/dl (%)	64 (8.97)	37 (25.3)	<0.001
NYHA class	1.75 ± 0.68	1.72 ± 0.69	0.58
Mean No. of antihypertensive drugs	1.60 ± 0.94	2.13 ± 0.87	<0.001
ACE inhibitor (%)	393 (55.1)	109 (74.7)	<0.001
β-Blocker (%)	518 (72.7)	124 (84.9)	0.001
Calcium channel blocker (%)	159 (22.3)	47 (32.2)	0.011
Diuretics (%)	62 (8.7)	25 (17.1)	0.003
Severity of coronary artery disease			<0.001
Normal	291 (40.8)	10 (6.8)	
1 vessel	138 (19.4)	12 (8.2)	
2 vessel	96 (13.5)	29 (19.8)	
3 vessel	188 (26.2)	95 (65.1)	
Left main	41 (5.8)	14 (9.6)	0.088

ARAS, atherosclerotic renal artery stenosis; NYHA, New York Heart Association; ACE, angiotensin converting enzyme.

Table 4. Multivariate Logistic Regression Analysis

Variable	β	Wald χ ²	p value	OR	95% CI
Age	0.75	32.79	<0.001	1.07	1.05–1.11
Severity of coronary artery disease	0.76	59.12	<0.001	2.13	1.76–2.95
Peripheral vascular disease	0.58	5.31	0.021	1.79	1.09–2.95

OR, odds ratio; CI, confidence interval.

Table 5. Serum Creatinine and Medication Taken by the Patients with Different Renal Artery Patency at the Time of Aortography

	Severe	Moderate	Mild	Insignificant	Normal	Statistics	p value
Patency index	<0.5	0.5–1	1–1.5	>1.5	2		
No. of patients	21	41	89	51	657		
Age (year) [#]	68.4 ± 9.2	68.4 ± 6.8	66.6 ± 9.1	64.7 ± 8.9	58.6 ± 10.6	24.5 [§]	<0.001
Serum creatinine (mg/dl) [*]	1.39 ± 0.58	1.22 ± 0.56	1.10 ± 0.44	1.07 ± 0.37	0.97 ± 0.30	0.194 ^{**}	<0.001
Mean No. of antihypertensive drugs [#]	2.38 ± 0.74	2.12 ± 0.93	2.06 ± 0.87	1.88 ± 0.95	1.58 ± 0.94	11.48 [§]	<0.001
ACE inhibitor (%) [†]	18 (85.7)	34 (82.9)	61 (68.5)	35 (68.6)	354 (53.9)	0.17 [‡]	<0.001
β-Blocker (%) [†]	17 (80.1)	34 (82.9)	78 (87.6)	41 (80.4)	473 (71.9)	0.12 [‡]	0.01
Diuretics (%) [†]	6 (28.6)	6 (14.6)	8 (8.9)	14 (27.4)	53 (8.1)	0.18 [‡]	<0.001
Calcium channel blocker (%) [†]	8 (38.9)	13 (31.7)	26 (29.2)	11 (27.5)	148 (22.5)	0.83 [‡]	0.207
Angiotensin receptor blocker (%) [†]	1 (4.8)	1 (2.4)	5 (5.6)	1 (2.0)	6 (0.9)	0.12 [‡]	0.014

[#] One-way ANOVA. [§] F value. ^{*} Spearman's correlation test. ^{**} Spearman's ρ. [†] Contingency of χ² test. [‡] Contingency coefficient. ACE, angiotensin converting enzyme.

Table 6. Association between Drug Usage and Serum Creatinine Levels Stratified by Severity of ARAS

Covariates in model	Severe (n = 21)		Moderate (n = 41)		Mild (n = 89)		Insignificant (n = 51)	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI
ACE inhibitor	1.14*	0.16–2.12	0.56	- 0.64–1.76	- 0.15	- 0.80–0.51	0.29	- 0.30–0.79
β -Blocker	0.984	- 2.02–0.66	0.44	- 0.27–1.14	- 0.25	- 1.25–0.63	0.64	- 0.52–1.80
Calcium channel blocker	1.60†	0.77–2.43	- 0.01	- 6.38– - 0.66	0.11	- 0.39–0.60	- 0.16	- 0.72–0.47
Diuretic	1.00*	0.21–1.78	- 0.50	- 1.01–0.02	- 0.22	- 0.68–0.23	- 0.33	- 0.92–0.26

β signifies the predicted serum creatinine level associated with different drug. All covariates were adjusted for age, diabetes, hypertension and congestive heart failure. β value and 95% CI of group of normal renal artery were not showed. Angiotensin receptor blocker was not analyzed due to infrequent use in this population. ARAS, atherosclerotic renal artery stenosis; CI, confidence interval; ACE, angiotensin converting enzyme. * $p < 0.05$, † $p < 0.001$.

ARAS were taking ACE inhibitors. The greater clinical utilization of these potent antihypertensive agents in this population may indicate that hypertension is relatively more difficult to control in patients with ARAS, or that comorbid conditions (*i.e.*, previous myocardial infarction) requiring ACE inhibitors are often present in patients with ARAS. In support of this association, the patients with ARAS were significantly older, and the prevalence of diabetes mellitus, peripheral vascular disease, previous myocardial infarction, renal insufficiency and coronary artery disease was significantly higher in patients with than in those without ARAS.

In their study, Van de Ven *et al.* (14) found that all patients with severe bilateral renovascular disease ($\geq 50\%$), or with severe renovascular disease in a single kidney, showed a 20% or greater elevation of plasma creatinine. Such an increase also occurred, though less commonly, in patients with lesser degrees of bilateral and unilateral renovascular disease. Clinically, severe renal artery lesions can cause renal dysfunction (1), and ARAS is common in patients with renal dysfunction and concomitant cardiovascular disease (15). It is clear that the degree of arterial stenosis in ARAS does worsen with time, and renal function in patients with ARAS often deteriorates over time (12). In reality, however, the renal function decline seen in ARAS owes more to chronic massive ischemia (16) or atherosclerotic nephropathy—both of which are related to age, scarring, micro-embolisation and hypertension (17). A complex interaction develops between main vessel occlusive disease and microvascular injury, in part associated with cholesterol and activation of the oxidative pathway (18). And more important is the potential for activation of fibrogenic cytokines to induce irreversible tissue damage (19). In addition, lowering blood pressure with any medication reduces renal perfusion pressure and can cause a deterioration of renal function in patients with severe renovascular disease (20). On the other hand, ACE inhibitors are specifically indicated for use in patients with chronic kidney disease in the JNC 7 (21). Therefore, the cause of the higher serum creatinine level in patients with ARAS who were taking ACE inhibitors is likely to be multifactorial.

The deleterious effect of ACE inhibition on glomerular filtration rate (GFR) in patients with bilateral renal artery

stenosis is well recognized (22, 23). It has been proposed that candidates for ACE inhibitor therapy be screened for occult ARAS before therapy (24, 25). However, most patients with heart failure and a vast majority of elderly patients with generalized atherosclerosis have already started treatment with ACE inhibitors. It is not possible to screen all such patients. It is thus important to remain vigilant for patients at risk and to monitor closely both serum creatinine and potassium during initiation of therapy (26), especially in patients with suspected ARAS or older patients with generalized atherosclerosis. Further studies will be needed to observe the prevalence of severe consequences of acute renal failure requiring dialysis treatment in this population, and to determine whether renal revascularization offers tangible benefits—*i.e.*, major improvement in blood pressure control or renal function, and decreased subsequent cardiovascular morbidity and mortality—in this subset of patients (27, 28).

In conclusion, we have demonstrated in this series that most patients with incidentally detected renovascular disease were treated with ACE inhibitors prior to the diagnosis of ARAS; and that ACE inhibitors are used more commonly with increasing degree of severity of ARAS. High risk patients, who might develop acute renal failure if they took ACE inhibitors and should be closely monitored, were found to be older patients with generalized atherosclerosis.

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