Progression of atherosclerotic renovascular disease: a prospective population-based study

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Objective: **Previous reports from select hypertensive patients suggest that atherosclerotic renovascular disease (RVD) is rapidly progressive and associated with a decline in kidney size and kidney function. This prospective, population-based study estimates the incidence of new RVD and progression of established RVD among elderly, free-living participants in the Cardiovascular Health Study (CHS).**
Method: **The CHS is a multicenter, longitudinal cohort study of cardiovascular risk factors, morbidity, and mortality among men and women aged >65 years old. From 1995 through 1996, 834 participants underwent renal duplex sonography (RDS) to define the presence or absence of significant RVD. Between 2002 and 2005, a second RDS study was performed in 119 participants (mean study interval, 8.0 ± 0.8 years). Significant RVD was defined as hemodynamically significant stenosis (renal artery peak systolic velocity [RA-PSV] exceeding 1.8 m/s) or renal artery occlusion. Prevalent RVD was significant RVD at the first RDS, and incident disease was defined as new significant RVD at the second RDS. Significant change of RVD was defined as a change in RA-PSV of greater than two times the standard deviation of expected change over time, regardless of hemodynamic significance or progression to renal artery occlusion.**
Results: **The second RDS study cohort included 119 CHS participants with 235 kidneys (35% men; mean age, 82.8 ± 3.4). On follow-up, no prevalent RVD (n = 13 kidneys; 6.0%) progressed to occlusion. Twenty-nine kidneys without RVD at the first RDS demonstrated significant change in PSV at the second RDS; including nine kidneys with new significant RVD (8 new stenoses; 1 new occlusion). Controlling for within-subject correlation, the overall estimated change in RVD among all 235 kidneys was 14.0% (95% confidence interval [CI], 9.2% to 21.4%), with progression to significant RVD in 4.0% (95% CI, 1.9% to 8.2%). Longitudinal increase in diastolic blood pressure and decrease in renal length were significantly associated with progression to new (ie, incident) significant RVD but not prevalent RVD.**
Conclusions: **This is the first prospective, population-based estimate of incident RVD and progression of prevalent RVD among free-living elderly Americans. In contrast to previous reports among select hypertensive patients, CHS participants with a low rate of clinical hypertension demonstrated a significant change of RVD in only 14.0% of kidneys on follow-up of 8 years (annualized rate, 1.3% per year). Progression to significant RVD was observed in only 4.0% (annualized rate, 0.5% per year), and no prevalent RVD progressed to occlusion. (J Vasc Surg 2006;44:955-63.)**

There are no prospective, population-based studies that define the natural history of atherosclerotic renovascular disease (RVD). Available information regarding RVD is extrapolated from angiographic case series and ultrasound examinations from retrospective reviews or from prospective studies of select hypertensive patients. The quality of these studies and the interpretation of their data vary widely. Most commonly, authors consider anatomic progression of RVD a certainty, one that is associated with an inevitable decline in kidney size and kidney function. This view is frequently cited to support intervention for RVD whenever discovered.[1]

In contrast to previous reports, this prospective, population-based study estimated the incidence of new RVD and the progression of established RVD among participants in the Cardiovascular Health Study (CHS). The CHS is a longitudinal, population-based study of coronary heart disease and stroke in elderly men and women.[2] Renal duplex sonography (RDS) was applied to the CHS Forsyth County, North Carolina, cohort to determine the presence of RVD in these elderly, free-living, community-dwelling participants.[3] A second RDS was applied to surviving CHS participants 8 years later. The specific points of interest included (1) the incidence of new significant RVD defined during the study period, (2) the progression of established RVD on follow-up, and (3) the relationship of incident and prevalent RVD with changes in blood pressure, excretory renal function, and kidney length.

METHODS

Subjects. The incidence of new RVD and the progression of established RVD were estimated by two RDS exam-

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inations among the Forsyth, North Carolina cohort of the CHS. The CHS is an observational, population based longitudinal study of risk factors for coronary heart disease and stroke in adults aged >65 years.[2] The sampling strategy, baseline characteristics, atherosclerotic risk factors, and clinical examination have been described in detail.[4-10] Briefly, the primary aim of the CHS is to identify and assess factors related to the onset of coronary heart disease and stroke in this age group. The CHS study design included four field centers from four different US communities (Forsyth County, NC; Sacramento County, Calif; Washington County, Md; and Allegheny County, Pa) to recruit and examine not less than 1250 men and women during the first study year beginning June 1989, for a total of at least 5000 subjects study wide.

Each community sample was obtained with a two-step process from Medicare eligibility lists of the Health Care Financing Administration. These lists were sampled from a random start to produce sampling frames of approximately 5000 potential participants in each community. Random samples were selected from the sampling frames with a customized program to produce a Forsyth County cohort with a 62:38 female/male ratio in each of four age strata, with the following distribution within each baseline strata: 65 to 69 years, 30%; 70 to 74 years, 29%; 75 to 79 years, 19%; and >80 years, 22%.

Those eligible to participate included all persons living in each sampled household who were aged ≥65 years, were not institutionalized, were expected to remain in the area for at least a 3-year follow-up period, were able to give informed consent, and did not require a proxy respondent at baseline. Excluded were individuals who were undergoing hospice treatment, radiation therapy or chemotherapy for cancer, or who were wheelchair bound. The overall Forsyth County participation rate was 61%. Those initially sampled comprised 70% of the overall CHS cohort, with the remaining 30% recruited from a shared household with the index participant.[11]

Between September 1992 and May 1993, 236 additional African American participants were recruited into the Forsyth County cohort with the same sampling and recruitment techniques. These techniques provided the following Forsyth County CHS enrollment distribution within each age strata: 65 to 69 years, 32%; 70 to 74 years, 29%; 75 to 79, 22%; and >80 years, 17%.

Participants from the Forsyth county cohort of the CHS were recruited for the first RDS between January 1995 and February 1997. The presence of significant RVD, defined as >60% diameter-reducing renal artery stenosis or occlusion, was estimated using RDS. These results were used to define the prevalence of significant RVD. Attempts were made to contact all 610 surviving Forsyth County CHS participants using contact information obtained from the last annual CHS follow-up exam in 1999. Of the 610, 494 were contacted and 119 (20%) were recruited for the second RDS between July 2002 and June 2005. Of the remaining 491 CHS participants, 375 deferred or declined to participate because of prior poor health or other reasons, and 116 participants could not be contacted. Both studies were approved by the Wake Forest University Human Subjects Review Committee.

Renal duplex sonography. As an ancillary study to the CHS, funded through the National Institute of Diabetes, Digestive and Kidney Diseases, and the General Clinical Research Center (GCRC), RDS was used to study CHS participants in the Forsyth County cohort. At the first RDS examination, participants scheduled for routine annual examination were contacted by telephone and informed of the ancillary project. Most of the first RDS studies were performed with the annual examination. Survivors among the Forsyth County CHS cohort were contacted by telephone and informed of the second RDS. The second RDS was performed through the GCRC.

The technique of RDS has been described in detail.[3,12-13] Briefly, after an overnight fast and written informed consent, the CHS participant was placed in the supine position and a 2.25 MHz or 3.0 MHz ultrasound probe was coupled to the abdominal skin with acoustic gel 3 or 4 cm inferior to the xiphoid process. Sagittal B-mode scan images were obtained of the upper abdominal aorta, celiac axis, and superior mesenteric arteries. Identification of these three arteries was confirmed by the characteristic fasting waveforms from each vessel.

After a sagittal aortic and superior mesenteric artery signal was obtained, the probe was rotated 90° to obtain a B-mode scan image of the aorta and proximal superior mesenteric artery in cross-section. The left renal vein was identified in longitudinal section. Using the left renal vein as a reference, the aortic origins of the main renal arteries were identified. While maintaining an angle of insonation of <60°, Doppler samples were taken from each renal artery from aortic origin to the renal hilum, for a total of approximately 10 Doppler sample sites per renal artery.

Renal artery peak systolic velocity (RA-PSV) and end-diastolic velocity were estimated from the spectral analysis of the Doppler-shifted signals. After Doppler interrogation in the supine position, RA-PSV was estimated from a flank approach with the participant in right or left lateral decubitus positions. B-mode scan imaging of each kidney determined the greatest longitudinal kidney length. The RDS study was considered negative or positive for *significant RVD* or inadequate for interpretation according to the following criteria: (1) RDS was negative for significant RVD when RA-PSV from aortic origin to renal hilum was <1.8 m/s, (2) RDS was positive for hemodynamically significant RVD when there was a focal increase in RA-PSV ≥1.8 m/s (≥60% renal artery diameter-reducing stenosis) or no Doppler signal was obtained from an imaged artery (renal artery occlusion), (3) RDS was technically inadequate for interpretation when RA-PSV could not be determined from the aortic origin to the renal hilum.

As a pilot study, we reviewed RDS results from 108 patients with repeat studies performed within a 12-month period at the Clinical Vascular Laboratory at Wake Forest University School of Medicine. The PSV proved highly reliable (Pearson correlation coefficient, $r = 0.95$). RDS

interpretation by established criteria for the presence of absence of hemodynamically significant renal artery stenosis or occlusion demonstrated complete agreement. These data demonstrated that PSV and interpretation of PSV for the presence or absence of significant RVD have excellent repeatability.

This study design used previously published estimates of disease progression to presume a 5% per year progression.[14] To detect progression of 2.5% per year with 80% power required 300 CHS participants for two RDS examinations over the 8-year period of study. *Prevalent RVD* was present at the first RDS. *Incident disease* was defined as new hemodynamically significant stenosis or occlusion on follow-up at second RDS. *Significant change of RVD* was considered present when PSV changed more than two times the estimated standard deviation of the mean change over time or RDS progressed to hemodynamically significant RVD.

Statistical analysis. After study data were keyed and verified, RDS results were matched with participant data provided by the CHS Coordinating Center. Variability of the expected longitudinal change in PSV was estimated using data collected in the Clinical Vascular Laboratory on an independent group of 435 patients undergoing serial RDS without intervention. From these 435 patients, 281 age-matched patients (mean 75.6 ± 6.5 years) underwent two or more RDS examinations (mean, 2.9 RDS; median, 2 RDS) between 1997 and 2003 (median follow-up, 2.0 years; range, 0.2 to 6.0 years). Random coefficient regression models were applied to this age-matched patient group to estimate the mean and variance of the annualized change in maximum RA-PSV.[15]

To estimate the expected progression for an individual CHS participant, the annualized rate estimated from the reference cohort was multiplied by the time (in years) between the initial and follow-up CHS RDS exams. By convention, a change in PSV over the time course exceeding two times the estimated standard deviation of the mean change in absolute value (renal artery [RA]-PSV change of ≥45 cm/s) was considered significant. Progression to renal artery occlusion was also considered significant.

Kidney-based estimates of change in RVD and univariate examination of associations between risk factors and change in RVD were obtained using generalized estimating equation models that controlled for within-person correlation.[16] Changes in renal length were examined using repeated measures linear regression models that controlled for within-person correlation.[17]

RESULTS

Between January 1995 and February 1997, 1245 Forsyth County participants returned to the CHS Field Center for annual examination. Among returning participants, 870 gave consent for their first RDS, providing 69.9% recruitment efficiency. The comparison of CHS participants with nonparticipants and the prevalence of RVD among recruited CHS participants have been described in detail.[3,11,18] Of 834 participants successfully studied with RDS, 57 (6.8%) had significant RVD at the first examination. Significant RVD was unilateral in 50 patients and bilateral in seven. Of 64 renal arteries with significant RVD, 57 kidneys had hemodynamically significant renal artery stenosis and seven arteries were occluded. Prevalent RVD had no significant association with either gender or ethnicity, but did demonstrate a significant and independent association with increasing participant age, decreased high-density lipoprotein cholesterol, and increased systolic blood pressure.[3]

Of the 834 technically satisfactory first RDS examinations, 610 surviving CHS participants were invited to return for a second RDS examination. Between 2002 and 2005, 119 (14.3%) from the first RDS cohort returned for a second RDS examination (mean study interval, 8.0 ± 0.8 years). The repeat study cohort was a mean age of 82.8 ± 3.4 years at the second RDS examination. The group included 65% women and 35% men, and 77% were white and 23% were African American. Table I defines atherosclerotic risk factors that were examined and compares surviv-

Table I. Demographics and baseline atherosclerotic risk factors among 610 Cardiovascular Health Study participants

*Variable/Definition**	*Recruited (n = 119)*	*Non-recruited (n = 491)*	P
Age in years†	81.9 ± 3.5	83.3 ± 4.4	<.001
Race			.870
African-American (%)	27 (33)	108 (22)	
White or other (%)	92 (77)	383 (78)	—
Gender			.781
Female (%)	77 (65)	311 (63)	—
Male (%)	42 (35)	180 (37)	—
Blood pressure (mm HG)			
Systolic	134 ± 19	136 ± 20	.489
Diastolic	72 ± 9	72 ± 10	.775
Clinical hypertension SBP >60 mm Hg *or* DBP >95 mm Hg *or* Anti-hypertensive meds (%)	14 (12) 65 (55)	64 (13) 251 (51)	.710 .493
Statin use (%)	10 (8)	28 (6)	.274
ACE inhibitor use (%)	6 (5)	51 (10)	.072
Diabetes mellitus (%)‡	19 (16)	71 (14)	.678
Cigarette smoking† Ever	49 (41)	222 (45)	0.427
Hypercholesterolemia Total cholesterol (mg/dL)	197 ± 31	205 ± 38	0.020
Elevated LDL-C (mg/dL)	123 ± 32	128 ± 33	0.140
Decreased HDL-C (mg/dL)	53 ± 15	54 ± 13	0.281
Obesity† (%) >130% ideal body weight	37 (31)	156 (32)	0.886

SBP, Systolic blood pressure; *DPB,* diastolic blood pressure, *ACE,* angiotensin converting enzyme; *LDL-C,* low-density lipoprotein cholesterol; *HDL-C,* high-density lipoprotein cholesterol.

*Data are presented as % or mean ± SD.

†At November 1, 2002.

‡Diabetes mellitus is defined as fasting glucose >140 mg/dL *or* 2-hr post-glucose load >200 mg/dL *or* insulin or oral hypoglycemic agent.

Table II. Retrospective angiographic studies of medically managed atherosclerotic renal artery stenosis

Author	*Year*	*Patients (n)*	*Renal arteries (n)*	*Mean follow-up (months)*	*Anatomic progression (% patients)*	*Progression to occlusion (% arteries)*	*Blood pressure change*	*Decrease in renal length (% patients)*	*SCr increase (% patients)*	*GFR decline (% patients)*
Wollenweber[19]	1968	109	252	42	59	—	—	—	—	—
Meaney[20]	1968	39	78	34	36	4	—	—	—	—
Schreiber[21]	1984	85	126	52	44	11	NS	46*	38	—
Tollefson[22]	1991	48	—	54	53†	9†	—	—	—	—
Crowley[23]	1998	1178	—	30	11	0.3	—	—	‡	—
Chabova[24]	2000	68	—	39	—	—	NS	—	15	—

SCr, Serum creatinine; *GFR,* glomerular filtration rate; *NS,* not significant.
*1.5 cm discrepancy in renal length.
†Percentage of renal arteries with baseline stenosis or stenosis in follow-up.
‡SCr increased among patients with anatomic progression to >75% stenosis.

ing CHS participants who returned for a second RDS study with those who did not.

Among 235 kidneys with a technically satisfactory RDS examination, significant RVD was present at the first examination in 13 kidneys (6%; 95% confidence interval [CI], 3.2% to 11.2%). No significant change of prevalent RVD was found on the second RDS study. No ≥60% diameter-reducing renal artery stenosis at the first examination progressed to occlusion on the second RDS.

At the second RDS, new hemodynamically significant RVD was identified in nine kidneys (incident disease: 8 new renal artery stenoses; 1 new renal artery occlusion). A significant increase in RA-PSV was observed in 29 kidneys, including the nine cases of incident RVD. A significant decrease in PSV was observed in 23 kidneys, including six kidneys with velocities indicative of RVD (ie, PSV ≥1.8 m/s) at the initial RDS exam had PSV values ≤1.8 m/s at follow-up exam.

In patients with repeat RDS, mean blood pressure was 136 ± 21/80 ± 9 mm Hg at first RDS and 145 ± 23/72 ± 12 mm Hg at the second examination. Mean serum creatinine concentration was 1.0 ± 0.3 mg/dL at first RDS vs 1.3 ± 0.3 mg/dL at follow-up. This reflected a mean increase of 0.29 mg/dL (SEM, 0.04; 95% CI, 0.21 to 0.37). For 228 kidneys with length measurements at the first and second RDS, maximum pole-to-pole renal length decreased by 0.37 ± 1.17 cm (SEM, 0.9; 95% CI, 0.20 to 0.55). By univariate analysis, longitudinal increase in diastolic blood pressure ($P = .01$) and decrease in renal length ($P < .001$) were significantly associated with incident RVD (ie, progression to hemodynamically significant RVD) but not prevalent RVD or significant change in RVD that equated to <60% renal artery stenosis or occlusion.

DISCUSSION

To our knowledge, this is the first prospective, population-based estimate of incident RVD and progression of prevalent RVD among free-living, elderly Americans. Anatomic progression to hemodynamically significant RVD was observed in only 4% of participants on a mean follow-up of 8 years, an annualized progression rate of 0.5% per year. Moreover, no cohort participant with significant RVD at the first examination progressed to renal artery occlusion on follow-up.

These study results contrast sharply with retrospective angiographic case series, prospective angiographic studies, and prospective duplex studies, which describe progression of RVD. Retrospective reports of serial aortography and progression of RVD are summarized in Table II.[19-24] Considered collectively, the retrospective angiographic case series suggest that atherosclerotic lesions of the renal arteries demonstrate significant anatomic progression over relatively short periods of follow-up. On mean follow-up of 44 months, roughly one third of renal artery lesions demonstrated radiographic progression, and 10% progressed to occlusion.

Although these early studies describe a dramatic progression of RVD, the application of these observations to the population at large is probably flawed. Each of these studies reported on highly select groups of patients with significant clinical disease that warranted serial aortography. With the exception of the report by Crowley et al,[23] renovascular hypertension was suspected in nearly all of the subjects and worsening hypertension was the most frequent indication for repeat study. Consequently, it is doubtful that the same rate of progression would apply to all individuals with RVD.

Prospective angiographic clinical studies of RVD are summarized in Table III.[25-29] More than 25 years ago, Dean et al[24] reported on patients with renovascular hypertension randomized to medical management or surgical revascularization. Randomized to medical management were 41 patients with high grade atherosclerotic renal artery stenosis and renovascular hypertension proven by renal vein renin assay, or split renal function studies, or both. These patients were monitored for an average of 44 months, during which 17 patients (41%) crossed over to the surgical arm. Although 15 of the 17 patients had controlled hypertension, each patient had declining renal function as defined by a 10% loss of renal length, a 100% increase in serum creatinine level, or a 50% reduction in measured glomerular filtration rate (GFR) or creatinine clearance (CrCl). Among the patients treated medically, 22 (54%) had no increase in serum creatinine, 47% of those

Table III. Prospective angiographic natural history studies of atherosclerotic renal artery stenosis

	Year	Patients (n)	Renal arteries (n)	Mean follow-up (months)	Anatomic progression (% patients)	Progression to occlusion (% arteries)	Blood pressure change	Decrease in renal length (% patients)	SCr increase (% patients)	GFR decline (% of patients)
Dean[25]	1981	41	—	44	17	12	—	37	46	3*
Plouin[26]	1998	26	—	6	—	—	−24/+12	—	NS	NS
Webster[27]	1998	30	—	—	13†	0†	−28/−16‡	—	NS	—
van Jaarsveld[28]	2000	50	100	12	20	5	−17/−7	—	NS	NS
Pillay[29]	2002	85	159	30	—	—	NS	NS	§	—

SCr, Serum creatinine; *GFR*, glomerular filtration rate; *NS*, not significant.
*>50% increase, data for 30 patients.
†Of eight patients with serial angiography.
‡From referral to last follow-up.
§Unilateral group had significant increase, bilateral group did not.

Table IV. Prospective duplex sonography natural history studies of atherosclerotic renal artery stenosis

	Year	Patients (n)	Kidneys (n)	Mean follow-up (months)	Anatomic progression (% arteries)	Progression to occlusion (% arteries)	Blood pressure change	Decrease in renal length >1 cm (% arteries)	SCr increase (% patients)	GFR decline (% patients)
Zierler[30]	1994	80	134	13	8*	3	—	8	—	—
Zierler[14]	1996	76	132	32	20	7	—	—	—	—
Caps[31]	1998	170	295	33	31	3	—	—	—	—
Caps[32]	1998	122	204	33	—	2	—	16	†	—

SCr, Serum creatinine; *GFR*, glomerular filtration rate.
*Progression at 12 months.
†Seven subjects with bilateral atrophy increased 0.33 mg/dL/year; remainder were NS.

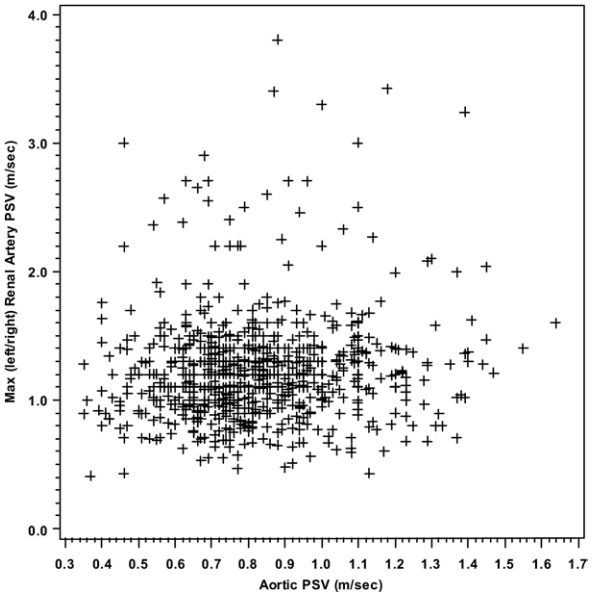
who underwent isotopic measurement of GFR or CrCl had no significant change, 37% had a <50% decline in GFR, and 2% (1 patient) experienced a >50% decline. Interestingly, four patients (13%) demonstrated improvement in measured CrCl or GFR when measured serially. Despite the severity of renovascular disease, the decline in renal function was variable, with 97% of patients losing <50% of measured GFR.

A recent prospective study by Pillay et al[29] described the change in blood pressure and serum creatinine among patients with RVD. In this multicenter, nonrandomized, observational study, 98 patients were noted to have ≥50% renal artery stenosis during aortography obtained to evaluate peripheral vascular disease. Complete data were available for 85 patients during a minimum 2-year follow-up. Among these, 64 patients with unilateral stenosis and 21 patients with bilateral stenosis were managed medically. Twelve patients with bilateral disease underwent angioplasty or open revascularization.

The overall 2-year estimated mortality was 32%. Mortality was the same for patients treated with renal artery intervention or treated medically. Most of the deaths were due to coronary artery disease; however, three (11%) died of complications from renal failure. Two of these deaths occurred in patients with unilateral RVD, suggesting renal parenchymal disease rather than ischemic nephropathy.

No change occurred in median blood pressure, number of antihypertensive agents, or renal size on follow-up among survivors. During the study period, a small but statistically significant increase in serum creatinine levels was observed in patients with both unilateral and bilateral RVD who underwent renal artery intervention. Patients with bilateral RVD treated medically had stable serum creatinine levels over 2 years. Although this study lacked a specific measure of glomerular filtration, it demonstrated stable renal length and stable serum creatinine levels, with controlled hypertension in medically managed patients who had bilateral RVD but no clinical indication for renal artery intervention.

The available prospective duplex ultrasound studies of RVD are summarized in Table IV. A series of consecutive reports described prospective investigation performed at the University of Washington.[14,30-32] These authors first reported on serial renal duplex sonography examinations performed on 80 patients with hypertension.[30] Renal arteries were classified according to four categories: normal, stenosis of <60%, stenosis of >60%, or renal artery occlusion. The rate of progression to >60% stenosis during 3 years of follow-up was 8% for renal arteries that were initially classified as normal and 43% for arteries initially classified as having <60% diameter-reducing stenosis. Incident renal artery occlusions were observed only in arteries previously classified as having >60% diameter-reducing stenosis. The 3-year risk for occlusion among the group was 7%. Factors associated with lesion progression included increasing patient age, increasing systolic blood pressure, smoking, female sex, and poorly controlled hypertension. Unfortunately, the number of study participants and the



Renal artery peak systolic velocity *(PVS)* vs aortic PSV for the 834 Forsyth County participants in the Cardiovascular Health Study.

low rate of progression of RVD in our report did not allow meaningful exploration of associations with significant change.

In this study from the University of Washington, a principle criterion for disease progression from <60% renal artery stenosis to >60% renal artery stenosis was an increase in the renal-aortic ratio (the ratio of RA-PSVs to aortic PSV) value to >3.5 among subjects with RA-PSV >1.8 m/s.[30] However, we have observed no association between RA-PSV and aortic PSV in the presence or absence of significant RVD in either population-based or clinical studies. Rather, the renal-aortic ratio can be considered an example of a spurious correlation. The association with the presence or absence of RVD resides entirely with RA-PSV. This interpretation is supported from 834 renal duplex exams performed initially among the Forsyth County CHS cohort (Fig).[3] Analysis from this cohort showed no relationship between aortic PSV and RA-PSV. Considered in light of these data, the patients with estimated stenosis of <60% based on a renal-aortic ratio of <3.5 but with a RA-PSV >1.8 m/sec could be considered to have significant RVD at baseline.

Perhaps the most informative prospective study of RVD using RDS was provided by Capps et al,[31] who described 5-year follow-up on 170 patients and 295 kidneys. In this extended report, disease progression was defined by a 100 cm/s increase RA-PSV or progression to occlusion. By these criteria, disease progression was detected in 91 (31%) of the renal arteries in this study. Nine arteries (3%) progressed to occlusion, and all of these were considered to be diseased at the baseline RDS. The authors created a model to predict the 2-year cumulative incidence of RVD progression. For renal arteries without ipsilateral or contralateral stenosis in a nondiabetic patient with systolic blood pressure (SBP) <160 mm Hg, the calculated risk of progression at 2 years was 7%. For arteries with high-grade ipsilateral and contralateral disease in a diabetic patient with a SBP >160 mm Hg, the risk was estimated at 65%. In contrast to these data among hypertensive patients, our population-based study suggests a much lower rate of significant change in RVD even though the criterion for significant change (ie, 45 cm/s change in RA-PSV) was less than half the criterion adopted by these authors.

The data reviewed in this report are frequently cited as rationale for intervention for RVD discovered incidentally during assessment of cardiac or vascular disease.[1] However, if one considers the potential value of prophylactic renal artery intervention in light of the associated risks in a normotensive individual without renal insufficiency, the unique benefit from prophylactic renal artery intervention is not justified.[33] Moreover, when considered in terms of the data provided by the current study, there appears to be no justification for prophylactic renal artery intervention, either as an open operative procedure performed in combination with aortic repair or as an independent catheter-based intervention.

Although this prospective study provides unique data, it suffers from a number of limitations. The index participants for CHS were selected through a two-step random process that included eligible members from the sampled individual's household. Although this strategy was adopted to enhance recruitment and retention, the final CHS cohort consisted of 70% of individuals initially sampled and 30% who shared the same household. Significant differences existed between randomly selected participants and those who chose not to participate in the CHS. The refusal rate was higher among women compared with men, although a notably higher percentage of women participated in the study.

The enrolled participants were younger, more highly education, more likely to be married, and less likely to be smokers.[11] This "healthy cohort effect" may have contributed to a decreased rate of progression of RVD and may have led to a potential survivorship effect. In previous reports, prevalent RVD has demonstrated significant and independent associations with both prevalent cardiovascular disease and subsequent adverse cardiovascular events.[18,34-35]

Finally, this prospective study was constructed with assumptions not met by observation. This study was originally constructed to include 300 participants, anticipating a 20% rate of progression during follow-up. However, a number of factors, including outdated follow-up information with the closure of the CHS, advanced participant age, and changes in participants' overall clinical conditions hampered our patient recruitment for the second RDS. Consequently, participant recruitment was less than half of that projected. When considered collectively, these limitations may have led to underestimation of RVD progression.

Another area of potential limitation with our methodology is the progression of RVD as defined by changes in RA-PSV. Progression of RVD at the subcritical level was

defined by changes in PSV greater than twice the standard deviation of predicted change (RA-PSV ≥45 cm/s). This predicted change in PSV was determined by using 281age-matched individuals with two or more studies over a median follow-up of 2 years. Ninety-five percent of these patients were hypertensive, 37% had a history of tobacco use, and men comprised higher percentage of participants (49%). Thus, the comparison group likely had a high rate of atherosclerotic vascular disease and may presumably have had a greater expected rate of RVD progression. Moreover, the variability of the estimated change in PSV among the independent cohort may be greater than that among the CHS group, thereby underestimating progression of RVD by this definition.

The observation of a significant decrease in RA-PSV in 23 kidneys deserves special comment. Because of the number of participants and the extended period of follow-up, three registered vascular technologists participated in the study. One technologist participated in both the first and second RDS examination, but two technologists participated in only one exam. Examination of interobserver differences at the first RDS suggested significant differences between technologists. Although the apparent bias associated with each sonographer was consistent, this bias may have contributed to an observed decrease in PSV when different sonographers performed the first and second RDS. In addition, significant technical improvements occurred in RDS during the course of study. Compared with the first RDS examination, the second study utilized technology that provided greater spatial resolution. Moreover, color-flow Doppler imaging, which was not available at the initial study, was used routinely to estimate the angle of insonation at the second study. Considered collectively, these differences may have contributed to the observed decline in RA-PSV.

Despite these potential limitations, the study of the Forsyth CHS cohort allows for longitudinal follow-up of a large, diffuse group of community-dwelling black and white men and women. As our population ages and as advanced imaging techniques define incidental vascular disease, anticipated RVD progression may be best estimated by change in RVD observed in this CHS cohort.

CONCLUSION

This prospective, population-based evaluation of prevalent RVD among free-living, elderly Americans suggests that the rate of significant changes in RVD is low. This low rate of progression, combined with no observed progression in significant RVD to renal artery occlusion, does not justify prophylactic intervention for asymptomatic renovascular disease in the elderly.

AUTHOR CONTRIBUTIONS

Conception and design: JP, ME, KH
Analysis and interpretation: JP, BC, KP, ME, KH
Data collection: BC, KP, ME
Writing the article: JP, BC, TC, ME, KH
Critical revision of the article: JP, TC, ME, KH
Final approval of the article: JP, BC, TC, KP, JS, ME, KH
Statistical analysis: BC, TC, JS
Obtained funding: KH
Overall responsibility: KH

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DISCUSSION

Dr R. James Valentine (Dallas, Texas). The purpose of this study was to determine the incidence and natural history of incidental renal artery stenoses in the general population of elderly patients. The study methods are sound, and the excellent technical results are commendable. Vascular surgeons should take note of the criterion used to define a hemodynamically significant renal artery stenosis. A peak systolic velocity of 1.8 m/s or more was chosen after many years of laboratory and clinical investigation, and it has been validated with renal arteriography. The Wake Forest group has one of the largest experiences with renal artery disease in the United States. The fact that 99% of their scans were technically satisfactory attests to their expertise in renal artery ultrasound.

The authors did a nice job of sampling the elderly population in the initial study, and recruiting limitations are acknowledged in the manuscript. However, only 14% of the original cohort returned for the second renal artery duplex examination, which represents less than 20% of the survivors in the Cardiovascular Health Study. This brings me to my first question: what happened to the other 80%? After 8 years, important differences may have emerged between the recruited and non-recruited subjects, challenging the notion that the study subjects represent the general population.

My second question relates to the 224 subjects who died after the initial study. At this meeting 13 years ago, we reported that incidental renal artery stenoses represent a marker for coronary artery disease in vascular patients. Did the deceased subjects have a higher incidence of renal artery disease than the survivors?

The take-home message from the present data is this: if you find an incidental renal artery stenosis in an elderly patient, leave it alone. Few lesions will progress. New, hemodynamically significant lesions can be expected to develop in less than 5% of patients. However, new lesions were significantly associated with an increase in diastolic blood pressure and a decrease in renal length. This brings me to my final question: could the affected patients have been identified on the basis of worsening hypertension or rising creatinine?

Dr Jeffrey Pearce. We practice and believe the results of the study support the continued observation and not intervention for incidentally found asymptomatic renal artery lesions, particularly in those patients with normal or well-controlled blood pressure and preserved renal function.

With regard to your first question, you correctly noted that 80% of the surviving participants did not return for a second duplex. With the use of our institution's GCRC, we attempted to contact all surviving participants. Unfortunately with closure of the CHS and lack of further annual follow-up exams, some of the contact information was inaccurate. Furthermore, many of these octogenarians are now living in nursing facilities, limiting their ability to participate in the exam.

Regarding the question on the prevalence of RVD in those surviving participants, I cannot give you a definitive answer but I might be able to shed some light on the issue. We have previously reported a twofold increase of subsequent cardiovascular events in participants with RVD, even when controlling for prevalent cardiovascular risk factors. Though the presence of RVD did not confer an overall survival disadvantage, we believe these participants are having more cardiac events. Thus, some of them may have succumbed in the study interval due to cardiac disease.

And then finally with regard to your question on patient screening for duplex examinations, we looked critically at those participants that had RVD in this cohort and none of these participants smelled of renovascular disease. None of them had severe hypertension. None of them had renal insufficiency. Therefore, none of these participants would have met our screening criteria, which is for those folks with worsening uncontrolled or severe hypertension or with progressive renal insufficiency.