Left Ventricular Morphology and Function in Patients with Atherosclerotic Renovascular Disease

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Atherosclerotic renovascular disease (ARVD) is associated with heart disease. There has been no systematic study of cardiac structure and function in patients with this condition. In this study, the epidemiology of cardiac changes and their relationship to renal function, renovascular anatomy, and BP are delineated. With the use of a cross-sectional design, 79 patients with ARVD and 50 control patients without ARVD underwent echocardiography and 24-h ambulatory BP monitoring. Clinical and biochemical data were collected. Results were analyzed according to renal function, residual renal artery patency, and unilateral or bilateral ARVD. Only 4 (5.1%) patients with ARVD had normal cardiac structure and function. Patients with ARVD (age 70.7 ± 7.5 yr; estimated GFR 36 ± 19 ml/min) had significantly more cardiovascular comorbidity (77.2 *versus* 42.0%; $P < 0.001$), greater prevalence of left ventricular (LV) hypertrophy (78.5 *versus* 46.0%; $P < 0.001$) and LV diastolic dysfunction (74.6 *versus* 40.0%; $P < 0.001$), and greater LV mass index (183 ± 74 *versus* 116 ± 33 g/m^2; $P < 0.001$) and LV end-diastolic volume index (82 ± 35 *versus* 34 ± 16 ml/m^2; $P < 0.001$) than control subjects. BP was similar for both patient groups. For patients with ARVD, neither renal function nor renal artery patency predicted a difference in echocardiographic or ambulatory BP monitoring parameters. Patients with bilateral ARVD had greater LV mass index and LV dilation than patients with unilateral disease. Patients with ARVD exhibit a high prevalence of cardiac morphologic and functional abnormalities at early stages of renal dysfunction. Such patients must be identified early in their disease course to allow risk factor modification.

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Atherosclerotic renovascular (ARVD) disease is common, associated with aging (1), and frequently with hypertension and renal failure. It often occurs in association with other atheromatous macrovascular disease, such as ischemic heart disease (2), peripheral vascular disease (3,4), aortic atheroma or aneurysm (5), and carotid artery disease (6). Coexistent symptomatic cardiac disease is common and can manifest in several ways. The relationship between coronary artery disease (CAD) and ARVD is already well defined, particularly since the large-scale epidemiologic studies performed at Duke University. Up to 30% of patients with symptomatic CAD are known to have ARVD (2), and significant ARVD is more likely to occur in patients with greater severity of CAD. Also, >10% of patients with ARVD may present with sudden-onset "flash" pulmonary edema (7), and ARVD is commonly seen in more chronic heart failure, with more than one third of elderly patients with congestive heart failure (CHF) having significant ARVD (8).

Patients with ARVD have a high mortality (9), which is due in part to their older age, underlying vascular disease, and, especially, cardiac disease (10). However, recent studies have also shown that proteinuria and severe renal failure are predictors of poor outcome in patients with ARVD (11,12). Proteinuria is a marker of hypertension-related renal parenchymal damage, and this, rather than purely the extent of proximal renal artery stenosis (RAS) lesions, is often the most important determinant of renal functional outcome (13,14). It is likely that microvascular disease also occurs in the heart of patients with ARVD and contributes to their "cardiomyopathy."

There is evidence for a strong synergistic relationship between heart and renovascular disease that influences the outcome of patients. First, the prognosis of patients with CAD is adversely influenced by the comorbid presence of ARVD (15), and mortality of these patients increases with increasing severity of the RAS lesions (16). Revascularization of high-grade RAS lesions in patients with flash pulmonary edema can prevent its recurrence (17), and there is emerging evidence that renal revascularization may lead to resolution of crescendo angina (18) and symptoms of chronic heart failure (19–21).

No previous studies have systematically investigated the cardiac changes that occur in patients with ARVD (22), but in a group of patients with such high cardiac morbidity and mortality, it is vital that our understanding be increased. In this cross-sectional study, we wished to delineate the epidemiology of cardiac morphologic and functional changes that occur in

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ARVD and to assess the relationship of these cardiac changes to renal function, renovascular anatomy, and BP.

The objectives of the study were to describe the following cross-sectional parameters and associations in patients with angiographically proven ARVD: (*1*) Left ventricular (LV) morphology and function, (*2*) Compare LV morphology and function with an otherwise similar control group that did not have ARVD, and (*3*) associations of LV morphology and function.

Materials and Methods

Patient Population

Patients who attended general nephrology and low creatinine clearance clinics at the Renal Centre at Hope Hospital from December 2000 to September 2002, had angiographic evidence of ARVD, and consented to take part were included in the study. ARVD was defined as RAS >50% or renal artery occlusion, as determined by digital subtraction angiography. Patients who were not followed up by the renal services at Hope Hospital after diagnosis were excluded from the study. Patients who had coexistent diabetic nephropathy (biopsy proven or with >1 g/d proteinuria with evidence of retinopathy or neuropathy) were excluded from the ARVD group. An unmatched random sample of patients who had a similar degree of renal dysfunction, age, and gender mix and had alternative renal diagnoses other than ARVD were also included in the study as a control group. Many of these patients had undergone renal angiography as part of the diagnostic work-up (*e.g.*, most of those with diabetes and all of those with bilaterally small kidneys of uncertain cause).

Ethical Approval and Consent

Ethical approval for the study was sought and received from The Salford and Trafford Research Ethics Committee.

Clinical Data Collection

The following data were collected prospectively from the time of patient inception in this cross-sectional study: (*1*) Age and demographics, (*2*) comorbidity (ischemic heart disease, CHF, stroke or transient ischemic attack, and peripheral vascular disease), (*3*) medications, (*4*) blood tests (serum creatinine, from which estimated GFR [eGFR] was determined, using the Cockcroft and Gault formula [23], hemoglobin, total serum cholesterol, parathyroid hormone [PTH], calcium-phosphate product), (*5*) 24-h urinary protein excretion, and (*6*) renal artery anatomy. Within 3 mo of consenting to enter the study, patients underwent 24-h ambulatory BP monitoring (24 h ABPM) and transthoracic echocardiography.

Echocardiographic Protocol

When fluid overload was present, we attempted to achieve clinical euvolemia before echocardiography. Echocardiography was performed according to American Society of Echocardiography guidelines, using a leading edge to leading edge approach Penn convention (24). Simpson's method of discs (25) was used to measure left ventricular (LV) ejection fraction (LVEF). Resting LV wall motion abnormalities were graded from 0 to 4 (0 = not seen, 1 = normal, 2 = hypokinetic, 3 = akinetic, 4 = dyskinetic), using conventional 16-segment analysis. The LV wall motion asymmetry index was defined as the sum of LV wall segment motion scores/number of wall segments visualized. LV mass was estimated using the Devereux formula (24) and indexed to body surface area (26). LV hypertrophy (LVH) was defined as a LV mass index (LVMI) of >130 g/m^2 for men and >110 g/m^2 for women. Other standard structural parameters included LV end-diastolic diameter (LVEDD; normal <5.9 cm for men and <5.2 cm for women) and volume (LVEDV; normal <166 ml for men and <129 ml for women). For analysis purposes, LVEDV was also indexed for body surface area. LV diastolic function (LVDF) was assessed by three measures: Transmitral E:A velocities ratio (normal range 0.7 to 3.1; 0.5 to 1.7 >70 yr of age), mitral flow E wave deceleration time (normal range 139 to 219 ms; 138 to 282 ms >70 yr of age), and isovolumetric relaxation time (IVRT; normal range 54 to 98 ms; 56 to 124 ms >70 yr of age). All echocardiograms were performed after 10 min of rest in the semisupine position by one of two senior cardiac technicians and were reported by one physician, who was blinded to other clinical data.

24-Hour ABPM

Noninvasive BP monitoring was performed over a 24-h period. BP was measured approximately every 30 min during the day interval (7:00 a.m. to 10:59 p.m.) and every hour during the night interval (11:00 p.m. to 6:59 a.m.). For the purposes of this study, a nocturnal dip in BP was defined as >10% dip in average systolic, diastolic, or mean arterial BP (MAP).

Definitions of Comorbid Vascular Disease

Ischemic heart disease (IHD) was defined as symptomatic angina, positive exercise stress test, coronary angiographic evidence of CAD, or history of previous myocardial infarction. Cerebrovascular disease (CVD) was defined as history, clinical signs, and/or radiologic confirmation of a transient ischemic attack or cerebrovascular accident. CHF was defined as history of shortness of breath on exertion with no other causation, orthopnea or paroxysmal nocturnal dyspnea, clinical signs of extra heart sounds, raised jugular venous pulse, bilateral pulmonary basal crackles, or x-ray evidence of pulmonary edema. Peripheral vascular disease (PVD) was defined as symptoms of intermittent claudication, previous surgery for lower limb arterial insufficiency and/or angiographic evidence of significant stenosis in one or more blood vessels that supply the lower limbs, or abdominal aortic aneurysm.

Data Analysis

For the purposes of differentiating the influences of renal dysfunction, renovascular anatomy, and other parameters upon cardiac morphology and function, patients with ARVD were grouped for analysis in three different ways: (*1*) By renal function, (*2*) by residual renal artery patency as determined by angiography, or (*3*) by unilateral or bilateral ARVD as determined by angiography

Grouping by Renal Function. Patients were grouped by baseline eGFR as follows: 10 to 25 ml/min, severe renal failure; 26 to 50 ml/min, moderate renal failure; or >50 ml/min, mild renal dysfunction.

Grouping by Renal Artery Patency. The severity of renal artery lesions as determined by digital subtraction angiography was represented by a residual proximal renal artery patency score (13) as follows: Patency <0.5, severe ARVD; patency 0.5 to 1.0, moderate ARVD; or patency 1.1 to 1.5, mild ARVD. The cross-sectional data sets were compared between ARVD and control group patients, and this comparison was also undertaken after stratification by eGFR. Data were also analyzed for the ARVD group alone according to renal artery patency score, whether patients had unilateral or bilateral renal artery disease, and after eGFR stratification.

Statistical Analyses

Data that followed a normal distribution (*e.g.*, age, eGFR, proteinuria, BP) were described in terms of the mean and SD. Quantitative data (*e.g.*, number of patients with IHD, CHF, CVD, PVD) were described as a percentage of the grouping. Data that followed a normal distribution

were compared by one-way ANOVA tests for significance. Nonnormal data were compared by Pearson χ^2 tests. Bivariate analysis was used to reveal correlations between normally distributed data. Binary logistic regression for the multivariate analysis of factors related to the presence of LVH was used to adjust for age, gender, renovascular anatomy, renal function, proteinuria, BP, hemoglobin, PTH level, and IHD. A statistical difference was considered significant at a level of $P < 0.05$.

Results

Characteristics of ARVD Study Population

Demographic and Clinical Data. Seventy-nine patients (46 men, 33 women) with ARVD entered the study. Their mean ± SD age was 70.7 ± 7.5 yr, eGFR was 36 ± 19 ml/min (range 11 to 93 ml/min), and proteinuria was 0.4 ± 0.5 g/24 h (range 0 to 2.5). Nineteen patients had diabetes (17 type 2 and two type 1). Mean 24-h BP was 140 ± 19/73 ± 13 mmHg (MAP 96 ± 14 mmHg). Only four patients demonstrated nocturnal BP dipping. Patients were prescribed a mean of 2.5 antihypertensive drugs (range 0 to 5). A total of 40.5% of patients were receiving either an angiotensin-converting enzyme inhibitor (ACE-I) or an angiotensin II receptor blocker (AIIRB); one patient was taking both classes of drug. Sixty-one (77.2%) patients had at least one cardiovascular comorbidity, and three patients had all four comorbidities (mean 1.5 per patient); hence, IHD was present in 32.9%, CHF was present in 48.1%, PVD was present in 45.6%, and CVD was present in 21.5%.

Echocardiographic Data. Only four (5.1%) patients had normal LVEF (>60%), no evidence of LV diastolic dysfunction, and no LVH. Mean LVEF was 53 ± 12%. Clinical symptoms of IHD were reported in 26 (32.9%) patients; resting LV wall motion abnormalities were actually detected in 47 (59.5%) patients. There was significant correlation between the LV wall motion asymmetry index and both LVEDD ($R^2 = 0.424$; $P < 0.001$) and LVEF ($R^2 = -0.722$; $P < 0.001$). Mean LVMI was 189.6 ± 78.7 g/m^2 (range 80.6 to 471.1 g/m^2) for men and 163.7 ± 57.9 g/m^2 (50.9 to 336.5 g/m^2) for women. LVH was present in 78.5% of the ARVD population: 36 (78.3%) men and 26 (78.8%) women. In a binary logistic regression model, the following factors correlated significantly with the presence of LVH: low eGFR, bilateral ARVD, high 24-h systolic BP, and high 24-h MAP. LV dilation was detected in 22 (27.8%) patients when defined by an increased LVEDD and 27 (34.2%) patients when defined by an increased LVEDV.

Fifty-nine (74.6%) patients had evidence of abnormal LVDF (10.1% had abnormalities of all three measured parameters of diastolic function, whereas abnormalities of E:A ratio, E velocity wave deceleration, or isovolumetric relaxation times were present in 35.4, 48.1, and 41.8%, respectively). There were significant correlations ($P < 0.001$) between LVEDD and left atrial size ($R^2 = 0.39$), LVEF ($R^2 = -0.30$), and LVEDV.

Comparison of ARVD Group with the Control Group

Fifty patients (31 men, 19 women) from the general nephrology and low creatinine clearance population made up the control group for the study. Primary renal diagnoses were diabetic nephropathy ($n = 14$), chronic glomerulonephritis ($n = 8$), chronic pyelonephritis ($n = 6$), bilateral small kidneys of unknown cause (in whom ARVD had been excluded; $n = 6$), obstructive uropathy ($n = 5$), interstitial nephritis ($n = 3$), ANCA-associated vasculitis ($n = 2$), autosomal dominant polycystic kidney disease ($n = 2$), multicystic kidney disease ($n = 2$), renal tuberculosis ($n = 1$), and postacute chronic renal failure ($n = 1$). There was considerably less cardiovascular comorbidity in the control compared with the ARVD group (IHD 22%, CHF 18%, PVD 16%, and CVD 8%; overall prevalence 42%). Table 1 shows the comparison between the control and ARVD groups for other demographic and investigative data. Mean ± SD age (68.5 ± 8.8 yr), eGFR (33 ± 16 ml/min; range 10 to 81 ml/min), 24-h BP (138 ± 17/75 mmHg ± 12; MAP 97 ± 12 mmHg), and antihypertensive medication usage all were similar to the ARVD group, but proteinuria (1.4 ± 2.0 g/24 h; range 0 to 7.9 g/24 h), and ACE-I/AIIRB use (56 *versus* 40.5%; NS) were greater in the control group. Echocardiographic assessment revealed that LVMI, LVEDV, and prevalence of LVH and abnormal LVDF all were significantly greater in patients with ARVD than in the control group.

Comparison of Patients with Diabetes in the ARVD and Control Groups

A large proportion of the study population had diabetes, and in view of the accepted increased cardiovascular comorbidity of these patients, they were subjected to a separate subanalysis. There were 19 patients with diabetes in the ARVD group and 15 in the control group, 14 of whom had a diagnosis of diabetic nephropathy. There were no differences in age, eGFR, and BP between these subgroups or any differences in cardiovascular comorbidity.

The echocardiographic changes within this subgroup analysis reflected those of the main study comparison; patients with diabetes in the ARVD group had a significantly higher prevalence of LVH (73.7 *versus* 26.7%; $P < 0.02$) than those in the control group, with greater LVMI (169.5 ± 68.0 *versus* 109.3 ± 30.5 g/m^2; $P < 0.01$) and greater LVEDVI (83.5 ± 7.4 *versus* 30.7 ± 12.6 ml/m^2; $P < 0.001$). Patients with diabetes and ARVD also had longer IVRT (106 ± 45 *versus* 79 ± 24 ms; $P < 0.05$) and higher prevalence of diastolic dysfunction abnormalities.

Analysis of ARVD Patients by Renal Function Grouping

Table 2 displays demographic, clinical, BP, and echocardiographic data of patients with ARVD for the three renal functional subgroups. Compared with the group with mild renal failure, the age and the level of proteinuria of the other two patient groups were significantly higher. As would be expected, hemoglobin was significantly higher (134 ± 14 *versus* 125 ± 19 and 117 ± 19 g/L; $P < 0.001$) and PTH was significantly lower (75.2 ± 74.5 *versus* 92.5 ± 61.0 and 201.1 ± 159.0 pg/ml; $P < 0.001$) in the patients with mild renal dysfunction as compared with those with moderate and severe renal failure, respectively. There were no significant differences in BP across the three groups. There was a trend toward decreased LVEF with increasing severity of renal failure ($P = 0.06$), and LV wall motion asymmetry index was significantly increased in patients with severe renal failure (1.3 ± 0.4 *versus* 1.1 ± 0.2 and 1.2 ± 0.3 for moderate and mild renal dysfunction, respectively; $P < 0.05$). There was also a significantly higher prevalence of

Table 1. Demographic, BP, and echocardiographic data for ARVD and control groups[a]

	ARVD		P[b]	AOR (95% CI)[c] of ARVD	P[d]
	No (n = 50)	Yes (n = 79)			
Age (yr)	69 ± 9	71 ± 7	NS	1.04 (0.98 to 1.10)	0.2
Gender					0.9
male	38.0%	58.2%	NS	1	
female	62.0%	41.8%		0.93 (0.37 to 2.32)	
Diabetes	30.0%	24.1%	NS	0.81 (0.30 to 2.18)	0.7
Ischemic heart disease	22.0%	32.9%	NS	1.56 (0.55 to 4.42)	0.4
eGFR (ml/min)	33 ± 16	36 ± 19	NS	1.01 (0.98 to 1.03)	0.8
24-h urinary protein (g/d)	1.4 ± 2.0	0.4 ± 0.5	<0.001	0.21 (0.07 to 0.62)	0.005
24-h systolic BP (mmHg)	138 ± 17	140 ± 19	NS	1.02 (1.00 to 1.05)	0.07
24-h diastolic BP (mmHg)	75 ± 12	73 ± 13	NS	1.00 (0.96 to 1.04)	0.9
Hemoglobin (g/L)	124 ± 18	127 ± 20	NS	0.99 (0.97 to 1.02)	0.6
LV hypertrophy	46.0%	78.5%	<0.001	5.54 (2.04 to 15.02)	0.001
LVMI (g/m^2)	116 ± 33	183 ± 74	<0.001	1.04 (1.02 to 1.05)[f]	<0.001
LVEF (%)	57 ± 12	53 ± 12	NS	0.97 (0.94 to 1.01)	0.16
LVEDV index (ml/m^2)	34 ± 16	82 ± 35	<0.001	1.18 (1.09 to 1.28)	<0.001
Two or more LV diastolic function abnormalities[e]	12.0%	40.5%	<0.001	16.3 (3.9 to 68.5)	0.001

[a]AOR, adjusted odds ratio; ARVD, atherosclerotic renovascular disease; CI, confidence interval; eGFR, estimated GFR; LV, left ventricular; LVH, LV hypertrophy; LVMI, LV mass index; LVEF, LV ejection fraction; LVEDV, LV end-diastolic volume.
[b]Compared using the χ^2 test for categorical variable and ANOVA test for continuous variables.
[c]Using multiple logistic regression, with the presence (coded 1) or absence (coded 0) of ARVD as the dependent variable and adjusted for age, gender, diabetes, ischemic heart disease, eGFR, 24-h urinary protein, 24-h systolic BP, and hemoglobin.
[d]Adjusted for age, gender, diabetes, ischemic heart disease, eGFR, 24-h urinary protein, and hemoglobin.
[e]Categories were combined because no patient in the control group had three diastolic function abnormalities.
[f]Each 1-g/m^2 increment in LVMI is associated with a 4% increment in the AOR of ARVD.

Table 2. Demographic, BP, and echocardiographic data for ARVD patients stratified according to renal function[a]

Patients with ARVD (n = 79)	Preserved Renal Function	Moderate Renal Failure	Severe Renal Failure	P
n	16 (20.3%)	35 (44.3%)	28 (35.4%)	
Age (yr)	64.1 ± 7.5	72.5 ± 5.6	72.3 ± 7.7	<0.005
eGFR (μmol/L)	68 ± 12	36 ± 7	19 ± 4	<0.001
Proteinuria (g/L)	0.1 ± 0.2	0.3 ± 0.4	0.6 ± 0.6	<0.005
Overall systolic BP (mmHg)	134.6 ± 19.1	140.1 ± 16.1	141.4 ± 22.4	NS
Overall diastolic BP (mmHg)	71.6 ± 8.9	73.1 ± 13.7	72.7 ± 14.0	NS
Overall MAP (mmHg)	93.9 ± 9.9	96.9 ± 13.1	97.1 ± 16.1	NS
LVH (%)	68.8	82.8	78.6	NS
LVMI (g/m^2)	148.9 ± 45.5	184.9 ± 69.8	188.3 ± 82.5	NS
LVEF (%)	55.7 ± 14.0	54.9 ± 9.9	48.6 ± 11.9	NS
LVEDD (cm)	5.2 ± 0.6	5.4 ± 0.9	5.4 ± 1.2	NS
LVEDV (ml)	144.0 ± 44.3	134.5 ± 35.7	166.7 ± 87.7	NS
Cholesterol (mmol/L)	4.7 ± 1.2	4.7 ± 0.9	4.7 ± 1.4	NS
Calcium-phosphate product (mmol/L)	2.4 ± 0.6	2.5 ± 0.5	3.2 ± 0.8	<0.001

[a]MAP, mean arterial BP; LVEDD, LV end-diastolic diameter.

symptomatic CHF in patients with severe renal failure (57.1 *versus* 54.3 and 18.8% for moderate and mild renal dysfunction respectively; $P < 0.04$). There was no significant difference in the prevalence of echocardiographic LV diastolic functional abnormalities between the renal function groups. When control subjects and patients with ARVD were compared according to renal functional stratification, the LVMI of patients with ARVD was significantly increased for each renal function group (Table 3).

Table 3. LVMI and prevalence of LVH in ARVD patients compared with control patients and stratified according to renal functional grouping

	Control Group ($n = 50$)	ARVD Group ($n = 79$)	*P*
LVMI (g/m^2)			
preserved renal function	101.1 ± 24.9	148.9 ± 45.5	<0.05
moderate renal failure	110.8 ± 37.5	184.9 ± 69.8	<0.001
severe renal failure	126.7 ± 28.0	188.3 ± 82.5	<0.005
P (between renal function categories)	0.139	0.171	
Prevalence of LVH (%)			
preserved renal function	33.3	68.8	NS
moderate renal failure	43.5	82.8	<0.05
severe renal failure	52.4	78.6	NS
P (between renal function categories)	0.673	0.173	
Cholesterol (mmol/L)	4.4 ± 1.0	4.7 ± 1.1	NS
Calcium-phosphate product (mmol/L)	3.0 ± 1.0	2.7 ± 0.7	NS

Table 4. Demographic, BP, and echocardiographic data for residual renal artery patency groups and for unilateral and bilateral renal artery disease groups

Baseline ($n = 79$)	Mild ARVD	Moderate ARVD	Severe ARVD	*P*	Unilateral ARVD	Bilateral ARVD	*P*
n	26 (32.9%)	45 (57%)	8 (10.1%)		51 (64.6%)	28 (35.4%)	
Age (yr)	71.3 ± 5.0	70.4 ± 8.6	70.3 ± 8.6	NS	70.1 ± 8.1	71.9 ± 6.3	NS
eGFR (ml/min)	36.4 ± 20.6	35.9 ± 18.4	37.7 ± 20.9	NS	37.9 ± 19.2	33.3 ± 19.1	NS
Proteinuria (g/24 h)	0.4 ± 0.4	1.5 ± 0.3	0.5 ± 0.9	NS	0.3 ± 0.4	0.4 ± 0.6	NS
24-h systolic BP (mmHg)	141.0 ± 21.6	138.5 ± 19.1	139.6 ± 9.9	NS	141.5 ± 18.6	135.7 ± 19.6	NS
24-h diastolic BP (mmHg)	72.4 ± 14.1	72.1 ± 12.4	76.4 ± 12.0	NS	74.8 ± 13.1	68.9 ± 11.7	NS
24-h MAP (mmHg)	96.8 ± 15.2	95.6 ± 13.5	99.1 ± 9.1	NS	98.8 ± 13.7	92.1 ± 12.6	<0.05
LVH (%)	76.9	80.0	75.0	NS	74.5	85.7	NS
LVMI (g/m^2)	174.1 ± 49.7	181.5 ± 83.2	179.0 ± 67.3	NS	167.1 ± 58.8	200.2 ± 87.4	<0.05
LVEF (%)	49.2 ± 13.4	55.3 ± 9.9	50.93 ± 14.4	NS	53.5 ± 11.8	51.5 ± 11.8	NS
LVEDD (cm)	5.3 ± 0.6	5.4 ± 1.1	5.4 ± 0.8	NS	5.2 ± 0.8	5.8 ± 1.1	<0.01
LVEDV (ml)	150.9 ± 61.9	147.6 ± 65.9	139.0 ± 36.1	NS	141.4 ± 50.1	159.6 ± 78.3	NS
Cholesterol (mmol/L)	4.5 ± 1.0	4.8 ± 1.1	5.0 ± 1.5	NS	4.7 ± 1.1	4.7 ± 1.2	NS
Calcium-phosphate product (mmol/L)	2.6 ± 0.7	2.8 ± 0.8	2.5 ± 0.6	NS	2.7 ± 0.6	2.8 ± 1.0	NS

Analysis of ARVD Patients by Severity of Renovascular Disease

Table 4 displays data for the three different residual renal artery patency groups, showing that no differences existed in renal function, BP, and any of the echocardiographic parameters between the three groups, despite the differences in renovascular disease severity. Not surprising, the use of ACE-I and/or AIIRB was significantly higher in patients with mild ARVD (50%)—the majority of whom had unilateral renovascular disease—than in patients with moderate ARVD (35.6%) or severe ARVD (35.5%). When patients with bilateral ARVD were compared with those with unilateral disease, mean 24-h MAP was lower in the group with bilateral disease. Although the total number of antihypertensive medications was not significantly different between the two groups, the use of ACE-I and/or AIIRB again was greater in the unilateral than bilateral ARVD group (49.0 *versus* 35.0%). However, compared with the unilateral disease group, patients with bilateral disease did have a significantly higher LVMI and LVEDD, greater LV wall motion asymmetry index (1.29 ± 0.38 *versus* 1.14 ± 0.24; $P < 0.05$), and greater proportion of dysfunctional LV wall segments (number of abnormal segments/number of visualized segments, 0.26 ± 0.31 *versus* 0.13 ± 0.20; $P < 0.05$). There was no significant difference in the prevalence of echocardiographic LV diastolic functional abnormalities between the renal artery patency groups or between patients when classified into unilateral or bilateral renal artery disease. Accordingly, there was a significantly higher prevalence of symptomatic CHF in patients with bilateral compared with unilateral ARVD (67.9 *versus* 37.3%; $P < 0.01$).

Discussion

In this study, which systematically evaluated cardiac structure and function in patients with ARVD, almost all of the patients with ARVD were found to have abnormal hearts. Most particular, the prevalence of LVH, increased LVMI, and diastolic dysfunction all were considerably greater than in control subjects who did not have ARVD and had similar age and degrees of renal dysfunction.

In unselected renal failure populations, the prevalence of LVH increases with declining renal function (*e.g.*, 27, 31, and 45% in patients with GFR >50, 25 to 50, and <25 ml/min, respectively) (27). In this study, the LVH prevalence and increased LVMI in the ARVD population were far more striking, and LVMI was greater than that of the control population at each stage of renal failure evaluated. A range of cardiac abnormalities are known to affect patients with chronic kidney disease as they progress to dialysis, and these include concentric LVH in 39%, LV dilation in 27%, and systolic dysfunction in 25% (28). It seems that patients with ARVD represent a particularly high-risk group, as they have even greater prevalence of these cardiac abnormalities but at comparatively early stages of renal dysfunction.

Analysis of the diabetic subgroup within the study provided important insights. Despite similar cardiovascular comorbidity burdens, the patients with diabetes and ARVD had significantly greater LVMI and LVEDV than those who had diabetes and no ARVD. These results suggest that ARVD may have an independent role in the development of cardiac structural changes and cardiovascular risk in a patient subgroup that is already prone to endothelial dysfunction and CAD. Both LVH and LV dilation are adaptive mechanisms that occur in response to an excessive hemodynamic burden in an effort to restore a declining stroke volume. In the early stages, at least, LVH and dilation are potentially reversible. These changes may precede the onset of symptoms of heart failure by some years, and this may explain the relative preservation of LV ejection fraction in the ARVD population in this study. Nevertheless, almost half of the patients with ARVD were noted to have symptomatic heart failure, and LV dilation and diastolic dysfunction were noted in one third and three quarters of patients, respectively. It should be noted that describing "heart failure" in patients with moderate to severe renal failure is inherently difficult as fluid overload can produce many of the same signs and symptoms. Few studies have reported the prevalence of LV diastolic dysfunction in patients with renal disease. Although difficult to measure using noninvasive methods, diastolic dysfunction is thought to precede systolic dysfunction in most cardiac diseases. Furthermore, general population studies suggest that LV systolic function is normal in 30 to 40% of patients with symptomatic congestive cardiac failure (29), leading to the conclusion that isolated LV diastolic dysfunction is in itself a cause of clinical heart failure. Abnormalities of LV diastolic filling are also commonly found in patients with chronic LV systolic dysfunction; when present, they are associated with adverse prognosis (30). The high prevalence of abnormal LVDF that we describe in patients with ARVD therefore is likely to be of prognostic importance.

In the general nonrenal population, the prognosis of heart failure is poor, with 50% of patients with severe heart failure dying within 2 yr of diagnosis, equally from sudden death and progressive heart failure. Mortality rates are also high in the ARVD patient population, and deaths are mainly of cardiovascular origin. In one prospective study that followed 98 predialysis patients with ARVD for a mean of 28 mo, 36% of patients died (81% from a cardiovascular-related cause) (11). In a more recent epidemiologic study of the US Medicare population, it was apparent that most patients with ARVD die before they reach ESRD (death rate 166.3/1000 patient-years compared with commencement of dialysis in 28.8/1000 patient-years) (31). It is highly likely that the increased LVMI and prevalence of cardiac dysfunction (81% of patients had LV systolic or diastolic dysfunction) that we have described in the ARVD population are major contributors to this excess mortality risk, but coexistent CAD is also highly prevalent in these patients (2,8,15). A limitation of the current study is that patients were not investigated with coronary angiography, and so the relationship of the cardiac functional abnormalities to underlying CAD could not be ascertained. Nevertheless, one third of patients with ARVD had symptomatic IHD, with almost double this proportion having resting LV wall motion abnormalities. The interpretation of this is uncertain as wall motion abnormalities may have several causes, including asymptomatic CAD and small-vessel disease associated with LVH, and are also seen in patients with dilated cardiomyopathy (with angiographically normal coronary arteries).

The study showed that patients with bilateral ARVD had increased LVMI, LV wall asymmetry index, and likelihood of heart failure compared with patients with unilateral disease. One possible explanation is that the extent and the severity of CAD can be linked to RAS disease severity (2,15); alternatively, similar risk factors and shared cause may account for this. However, a similar relationship was not evident when ARVD severity was stratified by residual renal artery patency. This perhaps is surprising as it may be hypothesized that decreased patency may be reflected in increased LVMI as a result of hypertension or of activated neurohormonal systems that lead to salt and water retention or that have important direct myocardial effects such as promoting LVH and abnormalities of myocardial matrix. Several previous studies have also shown that proximal renal artery disease severity may not be predictive of the extent of renal failure in ARVD (12,13), and the link between "functional" significance and anatomic severity of RAS lesions is in need of better clarification.

This need is emphasized further by the fact that only one third of patients with moderate to severe ARVD and fewer than half of the overall ARVD group were receiving ACE-I or AIIRB therapy in this study, even though their range of cardiac abnormalities would be expected to benefit significantly from such therapy. This might have been anticipated in view of the general concerns regarding adverse renal functional effects of ACE-I/AIIRB in patients with severe ARVD, but it was not possible to assess whether the slightly increased use of these agents in the control patients had an impact on the cardiac findings in the study. Certainly ACE-I usage in patients with

chronic heart failure and hypertension has beneficial effects on LV remodeling in terms of LV size and hypertrophy. However, in light of the magnitude of the difference in LVH prevalence and LVMI between the groups, with there being only a trend toward increased use of ACE-I/AIIRB in the control group, it is unlikely that this differential use of therapy was a major contributor to the difference in cardiac changes.

From this cross-sectional study, it is not possible to determine whether the increased cardiac abnormalities that occur in patients with ARVD are merely reflective of shared underlying risk factors (*e.g.*, calcium-phosphate product, previous hypertension) or whether ARVD *per se* contributes to LVH and LV dilation *via* enhanced neurohormonal abnormalities. Intuitively, we believe that they are likely to represent a combination of these pathways. Risk factors for ARVD development will also be manifest on the heart and aorta with endothelial abnormalities and atherosclerosis. However, as ARVD progresses, it is likely that an exaggerated effect on LV remodeling will occur *via* activated renin-angiotensin-aldosterone and sympathetic nervous systems. It is widely recognized that angiotensin II and aldosterone are particularly potent stimuli for cardiac growth and abnormal intracellular matrix formation. Although the design of this study did not attempt to address the impact of activated neurohormonal systems on cardiac changes in ARVD, we believe that the study provides a basis on which other investigations can be planned.

Two potential limitations of this study relate to the fluid status of the participants and the influence of previous hypertension on the range of observed cardiac abnormalities. Achieving euvolemia in a group of patients with chronic renal disease, who are not on dialysis, has inherent difficulties, as such patients respond less predictably to diuretic dose. However, the ARVD group and the control group had similar renal dysfunction and cardiovascular comorbidity and were clinically stable and treated as out-patients at the time of investigation, and it is unlikely for there to have been a significant difference in fluid status between the groups. It is also highly unlikely that fluid status alone would account for changes in LVEDV.

The relationship of previous hypertension and BP control to the cardiac abnormalities observed in this study could not be ascertained, especially as overall 24-h BP control seemed to be reasonable at the time of investigation. This confounding effect of BP is not unexpected as a result of the cross-sectional nature of the study; such an effect is evident in most studies that involve patients with chronic renal disease, as a result of the paucity of accurate BP data before study entry. Nevertheless, it is highly likely that previous hypertension in the ARVD population has contributed to the high prevalence of LVH reported here. It is plausible that hypertension in the control group may be secondary to renal disease *per se*, whereas in the ARVD population, hypertension may play a causal role in renal damage that itself then perpetuates the hypertension. Furthermore, only 5% of patients with ARVD were noted to have nocturnal dipping of BP, but this is of no surprise given the high LVH prevalence and reported mortality of this group of patients.

Patients with cardiac disease now are treated with strategies that modify multiple risk factors, and these include use of statins, ACE-I and/or AIIRB, optimal BP control, and antiplatelet therapy. It is apparent from this study that such treatment strategies are highly applicable to patients with ARVD to slow or reverse the manifold cardiac abnormalities to which they are subjected. Accordingly, it is important that ARVD be diagnosed early and that patients with newly diagnosed ARVD receive expedient and optimal treatment for cardiovascular risk factors in an effort to break the deadly synergy between renal and cardiac disease in patients with ARVD.

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