Risk of Ascending Aortic Aneurysm in Patients With Autosomal Dominant Polycystic Kidney Disease

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In recent years, simple renal cysts have been associated with an increased risk of aortic aneurysms. There is little data regarding aortic dilation in patients with autosomal dominant polycystic kidney disease (ADPKD). The aim of this study was to compare Sinuses of Valsalva (SoV) and tubular ascending aorta diameters in ADPKD patients with matched controls. From 2008 to 2016, 61 consecutive ADPKD patients who had an echocardiogram performed in our institution were matched 1:1 with controls for sex, age, blood pressure, and β-blocker therapy use. SoV and tubular ascending aorta were measured at end-diastole, using the leading-edge to leading-edge convention. Paired *t* Tests were used for quantitative variables and McNemar-tests for qualitative variables. The mean age of patients was 56 ± 12 years, 54% were men, 38% received β-blockers, and mean systolic and diastolic BP were 137 ± 25 and 78 ± 19 mm Hg. SoV diameters were significantly larger in ADPKD patients than in controls (36.4 ± 4.1 vs 34.0 ± 3.7 mm, p <0.0001). The Z-scores (normalized for sex, age, and body surface area) were significantly higher in ADPKD patients, both for SoV and tubular ascending aorta. Moreover, aortic aneurysms, as defined by a Z score >2 standard deviations, were present in 27 ADPKD patients (44%) versus 9 controls (15%, p <0.001). In conclusion, there is an increased prevalence of aortic aneurysms in ADPKD patients as compared with controls matched for common confounding factors for aortic dilation. **(Am J Cardiol 2019;123:482−488)**

Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease, affecting around 1 in 1,000 individuals.[1] In ADPKD, the high prevalence of intracranial aneurysms has led to the recommendation of early detection and intervention in these patients.[2] Few studies have focused on other vascular abnormalities in patients with ADPKD, such as aortic aneurysms.[1,3] A recent population-based cohort study found that ADPKD patients had a 5-fold greater risk for aortic aneurysm and dissection occurrence, as compared with their non-ADPKD counterparts (p <0.0001). However, there was no information regarding either laboratory data or medications used.[4] Given the lack of evidence, specific recommendations for echocardiographic screening are missing in this population[5,6]. The aims of this study were to: (1) compare aortic diameters (both at the level of the sinuses of Valsalva [SoV] and tubular ascending aorta [TAA]) in ADPKD patients and matched controls, (2) evaluate the prevalence of SoV and TAA aneurysms in ADPKD patients, and (3) analyze the factors associated with aortic aneurysms.

Methods

Between 2008 and 2016, 85 ADPKD patients were treated at our institution. Among them, 67 consecutive patients underwent systematic echocardiography. Since 6 echocardiographic examinations were not exploitable for aortic diameters, 61 ADPKD patients were included in the analyses and matched 1:1 for age, sex, blood pressure (BP), and use of β-blocker therapy with control patients who had undergone echocardiography within the same time frame. Controls were recruited from the nephrology outpatient clinic of our institution, in patients in whom the diagnosis of ADPKD had been ruled out. No patient had factors other than hypertension, known to be associated with aortic dilation (such as Marfan syndrome or bicuspid aortic valve) and none had severe aortic stenosis or regurgitation. A large proportion of ADPKD being hypertensive patients, the controls were matched for blood pressure to avoid bias due to aortic dilatation related to hypertension. The estimated glomerular filtration rate (eGFR) was calculated with the IDMS-calibrated creatinine-derived MDRD equation.[7] All patients provided their written consent for the scientific use of

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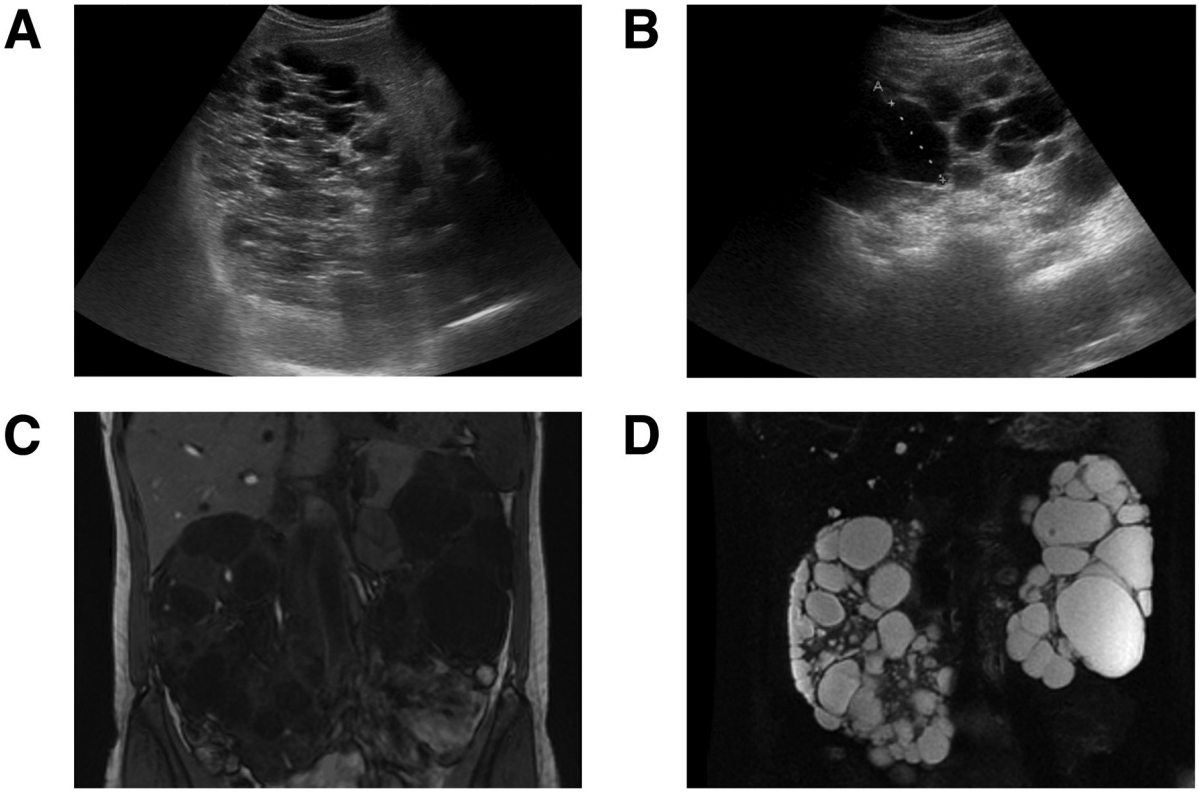

Figure 1. Imaging of ADPKD using renal US (Panels A & B) and MRI (Panels C & D). ADPKD = autosomal dominant polycystic kidney disease; MRI = magnetic resonance imaging; US = ultrasound.

their anonymous data. The study was approved by the local ethics committee.

The diagnosis of ADPKD relied on imaging according to the criteria proposed by Pei et al[6,8] (Figure 1). These criteria consist of the presence of at least 3 (unilateral or bilateral) renal cysts in individuals aged 15 to 39; 2 cysts in each kidney in patients aged 40 to 59 years; and at least 4 cysts in each kidney for subjects ≥60 years of age. As genetic testing for ADPKD is not routinely performed in clinical practice, mutation information was not available for the majority of our patients and was therefore not analyzed in this study.

We specifically studied 2 different parts of the ascending aorta: the SoV which correspond to the space between the superior aspect of each cusp of the aortic valve and the dilated portion of the wall of the ascending aorta; and the TAA which is located just above the coronary arteries implantation to the aorta until the aortic arch. SoV and TAA were measured according to guidelines at end-diastole, at the time of electrocardiography, in a strictly perpendicular plane to that of the long axis of the aorta using the leading-edge to leading-edge convention.[9] (Figure 2) Measurements were performed by 2 senior echocardiographers blinded to the diagnosis of patients. We used the reference values for thoracic aortic dilatation screening purposes, according to the guidelines.[10] The Z-score based on the publication by Campens et al (normalized for sex, age, and body surface area [BSA]) was obtained for both SoV and TAA.[10] The BSA was calculated with the Dubois and Dubois formula.[11] An aortic aneurysm was defined as a Z-score >2, indicating a diameter greater than 2 standard deviations above the mean, as recommended.[10]

Quantitative variables were expressed as mean ± standard deviation or median (25th to 75th percentiles) as appropriate, whereas qualitative variables were expressed as numbers and percentages. The concordance between the 2 blinded radiologists' results was assessed using a Kappa test[12] Comparisons between matched groups were made using paired t-test for

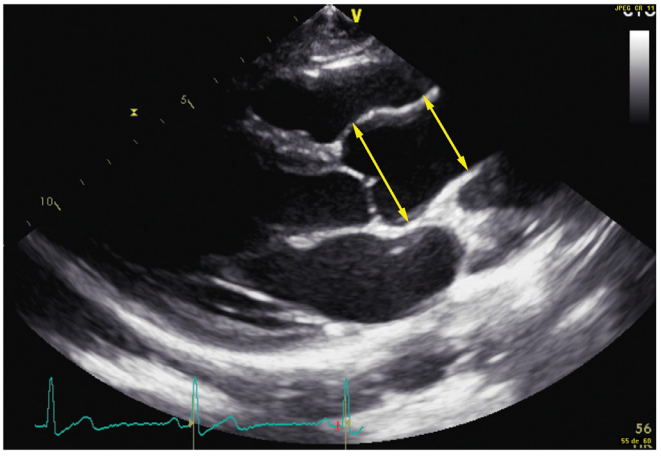

Figure 2. Echocardiographic assessment of aorta diameters (first arrow corresponds to SoV and second arrow to tubular ascending aorta). SoV = Sinuses of Valsalva.

quantitative variables and Mc Nemar chi-square test for qualitative variables. Comparisons between independent groups were performed using a Mann-Whitney U-test or a *t* Test for quantitative variables as appropriate and a Chi-square test for qualitative variables. Univariate analysis of the predictive factors for aortic aneurysm was performed using a logistic regression. Variables with $p < 0.1$ were entered in a multivariate analysis and selected by a backward procedure with a threshold of $p = 0.05$. The results were considered significant when 2-sided p values were <0.05. All analyses were performed using SPSS statistical software (SPSS V.23, Inc, Chicago, Illinois).

Results

The main characteristics of the 61 ADPKD patients and their matched controls are detailed in Table 1**.** In both groups, mean age was 56 years with 46% of patients being women. Patients in the ADPKD group had a more slender silhouette, compared to their matched controls. In the ADPKD group, 5 patients had an intracranial aneurysm, of which 2 experienced rupture and 1 had a history of aortic dissection of the descending thoracic aorta associated with an aneurysm of the ascending aorta, whereas none were reported in the control group

We assessed the interobserver variability between the 2 readers. Reader no 2 having the greatest experience was considered the reference value. According to a threshold of 40 mm for aortic dilatation,[13] both readers found no dilatation in 97 patients (80%), an aortic dilatation in 17 patients (14%) and there were discordant measures for 8 patients. There was overall a substantial concordance as attested by a Kappa value of 0.77. According to a threshold of Z-score >2 to define aortic aneurysm, both readers found no aneurysm in 81 patients (66%), an aortic aneurysm in 34 patients (28%) and there were discordant results for 7 patients: 3 patients were considered as having an aortic aneurysm for reader 2 and not reader 1, and 4 patients as not having an aortic aneurysm. There was overall an excellent concordance as attested by a Kappa value of 0.87.

SoV diameters were significantly larger in ADPKD patients than in controls ($p < 0.0001$), as detailed in Table 1. When the SoV diameters were normalized according to equations based on the publication by Campens et al,[10] the Z-scores were significantly higher in ADPKD patients than in controls ($p < 0.0001$). The histograms of Z-scores for the 2 groups as well as their density of distribution are plotted in Figure 3. Although Campens takes into account height (through BSA), SoV diameters were also normalized for height alone due to the taller height observed in the ADPKD group: the indexed SoV diameters remained significantly greater in ADPKD patients as compared with controls ($p = 0.01$).

A SoV diameter >40 mm, being widely considered as the threshold for aortic dilatation,[13] was found in 15 ADPKD patients (25%) versus 5 controls (8%); $p < 0.01$. As recommended, we relied mainly of the standardized Z-score and found SoV aneurysm, as defined by a Z score >2, to be present in 15 ADPKD patients (25%) versus 4 controls (7%); $p < 0.01$. The main characteristics of patients according to the presence or the absence of SoV aneurysm are presented in Table 2. The 5 variables associated with SoV aneurysm in univariate analysis were entered in the multivariate analysis. Multivariate analysis identified 2 factors associated with SoV aneurysm: a lower weight (adjusted odds ratio [OR] = 0.95 per Kg 95% confidence interval [CI] 0.91 to 0.99; $p = 0.02$) and the presence of ADPKD (adjusted OR = 4.02 95% CI 1.22 to 13.27; $p = 0.02$), as presented in Supplementary Table 1.

We equally studied diameters of the TAA, derived Z-scores, and prevalence of aneurysms (Table 1). Accurate measurements of the TAA were available in 57 of the 61 patients. Mean TAA diameters and Z-Scores were significantly higher in the ADPKD group. Prevalence of TAA

Table 1
Main clinical and echocardiographic characteristics of the autosomal dominant polycystic kidney disease (ADPKD) population and of the matched controls

Variable	ADPKD group (n = 61)	Control group (n = 61)	p
Age (years)	56.0 ± 12.4	56.8 ± 12.4	0.12
Female	28 (46%)	28 (46%)	1
Height (cm)	170 ± 9	167 ± 10	0.001
Weight (kg)	71 ± 16	76 ± 16	0.08
Body surface area (m^2)	1.8 ± 0.2	1.9 ± 0.2	0.18
Systolic blood pressure (mm Hg)	137 ± 25	133 ± 23	0.23
Diastolic blood pressure (mm Hg)	78 ± 19	79 ± 13	0.89
Known hypertension	56 (92%)	49 (80%)	0.07
Smoker	8 (13%)	5 (8%)	0.55
Diabetes mellitus	7 (12%)	10 (16%)	0.61
Dyslipidemia*	23 (38%)	23 (38%)	1
Coronary artery disease†	6 (10%)	7 (12%)	1
Aortic dissection	1 (2%)	0	1
Intracranial aneurysm	5 (8%)	0	0.06
Estimated glomerular filtration rate (ml/min/1.73 m^2)	42.2 ± 23.1	45.9 ± 22.3	0.39
Treatments			
Beta-blockers	23 (38%)	23 (38%)	1
Angiotensin receptor blocker	21 (34%)	32 (52%)	0.06
Angiotensin converting enzyme inhibitor	16 (26%)	11 (18%)	0.41
Statin	23 (38%)	32 (53%)	0.18
Insulin	4 (7%)	4 (7%)	1
Diuretics	30 (49%)	30 (49%)	1
Echocardiographic results			
Sinuses of Valsalva (mm)	36.4 ± 4.1	34.0 ± 3.7	<0.0001
Sinuses of Valsalva/ height (mm/m)	21.3 ± 2.3	20.5 ± 1.9	0.01
Z score (Sinuses of Valsalva)	1.2 ± 1.1	0.4 ± 1.0	<0.0001
Sinuses of Valsalva aneurysm	15 (25%)	4 (7%)	0.01
Tubular ascending aorta (mm)	33.9 ± 4.7	32.4 ± 3.9	0.05
Z score (tubular ascending aorta)	1.2 ± 1.2	0.7 ± 1.3	<0.05
Tubular ascending aorta aneurysm	15/57 (26%)	7/57 (12%)	0.45
Aortic aneurysm (Sinuses of Valsalva or tubular ascending aorta)	27 (44%)	9 (15%)	0.001

Data are presented as mean ± SD or n (%).

* Dyslipidemia: Hypercholesterolemia or hypertriglyceridemia currently treated with medication.

† Coronary artery disease corresponds to at least one of the following condition: angina with coronary artery stenosis ≥70% (or ≥50% for the left main artery); previous myocardial infarction, coronary angioplasty and/or stenting or coronary artery bypass grafting.

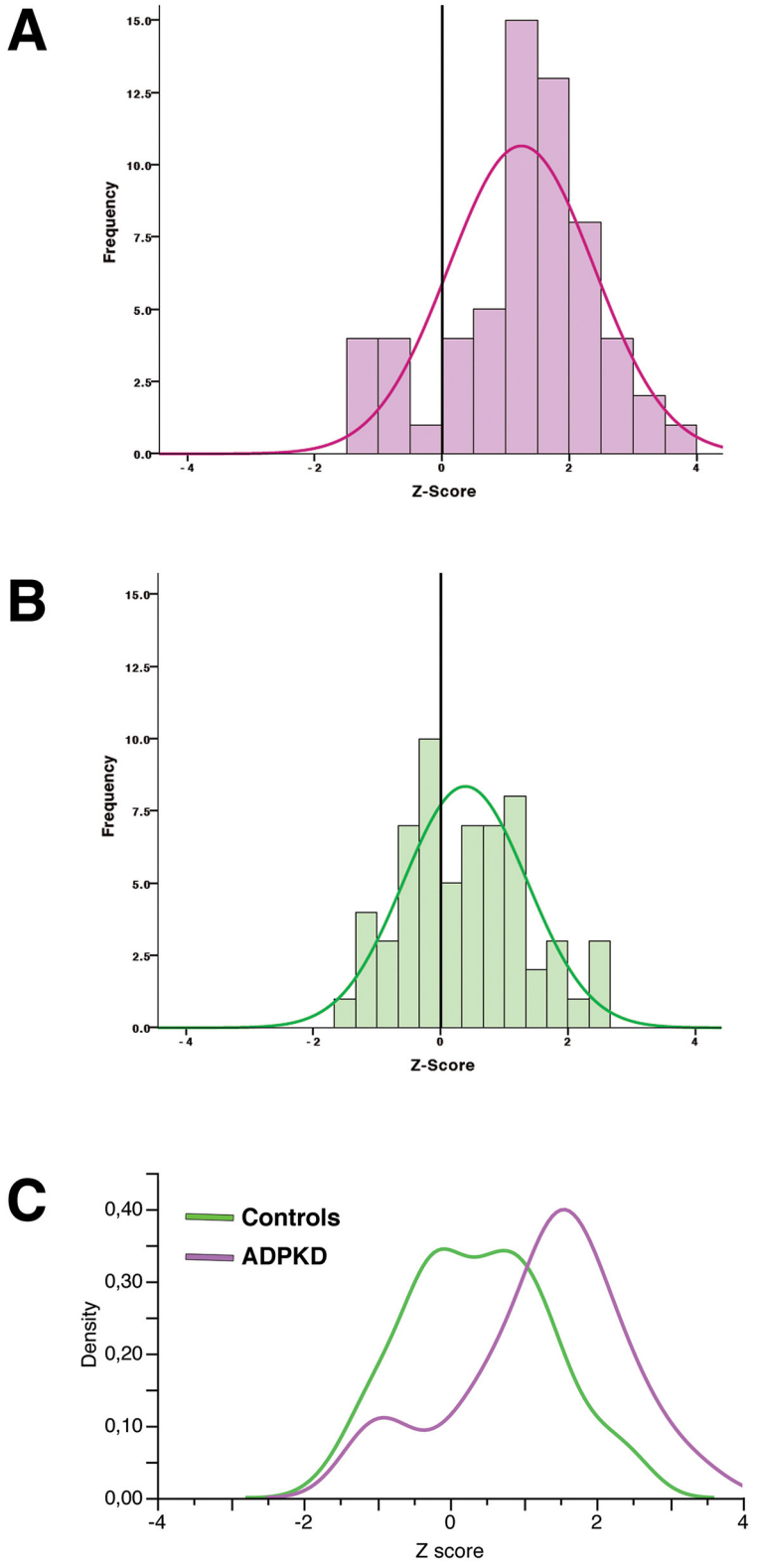

Figure 3. Histograms of the distribution of Z scores for SoV in ADPKD and control groups (panels A & B, respectively). Density of distribution in both groups (panel C).

Table 2
Patients' characteristics according to the presence of a Sinuses of Valsalva aneurysm

Variable	Sinuses of Valsalva aneurysm		p
	Yes (n = 19)	No (n = 103)	
Age (years)	50 (43−58)	57 (48−68)	0.03
Female	8 (42%)	48 (47%)	0.72
Autosomal dominant polycystic kidney disease	15^t (79%)	46 (45%)	0.006
Height (cm)	174 (161−177)	167 (162−175)	0.59
Weight (kg)	64 (55−73)	74 (62−85)	0.007
Body surface area (m^2)	1.8 (1.6−1.9)	1.8 (1.7−2.0)	0.11
Systolic blood pressure (mm Hg)	135 (112−155)	132 (121−149)	0.65
Diastolic blood pressure (mm Hg)	69 (65−96)	78 (69−86)	0.42
Known hypertension	17 (89%)	88 (85%)	0.64
Smoker	3 (16%)	10 (10%)	0.43
Diabetes mellitus	3 (16%)	14 (14%)	0.80
Dyslipidemia	9 (47%)	38 (37%)	0.39
Coronary artery disease	3 (16%)	10 (10%)	0.43
Intracranial aneurysm	3 (16%)	2 (2%)	<0.05
Aortic dissection	1 (2%)	0	1
Estimated glomerular filtration rate (ml/min/1.73 m^2)	41.0 (22.6−55.6)	43.5 (30.4−57.6)	0.91
Transthoracic echocardiography			
Sinuses of Valsalva (mm)	40 (38−43)	35 (31−37)	<0.0001
Tubular ascending aorta (mm)	34 (32−35.3)	33 (29.8−36)	0.21
Treatments			
Beta-blockers	7 (37%)	38 (37%)	1
Angiotensin receptor blocker	6 (32%)	47 (46%)	0.26
Angiotensin converting enzyme inhibitor	4 (21%)	23 (22%)	0.90
Statin	7 (37%)	48 (47%)	0.43
Insulin	3 (16%)	5 (5%)	0.08
Diuretics	9 (47%)	51 (50%)	0.86

Data are presented as median (25th−75th percentiles) or n (%).

aneurysms tended to be higher in the ADPKD group, but the difference did not reach statistical significance.

Lastly, we studied the prevalence of aortic aneurysms, either at the SoV or the TAA. An aortic diameter >40 mm was found in 18 ADPKD patients (30%) versus 5 controls (8%); p <0.0001. According to the more standardized evaluation using Z score, prevalence of aortic aneurysms was significantly higher in the ADPKD group, as compared with controls: 44% versus 15%; p <0.001. As presented in Supplementary Table 2, univariate analysis identified 5 variables related to the presence of aortic aneurysms, namely a younger age, a lower weight, a lower BSA, a lower systolic BP and the presence of ADPKD. Because of colinearity between BSA and weight, we performed 2 multivariate analyses: the Model 1 included the variable «BSA» whereas the Model 2 included the variable «weight». Multivariate Model 1 identified 3 factors associated with an aortic aneurysm: the presence of ADPKD (adjusted OR = 5.04 95% CI 1.97 to 12.91; p = 0.001), a lower BSA (adjusted OR = 0.08 95% CI 0.008 to 0.74; p = 0.03), and a younger age (adjusted OR = 0.94 95% CI 0.91 to 0.98; p = 0.003), as presented in Supplementary Table 3A. Multivariate Model 2 identified 3 predictive factors: the presence of ADPKD (adjusted OR = 4.69 95% CI 1.83 to 12.02; p = 0.001), a lower weight (adjusted OR = 0.96 95% CI 0.93 to 0.99; p = 0.02) and a younger age (adjusted OR = 0.95 95% CI 0.91 to 0.99; p = 0.007), as presented in Supplementary Table 3 B.

Interestingly, in both models, the most important factor was the presence of ADPKD.

Discussion

We found that ADPKD patients had significantly increased aortic diameters (both SoV and TAA) as compared with controls matched on sex, age, BP, and β-blocker therapy. Given the slender morphotype of ADPKD patients, we normalized the SoV diameters for height and the difference between groups remained significant. After normalization of the diameters for age, sex, and BSA (Campens Z-scores), there was still a significant difference between groups. Finally, we found that 44% of ADPKD patients versus only 15% of control patients exhibited an aortic aneurysm, a significant difference. In multivariate analysis, ADPKD was the strongest predictive factor for the presence of an aortic aneurysm.

Diverse vascular manifestations such as aneurysms and/or dissections have been reported in ADPKD, mainly involving the intracranial arteries, but also the aorta and the cervicocephalic, vertebral, and coronary arteries.[14−16] The presence of this wide array of vascular abnormalities has led to the hypothesis that polycystins, the proteins encoded by the PKD genes and expressed in vascular smooth muscle cells, might be required to maintain vascular integrity.[1,17−19] In the present study, besides the increased prevalence of SoV and TAA aneurysms, 1 patient in the ADPKD group experienced an aortic dissection of the descending aorta. He had undergone no previous echocardiographic screening and had received no β-blocker therapy before the dissection. Echocardiographic examination revealed an associated ascending aorta aneurysm. The prevalence of intracranial aneurysms is known to be more frequent in ADPKD patients, hence the recommendation for detection in affected relatives.[2,20,21] In this study, 5 patients (9%) in the ADPKD group had an intracranial aneurysm, of whom 3 had an associated aortic aneurysm. There was no significant association between intracranial aneurysm and aortic dilation given the limited number of patients, but this raises the question of a diffuse arterial vulnerability.

In this study, we found that ADPKD patients exhibited a more slender silhouette than their matched controls, with a taller height and a clear trend toward a lower weight. This result requires confirmation in a larger cohort but raises, as have previous studies, the question of a relation between ADPKD and Marfan-like features.[22−24] Furthermore, ADPKD patients presented with significantly more SoV aneurysms, as compared with controls, whereas the difference regarding TAA aneurysms did not reach significance. Interestingly, the typical morphology of aortic dilation in Marfan syndrome predominantly affects the SoV whereas

in hypertensive patients it is an unusual finding, with TAA aneurysms being more common. No genetic association between the Marfan syndrome and ADPKD has been shown[25] but a clinical spectrum of connective tissue disorders that contains elements of Marfan syndrome, such as skeleton signs and aortic dilation, has been described in ADPKD patients.[26] The slender morphotype of ADPKD patients and the hypothesis of a diffuse arterial disease deserve to be examined in more detail in future studies.

The following limitations should be acknowledged. Firstly, due of the single-centre nature of this study conducted in a large nephrological and cardiological tertiary center, referral bias cannot be excluded. The control subjects reflect the population treated in the nephrology department. Secondly, the retrospective nature of this study led to the exclusion of patients with no or incomplete echocardiography data. Thirdly, mutation information for ADPKD patients was not available since the diagnosis relies on clinical criteria and genetic testing is therefore rarely performed in routine clinical practice. Finally, the limited number of patients with aortic aneurysms leads us to consider the results of the multivariate analysis with caution.

The high prevalence of aortic aneurysms in ADPKD patients raises the question of the need for specific echocardiographic screening in these patients. Currently, there is no such recommendation. A recent paper showed that ADPKD patients had a 5-fold greater risk for aortic aneurysm and dissection occurrence, as compared to non-ADPKD patients, in line with some evidence in preclinical murine models.[4,27] The understanding of the pathogenesis of the vascular manifestations of ADPKD remains, however extremely limited. Larger prospective studies are needed to confirm these preliminary results and support larger screening of ADPKD patients for aortic aneurysms. Finally, β-blockers are indicated for the initiation and maintenance of antihypertensive treatment and are the preferred class of drugs in case of aortic aneurysm, according to the European Society of Cardiology guidelines.[28] Given the high prevalence of both hypertension and aortic aneurysms in ADPKD patients, it could be useful to use β-blockers on top of angiotensin-converting enzyme inhibitors and/ or angiotensin receptor blockers in this particular population.

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Disclosures

All authors have declared to have no conflicts of interest relevant to the content of this paper.

Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.amjcard.2018.10.030.

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