Increased Occurrence of Pericardial Effusion in Patients with Autosomal Dominant Polycystic Kidney Disease

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Background and objectives: Autosomal dominant polycystic kidney disease (ADPKD) is a common hereditary disease with prominent connective tissue manifestations. A frequent occurrence of asymptomatic pericardial effusion has been observed in patients with ADPKD.

Design, setting, participants, & measurements: Consecutive computed tomography scans from 60 patients with ADPKD (group 1), 100 patients without ADPKD and with serum creatinine concentration of \( > 1.1 \text{ mg/dl} \) (group 2), and 100 potential kidney donors (group 3) were retrospectively examined. Pericardial effusion was graded from 0 to 4 on the basis of the distance between the parietal and visceral pericardia at mid, mid-low, and low levels of the heart on transaxial computed tomography scan sections.

Results: Twenty-one (35%) of 60 patients in group 1 were found to have pericardial effusion, compared with 9 (9%) and 4 (4%) patients in groups 2 and 3, respectively. Ten of the 21 patients with pericardial effusion in group 1 but none of the patients in groups 2 and 3 had moderate to high effusion scores. The presence and severity of pericardial effusion were not associated with age, renal dysfunction, or hypertension. All pericardial effusions were asymptomatic.

Conclusions: Pericardial effusion occurs with an increased frequency in patients with ADPKD, possibly as a result of increased compliance of the parietal pericardium. Although frequently moderate to large, these effusions are generally well tolerated and clinically inconsequential.


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utosomal dominant polycystic kidney disease (ADPKD), a common hereditary disease with an estimated prevalence of 1 in 400 to 1000 live births, is a systemic disorder with renal and extrarenal, cystic and noncystic manifestations (1). Connective tissue defects, including an increased occurrence of arterial dissection, cardiac valvular abnormalities, meningeal diverticula, abdominal wall hernias, and intestinal diverticula, are widely known manifestations of ADPKD.

We have observed a frequent occurrence of asymptomatic pericardial effusions in patients with ADPKD. In some cases, these have led to extensive investigations. To determine the prevalence and clinical significance of pericardial effusion in ADPKD, we retrospectively examined consecutive computed tomography (CT) scans in patients with and without ADPKD and their relevant clinical histories. We found a significantly increased occurrence of asymptomatic and clinically inconsequential pericardial effusions in patients with ADPKD.

Concise Methods

Study Protocol/Data Collection

The study was approved by the institutional review board. Consecutive CT scans of the abdomen including the heart and low pulmonary fields obtained on the same scanner in the Department of Radiology, Mayo Clinic (Rochester, MN) were reviewed backward starting from December 2006. Sixty consecutive CT scans from patients with a clinical diagnosis of ADPKD (2) (group 1), 100 from patients with creatinine concentration \( \geq 1.1 \text{ mg/dl} \) and without ADPKD (group 2), and 100 from potential kidney donors (group 3) were reviewed by a radiologist (R.P.H.) and a nephrologist (Q.Q.). Patients with ADPKD underwent CT scans mainly to establish the extent of the disease and to rule out associated complications; the patients in group 2 underwent noncontrast CT scan for a wide range of indications unrelated to any symptom attributable to pericardial effusion; the potential kidney donors underwent CT scans as a part of pretransplantation evaluation. Medical records of all patients were reviewed; their characteristics are summarized in Table 1.

Grading of Pericardial Effusions

The normal pericardium was defined on CT scan as a sharply outlined density with a thickness of 1 to 2 mm (3) and smooth margins located in the expected anatomic position surrounding the heart (4). Each transaxial CT scan was examined at three levels: mid, mid-low, and low levels of the heart, as shown in Figure 1. As observed by others, the pericardium over part of the left ventricle was, in general, less well visualized than that over the atriums and right ventricle (4). Pericardial effusion was identified as a uniform attenuation consistent with fluid within the pericardial cavity at the levels examined. The
amount of the effusion was graded on a scale of 0 to 4 on the basis of the distance between the parietal and visceral pericardia at each of the three levels: 0 = no discernible pericardial effusion; 1 = slight increase in the distance but ≤3 mm and blunting of subpericardial fatty tissues; 2 = a distance of >3 and ≤5 mm; 3 = a distance of 5 to 10 mm; and, 4 = a distance of >10 mm. The highest score at the three levels from each CT scan was used for analysis. Evidence for hemodynamically significant pericardial effusion or pericardial tamponade was defined as a loss of definition of the subepicardial space combined with collapse of the right atrium or ventricle and/or dilation of the inferior vena cava (5).

**Statistical Analysis**

Each value was reported as the mean ± SEM. Paired data were compared by t test. P < 0.05 was considered significant.

**Results**

**Patient Characteristics**

Patient characteristics in groups 1 and 2 were similar, with the exception of a younger age in the group 1 (47.1 ± 1.98 versus 57.6 ± 1.12; P < 0.01). No significant differences were detected in serum creatinine concentration (Table 1) or the percentages of patients who were on maintenance hemodialysis (7 and 6% in groups 1 and 2, respectively). The prevalence of hypertension, level of BP control, and percentage of patients receiving diuretics were similar in groups 1 and 2. As expected, group 1 patients more frequently had hypertension and higher serum creatinine concentrations than those in group 3. The ages of groups 1 and 3 patients were comparable. None of the patients in the three groups had identifiable risk factors for pericardial effusion, including histories of tuberculosis or fungal infections, pericardial tumors, decompensated congestive heart failure, inflammatory connective tissue disorders, or overt volume overload at the time of the CT scan.

**Higher Prevalence of Asymptomatic Pericardial Effusions in Patients with ADPKD**

As shown in Figure 2A, 21 (35%; 11 female, 10 male) of the 60 patients in group 1 had grades 1 to 4 pericardial effusion, as compared with 9 (9%; three female, six male) of the 100 patients in group 2 (P < 0.01) and four (4%; three female, one male) of the 100 potential kidney donors in group 3 (P < 0.01).

Ten of the 21 patients with ADPKD and pericardial effusion had moderate or large effusions with scores of 3 and 4. By
contrast, with the exception of one patient who had a score of 2, patients in groups 2 and 3 with pericardial effusion had only trace fluid or blunting of the subpericardial fatty tissues and qualified for an effusion score of 1 (Figure 2B).

No symptoms attributable to pericardial effusion were detected in any of these patients. Hemopericardium, pericardial calcification, collapse of the cardiac chambers, or dilation of the inferior vena cava, suggestive of tamponade, was not detected in any patient. Trace to small pleural effusions were detected on the same CT scan in 1, 4, and 0 patients with pericardial effusion in groups 1, 2, and 3, respectively.

Lack of Association with the Presence of Hypertension and Its Treatment

As shown in Table 2, the prevalence of hypertension in patients with ADPKD and with and without pericardial effusion was similar. Seventeen (81%) of the 21 and 30 (76.9%) of the 39 with and without pericardial effusion, respectively, had documented hypertension. Average BP at the time of CT scans were 135/78 mmHg (range 116 to 161/63 to 94 mmHg) and 128/77 mmHg (range 105 to 154/59 to 95 mmHg) in the patients with and without pericardial effusion, respectively. Although patients with effusion tended to have higher systolic BP, the difference was not statistically significant. Conversely, the prevalence of pericardial effusion in this group of patients with or without a history of hypertension was similar: 17 (36.2%) of 47 versus 4 (30.8%) of 13.

Choices of antihypertensive agents in patients with ADPKD and with or without pericardial effusion were similar. Eight (47.1%) of the 17 patients with hypertension and a pericardial effusion were treated with an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker (ACEI/ARB)-containing antihypertensive regimen. Four (23.5%) patients were treated with diuretics, five (29%) with blockers, and four (23.5%) with calcium channel blockers. Ten, six, and one patients were taking one, two, or three antihypertensive agents, respectively. Eighteen (60%) of the 30 patients who had hypertension and ADPKD without pericardial effusion were treated with an ACEI/ARB-based regimen, 10 (33.3%) with diuretics, 15 (50%) with blockers, and five (16.7%) with calcium channel blockers. Nine, 12, and eight patients were taking one, two, and three or more antihypertensive agents, respectively. One patient who was on maintenance hemodialysis had been taken off antihypertensive medication at the time of the CT scan.

The prevalence of hypertension in the patients in group 2 with and without pericardial effusion was also similar. As shown in Table 3, seven (77.8%) of the nine patients with and 66 (72.5%) of 91 patients without pericardial effusion had a documented history of hypertension. The average BP at the time of CT scans were 125/71 mmHg (range 102 to 149/60 to 84 mmHg) in the patients with and 128/74 mmHg (range 92 to 159/40 to 104 mmHg) in the patients without effusion.

Choices of antihypertensive agents in the hypertensive patients with ADPKD and with and without pericardial effusion include were as follows: Three (42.9%) of seven on ACEI/ARB, five (71.4%) on diuretics, four (57.1%) on blockers, and one (14.3%) on a calcium channel blocker–containing regimen. Three, two, one, and one were taking one, two, three, and four antihypertensive agents, respectively. For hypertensive patients without ADPKD and pericardial effusion, 24 (33%) were on ACEI/ARB, 21 (31.8%) were on diuretics, 36 (54.5%) were on blockers, and five (7.6%) were on a calcium channel blocker–containing reg-

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Table 2. Hypertension in patients with ADPKD and with and without pericardial effusion

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<thead>
<tr>
<th>Parameter</th>
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<td>With Pericardial Effusion</td>
</tr>
<tr>
<td>No. of patients</td>
<td>21</td>
</tr>
<tr>
<td>Age (yr [mean ± SEM])</td>
<td>50.05 ± 3.15</td>
</tr>
<tr>
<td>Hypertension (n [%])</td>
<td>17 (81)</td>
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<tr>
<td>BP (mmHg; average)</td>
<td>134.5/77.5</td>
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<tr>
<td>No. of antihypertensives</td>
<td>1.4</td>
</tr>
<tr>
<td>Patients on diuretics (n [%])</td>
<td>4 (23.5)</td>
</tr>
<tr>
<td>Creatinine (mg/dl [mean ± SEM])</td>
<td>1.88 ± 0.35</td>
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</table>
Table 3. Hypertension in patients without ADPKD and with and without pericardial effusion

<table>
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<th>Parameter</th>
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<td>With Pericardial Effusion</td>
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<td>No. of patients</td>
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</tr>
<tr>
<td>Age (yr [mean ± SEM])</td>
<td>60.9 ± 2.65</td>
</tr>
<tr>
<td>Hypertension (n [%])</td>
<td>7 (77.8)</td>
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<tr>
<td>BP (mmHg; average)</td>
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<tr>
<td>No. of antihypertensives</td>
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<tr>
<td>Patients on diuretics (n [%])</td>
<td>5 (71.4)</td>
</tr>
<tr>
<td>Creatinine (mg/dl [mean ± SEM])</td>
<td>1.99 ± 0.29</td>
</tr>
</tbody>
</table>

Lack of Association with Age and Degree of Renal Dysfunction

There was no statistically significant difference in the ages of study patients with or without pericardial effusion: 50.1 ± 3.2 versus 46.4 ± 2.5 (P = 0.41) in group 1, 60.9 ± 3.1 versus 57.3 ± 1.2 (P = 0.30) in group 2, and 35.8 ± 8.8 versus 43.7 ± 1.2 (P = 0.44) in group 3. There were no significant age differences between the ADPKD subgroups with different grades of pericardial effusion: Mean age (range) of 44.4 (29 to 61), 48.3 (20 to 72), 53 (25 to 73), and 50.2 yr (32 to 78 yr) for the pericardial effusion scores of 1, 2, 3, and 4, respectively.

Serum creatinine concentration was significantly higher in group 1 patients than in group 3 potential kidney donors; however, serum creatinine concentrations in groups 2 and 3 were comparable (Table 1). There was no significant difference in serum creatinine concentrations in patients with and without pericardial effusion within these groups: 1.88 ± 0.35 versus 1.76 ± 0.25 (P = 0.41) for group 1 and 1.99 ± 0.29 versus 1.93 ± 0.12 (P = 0.49) for group 2. Serum creatinine concentrations among the subgroups with different pericardial effusion scores were also similar (Figure 2C).

One of the patients with ADPKD, an effusion score of 4, and a creatinine concentration of 7.5 mg/dl was on maintenance hemodialysis (Figure 2C) at the time of CT scan. This patient underwent a successful kidney transplant. Two years later, with a serum creatinine level of 1.5 mg/dl, a CT scan showed a large pericardial effusion unchanged from the initial CT scan.

Discussion

The main findings of this study are that pericardial effusion occurs with an increased frequency in patients with ADPKD and that these effusions are usually asymptomatic and without discernible clinical consequences. Although pericardial effusion has been previously reported in a patient with ADPKD (6), it has been deemed to be secondary to uremia. Our observations suggest that pericardial effusion is a previously unrecognized extrarenal manifestation of ADPKD. The existence of this association and its benign nature should be taken into consideration in the evaluation of patients with ADPKD to avoid unnecessary diagnostic or therapeutic interventions.

The pathogenesis of pericardial effusion in ADPKD is uncertain. It may reflect a defect in the structure and function of connective tissue and extracellular matrix, which may also underlie other extrarenal manifestations of ADPKD, such as intracranial and thoracic aortic dissections and aneurysms, cardiovascular abnormalities, meningeal diverticula, abdominal wall hernias, and possibly colonic and extracolonic diverticula. In some families with ADPKD, connective tissue/extracellular matrix defects may contribute to skeletal abnormalities such as pectus abnormalities, pes planus, joint laxity, arachnodactyly, scoliosis, dolichostenomelia, and high arched palate (7). These abnormalities are reproduced by targeted mutations of the Pkd1 gene in mice (8,9).

The role of connective tissue and extracellular matrix defects in the pathogenesis of renal and extrarenal phenotypes of ADPKD is complex and not well understood. Cellular defects associated with PKD mutations may lead to an abnormal production of matrix components, matrix degrading enzymes, and inhibitors of metalloproteinases (10–12). Conversely, primary defects in connective tissue and extracellular matrix components may lead to a cystic phenotype. For example, a hypomorphic mutation of laminin α5, a major tubular basement membrane component, results in aberrant accumulation of laminin and cystic renal disease in mice (13). Various connective tissue dysplasias have also been associated with cystic kidneys in humans (14).

The pericardium is a fibrous sac that encloses the heart, the proximal part of the ascending aorta, the pulmonary trunk, and a short segment of the left pulmonary vein (15). It consists of visceral and parietal layers. The visceral pericardium is composed of a single layer of mesothelial cells that adhere to the cardiac epicardium. The parietal pericardium, also lined by a layer of mesothelial cells, is a 2-mm-thick fibrocollagenous structure that is composed primarily of collagen with interposed elastic fibrils. The two layers of the pericardium are separated by a potential space that normally contains 15 to 30 ml of pericardial fluid, an ultrafiltrate of the plasma generated by hydrostatic force (16). Abnormal distensibility of the connective tissue (increased compliance and impaired recoil), possibly combined with a slightly increased extracellular volume (17,18), could facilitate the development of pericardial effusion in patients with ADPKD.

CT scan is a well-established method to detect the existence and severity of pericardial effusion (4, 19), although it is less sensitive than echocardiography to assess its hemodynamic impact (20). The lack of functional consequences by both the clinical presentation and CT criteria of tamponade physiology in patients with ADPKD and a moderate to large degree of pericardial effusion is consistent with a right shift of the pericardial pressure-volume relation and the passive nature of the fluid accumulation (21). Increased awareness of this phenome-
non in patients with ADPKD could prevent unnecessary invasive diagnostic and/or interventional procedures.

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Disclosures
None.

References