Reversal of left ventricular hypertrophy with angiotensin converting enzyme inhibition in hypertensive patients with autosomal dominant polycystic kidney disease

Tevfik Ecder, Charles L. Edelstein, Arlene B. Chapman, Ann M. Johnson, Lyn Tison, Edward A. Gill, Godela M. Brosnahan and Robert W. Schrier

Abstract
Background. Hypertension occurs commonly and early in the natural history of autosomal dominant polycystic kidney disease (ADPKD), affecting both renal and patient outcome. Activation of the renin–angiotensin–aldosterone system due to cyst expansion and local renal ischaemia plays an important role in the development of ADPKD related hypertension and left ventricular hypertrophy (LVH), a known important risk factor for cardiovascular morbidity and mortality. The aim of this study was to investigate the effects of an angiotensin converting enzyme (ACE) inhibitor, enalapril, on renal function, blood pressure and LVH in hypertensive ADPKD patients.

Methods. Fourteen hypertensive ADPKD patients (11 men, 3 women; mean age: 40 years) were included in the study. All patients had LVH and creatinine clearance (Cr) greater than 50 ml/min/1.73 m². The patients were followed for 7 years on enalapril therapy. The effects of enalapril on renal function, blood pressure and LVH were investigated.

Results. Baseline measurements of mean arterial pressure (MAP), Cr and left ventricular mass index (LVMI) were 110 ± 2 mmHg, 84 ± 6 ml/min/1.73 m² and 146 ± 4 g/m², respectively. After one year of enalapril therapy there was a significant decrease in MAP (94 ± 3 mmHg, P < 0.005) which remained stable until the end of the study at 7 years (94 ± 1 mmHg, P < 0.005 vs baseline). There was also a significant decrease in LVMI (131 ± 6 g/m², P < 0.05) after year 1 which continued to decrease until the end of the study reaching 98 ± 6 g/m² (P < 0.01 vs year 1 and baseline). Although Cr remained stable after year 1, a significant decrease was observed after 7 years of follow-up (59 ± 6 ml/min, P < 0.001 vs year 1 and baseline).

Conclusions. ACE inhibition in hypertensive ADPKD patients provided long-term reversal of LVH in association with a mean 3.6 ml/min/year decline of Cr.

Correspondence and reprint requests to: Robert W. Schrier, MD, Chairman, Department of Medicine, University of Colorado Health Sciences Center, 4200 East 9th Avenue, Denver, CO 80262, USA.

© 1999 European Renal Association–European Dialysis and Transplant Association
effect of enalapril on renal function and LVH. The patients have been randomized into moderate and intensive blood pressure control groups. In the moderate blood pressure control group, the target mean arterial pressure (MAP) is 100–107 mmHg, whereas in the intensive blood pressure control group the target MAP is less than 92 mmHg. Herein, we report the results of the first 14 patients who have finished the study after 7 years of enalapril treatment. Since the results of the moderate versus intensive blood pressure control groups are not available until the end of the study, only the effect of enalapril on blood pressure, renal function and LVH for all 14 patients will be reported.

All of the patients were hypertensive (blood pressure > 140/90 mmHg in sitting position or taking antihypertensive drugs). Eleven of them were male and three female with a mean age of 40 years. All patients had a creatinine clearance (CrCl) greater than 50 ml/min/1.73 m² and all had LVH (left ventricular mass index (LVMI) greater than 125 g/m² for males and greater than 110 g/m² for females). Echocardiographic studies were performed at baseline and at year 1 using a Hewlett Packard Sonos 2500 or 5500 imaging systems using 2.5 to 4.0-MHz phased array transducers. Two-dimensional images were used to direct the M-mode sweep. Measurements were made according to the conventions of the American Society of Echocardiography [8,9]. LVMI was calculated using the Penn equation and corrected for body surface area [10].

After withdrawal from antihypertensive medications and a washout phase of 2–4 weeks, the patients were started enalapril with a daily maximum dose of 40 mg orally. The patients were followed for 7 years on enalapril therapy. Six of the 14 patients only received enalapril during the 7 years of the study. As second-line therapy, eight patients also received hydrochlorothiazide, five patients spironolactone and three patients furosemide. In the first year of the study, four patients received amiodipine as initial therapy as part of a 1-year comparison study with enalapril. The total period of amiodipine therapy however comprised only 5% of the 7 year follow-up of all 14 patients. Changes over time of the three parameters (MAP, CrCl, and LVMI) were analysed with signed-rank analysis. Statistical significance was defined as $P < 0.05$; significant $P$ values are reported in the text. Variables are reported as the mean ± standard error of the mean (SEM).

Results

The demographic characteristics, mean arterial pressures, creatinine clearances and left ventricular mass indexes of the 14 patients are shown on Table 1. Baseline values of MAP were 110 ± 2 mmHg, Ccr 84 ± 6 ml/min/1.73 m² and LVMI 146 ± 4 g/m². After 1 year of follow-up, there was a statistically significant decrease in MAP (94 ± 3 mmHg, $P < 0.005$) and in LVMI (131 ± 6 mmHg, $P < 0.05$), while the Ccr remained stable. After the end of 7 years, there was an additional decrease in LVMI (98 ± 6 g/m²) which was statistically significant compared to baseline and year 1 ($P < 0.01$) (Figure 1). The MAP remained stable from year 1 to year 7, whereas there was a significant decrease in Ccr (59 ± 6 ml/min/1.73 m², $P < 0.001$) compared to baseline and year 1 (Table 1).

Discussion

It is well-known that hypertension has a negative effect both on kidney and patient survival in patients with chronic renal disease [11,12]. ADPKD patients with hypertension have a faster progression to ESRD than their normotensive counterparts [4]. In addition, LVH is a blood pressure-independent risk factor for cardiovascular morbidity and mortality both in essential hypertension and in ESRD [13,14]. In a 10-year follow-up study of patients with essential hypertension, Koren et al. [13] showed that cardiovascular deaths occurred

### Table 1. The demographic characteristics, mean arterial pressures, creatinine clearances and left ventricular mass indexes of the patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Weight (kg)</th>
<th>Mean arterial pressure (mmHg)</th>
<th>Creatinine clearance (ml/min/1.73 m²)</th>
<th>Left ventricular mass index (g/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Baseline</td>
<td>Year 1</td>
<td>Year 7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D.B.</td>
<td>M</td>
<td>47</td>
<td>101</td>
<td>113</td>
<td>77</td>
<td>87</td>
</tr>
<tr>
<td>C.C.</td>
<td>M</td>
<td>29</td>
<td>74</td>
<td>118</td>
<td>87</td>
<td>91</td>
</tr>
<tr>
<td>W.H.</td>
<td>M</td>
<td>47</td>
<td>103</td>
<td>112</td>
<td>84</td>
<td>95</td>
</tr>
<tr>
<td>K.H.</td>
<td>F</td>
<td>44</td>
<td>88</td>
<td>111</td>
<td>108</td>
<td>97</td>
</tr>
<tr>
<td>G.K.</td>
<td>M</td>
<td>44</td>
<td>118</td>
<td>121</td>
<td>91</td>
<td>89</td>
</tr>
<tr>
<td>A.L.</td>
<td>M</td>
<td>36</td>
<td>86</td>
<td>106</td>
<td>85</td>
<td>88</td>
</tr>
<tr>
<td>S.N.</td>
<td>F</td>
<td>42</td>
<td>63</td>
<td>116</td>
<td>107</td>
<td>103</td>
</tr>
<tr>
<td>R.S.</td>
<td>M</td>
<td>29</td>
<td>98</td>
<td>106</td>
<td>93</td>
<td>83</td>
</tr>
<tr>
<td>J.M.*</td>
<td>M</td>
<td>44</td>
<td>78</td>
<td>111</td>
<td>92</td>
<td>93</td>
</tr>
<tr>
<td>S.Y.*</td>
<td>F</td>
<td>49</td>
<td>65</td>
<td>104</td>
<td>110</td>
<td>97</td>
</tr>
<tr>
<td>J.A.W.*</td>
<td>M</td>
<td>32</td>
<td>77</td>
<td>96</td>
<td>90</td>
<td>94</td>
</tr>
<tr>
<td>J.O.W.</td>
<td>M</td>
<td>41</td>
<td>95</td>
<td>103</td>
<td>95</td>
<td>95</td>
</tr>
<tr>
<td>E.W.</td>
<td>M</td>
<td>40</td>
<td>88</td>
<td>107</td>
<td>98</td>
<td>98</td>
</tr>
<tr>
<td>J.Z.*</td>
<td>M</td>
<td>33</td>
<td>81</td>
<td>116</td>
<td>99</td>
<td>101</td>
</tr>
</tbody>
</table>

* Patients who have taken only enalapril (mean dose: 7.5 mg/day).

**P < 0.005 vs baseline; *P < 0.001 vs year 1 and baseline; **P < 0.05 vs baseline; *P < 0.01 vs year 1 and baseline.
in a higher proportion of patients with than without LVH (14% compared with 0.5%, *P < 0.001). Similarly, cardiovascular complications are more common in ADPKD patients with hypertension and LVH [5]. These facts underline the importance of the treatment of both hypertension and LVH to increase kidney and patient survival in ADPKD.

There are several experimental and clinical observations that show an increased activity of the RAAS in ADPKD patients. Graham and Lindop [15] demonstrated that kidneys obtained from nephrectomy or autopsy specimens of patients with ADPKD showed increased renin in juxtaglomerular apparatus as well as renin granules along the afferent arteriole and within cyst walls. Hypertensive ADPKD patients with normal renal function have significantly higher plasma renin activity and plasma aldosterone concentration while supine or upright and after captopril administration, as compared to patients with essential hypertension and similar blood pressures and renal function [6].

Angiotensin II has several potential detrimental effects on the progression of renal disease. Apart from its systemic vasoconstrictor effect, angiotensin II also has a more pronounced effect on the efferent arteriole than the afferent arteriole, thus causing intraglomerular pressure to rise. Moreover, angiotensin II, as a growth factor, may exert direct effects on cell proliferation and growth and also stimulate the expression of other vasoactive factors and cytokines, such as endothelin, transforming growth factor β1 (TGF-β1), basic fibroblast growth factor (bFGF) and platelet-derived growth factor (PDGF). These latter effects would lead to increased production of extracellular matrix components and promote glomerular and interstitial infiltration of inflammatory cells [16]. Angiotensin II has also been suggested to be one of the major pathogenetic factors in myocardial hypertrophy [17]. Support for this possibility is not only the effect of angiotensin II to increase blood pressure but also by stimulating RNA and protein synthesis in cardiac myocytes in both animals and cultured cells [18].

Given the potential detrimental renal and cardiac effects of angiotensin II, it is reasonable to treat hypertensive ADPKD patients with ACE inhibitors. ACE inhibitors have been shown to be the most effective in terms of regression of left ventricular muscle mass in essential hypertension [19,20]. ACE inhibitors also are effective in inducing regression of left ventricular hypertrophy in hypertensive patients with chronic renal failure [21].

Here we are reporting a 7 year follow-up of 14 ADPKD patients with hypertension and LVH. ACE inhibition with enalapril as initial therapy caused a significant decrease both in MAP and LVMI in our hypertensive ADPKD patients. After 7 years of enalapril therapy, a significant decrease in GFR was observed. Administration of ACE inhibitors may cause an initial fall in GFR, particularly in ADPKD patients with large kidneys and decreased renal function [22]. After any initial fall in GFR, however, the slope of the decrease in GFR may stabilize and result in a long-term beneficial effect on progression of chronic renal diseases. In the present study, there was no statistically significant difference in GFR after 1 year of enalapril treatment. The statistically significant decrease that was seen after 7 years of follow-up could therefore be related primarily to the natural progression of the disease. The mean annual decrease of creatinine clearance in our patients was 3.6 ml/min. In the Modification of Diet in Renal Disease (MDRD) study, patients with ADPKD have been reported to average a GFR loss of 6 ml/min/year [23]. In contrast to present study, however, the MDRD study was performed in ADPKD patients with advanced renal disease (GFR < 55 ml/min) and the mean follow-up period was only 2.2 years. Since our patients’ mean age after 7 years follow-up was 47 years, at an annual rate of 3.6 ml/min/1.73 m² renal functional loss, end-stage renal disease would not be expected to occur until nearly 70 years old. In contrast, hypertensive ADPKD patients with uncontrolled blood pressure and LVH have been observed to have ESRD at age 44 years [4]. Therefore, early treatment of ADPKD patients may afford important protection of renal as well as cardiovascular function.

In conclusion, ACE inhibition with enalapril in hypertensive ADPKD patients provided long-term control of blood pressure, reversal of LVH and perhaps a slowing of renal functional loss. These preliminary results have potential important implications for cardiovascular and renal protection in ADPKD patients. Optimal results may necessitate treatment of ADPKD patients early in one course of their disease.

References

4. Gabow PA, Johnson AM, Kaehny WD et al. Factors affecting


13. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relationship of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. *Ann Intern Med* 1991; 114: 345–352.


Received for publication: 5.3.99
Accepted: 10.3.99