Heart

Regression of Left-Ventricular Hypertrophy in Children and Adolescents With Hypertension During Ramipril Monotherapy

Tomáš Seeman, Jiří Gilík, Karel Vondrák, Eva Šimková, Hana Flögelová, Marie Hladíková, and Jan Janda

Background: Left-ventricular hypertrophy (LVH) is a risk factor for cardiovascular morbidity. Antihypertensive treatment with angiotensin-converting enzyme inhibitors (ACEI) is able to induce the regression of LVH in adults. However, there has been no study of the ability of ACEI to induce the regression of LVH in children. Our aim was to investigate the effect of ramipril on left-ventricular mass and blood pressure (BP) in hypertensive children.

Methods: Twenty-one children (median age, 15 years) with renal (76%) or primary (24%) hypertension were prospectively treated with ramipril monotherapy for 6 months. Blood pressure was evaluated using ambulatory BP monitoring, with hypertension defined as mean BP ≥95th percentile. Left-ventricular hypertrophy was defined either as left-ventricular mass index (LVMI) >38.6 g/m².7 (pediatric definition) or as LVMI >51.0 g/m².7 (adult definition).

Results: Nineteen children completed the study. The median LVMI decreased from 36.8 g/m².7 (range, 18.9 to 55.8 g/m².7) to 32.6 g/m².7 (range, 19.0 to 52.1 g/m².7; P < .05) after 6 months. The prevalence of LVH decreased from 42% to 11% using the pediatric definition (P < .05) and did not change using the adult definition (ie, it remained at 5%). The median ambulatory BP decreased by 11, 7, 8, and 7 mm Hg for daytime systolic, daytime diastolic, nighttime systolic, and nighttime diastolic BP (P < .05), respectively. A positive correlation was found between LVMI and nighttime systolic BP at the start of the study (r = 0.46, P < .05).

Conclusions: Ramipril is an effective drug in children with hypertension, for its ability to reduce not only BP but also left-ventricular mass and induce regression of LVH. Am J Hypertens 2007;20:990–996 © 2007 American Journal of Hypertension, Ltd.

Key Words: Left-ventricular hypertrophy, regression, ramipril, children, hypertension.

Left-ventricular hypertrophy (LVH) is an important sequela of hypertension and an independent risk factor for cardiovascular morbidity and mortality in adult patients with hypertension.1,2 Regression of LVH is associated with decreased cardiovascular risk.3,4 Therefore, regression of LVH has become one of the goals of antihypertensive therapy in adults.5 The regression of LVH during antihypertensive therapy was well documented in adult hypertensive patients with primary and renal hypertension.3,5,6,7 Ambulatory blood-pressure monitoring (ABPM) is superior to office blood pressure (BP) in predicting the treatment-induced regression of LVH.8 Left-ventricular hypertrophy is also a form of target-organ damage frequently seen in hypertensive children; it occurs in 8% to 41% of subjects.9–12 Contrary to the case with adults, there are no prospective studies showing that antihypertensive therapy can induce regression of LVH in children with hypertension. Only case reports showing that regression of LVH is possible in hypertensive children have been published.13

The aim of our prospective interventional study was to investigate the effect of ramipril treatment on left-ventricular mass and the prevalence of LVH in children with primary and secondary hypertension.
Methods
Study Population

Twenty-one children and adolescents (median age, 15 years; range, 3.3 to 17.8 years; 14 boys) who fulfilled the inclusion criteria (primary or renal hypertension confirmed by ABPM, echocardiography evaluation at the time of ABPM, and no treatment with antihypertensive agents) were included in this prospective study. They were selected consecutively over a period of 4 years (2001 to 2004) in our two centers. The children were prospectively treated for 6 months with ramipril monotherapy. No child received any other treatment for primary renal disease other than ramipril (no steroids and no immunosuppressive drugs). Ten children had already been included and evaluated in our previous study, which investigated the effect of ramipril on ambulatory BP and proteinuria in children with chronic kidney diseases.14 Four children had primary hypertension, and 17 children had renal hypertension. Primary renal diseases included polycystic kidney diseases (n = 8); autosomal-dominant polycystic kidney disease in 5 children and autosomal-recessive polycystic kidney disease in 3 children), reflux nephropathy (n = 5), renal dysplasia (n = 2), residual renal abnormalities after hemolytic uremic syndrome (n = 1), and IgA nephropathy (n = 1).

Ambulatory BP was measured by ABPM, using an oscillometric device (SpaceLabs 90207 or 90217; SpaceLabs, Redmond, WA). A cuff of an appropriate width for the arm circumference was chosen. Blood pressure was automatically recorded every 20 min during the day and every 30 min at night. A record of daily activities and sleep during the day was obtained for each child. Hypertension was defined as a mean ambulatory systolic or diastolic BP during the night was obtained for each child. Hypertension was defined as a percentage of mean nighttime BP decline compared with mean daytime BP. The office BP was measured in the same day as ABPM, according to the recommendations of the American Society of Echocardiography.17

Left-ventricular mass (LVM) was calculated according to the formula of Devereux et al from the left-ventricular internal dimension at end diastole, interventricular septal thickness, and left-ventricular posterior wall thickness.18 Left-ventricular mass was indexed to height2.7 (left-ventricular mass index, LVMi) to account for body size.19 Left-ventricular hypertrophy was defined either as LVMi >38.6 g/m²,2.7 which corresponds with the 95th percentile of normative pediatric LVMi data,19 or as LVMi >51.0 g/m²,2.7 which in adults was found to correlate with a fourfold greater risk of cardiovascular events.20

The intraobserver reliability of echocardiographic measurements was adequate, insofar as the difference of repeated measurements of LVM in the same patient under similar conditions was 1.197 ± SEM of 1.901 (89.595 on the first measurement and 88.397 on the second measurement). This difference was not statistically significant (P = .53, 95% confidence interval for differences of means, −2.659 to 5.053).

The glomerular filtration rate was classified according to National Kidney Foundation guidelines.21 It was normal (calculated creatinine clearance according to the formula of Schwartz et al,22 ≥90 mL/min/1.73 m²) in all children with primary hypertension and in 12 children with renal hypertension, mildly reduced (creatinine clearance, 60 to 89 mL/min/1.73 m²) in 4 children, and moderately reduced (creatinine clearance, 30 to 59 mL/min/1.73 m²) in 1 child. Body mass index (BMI) was expressed in absolute values (kg/m²) and in percentiles of the healthy Czech child population.23 Overweight was defined as a BMI >85th percentile (six children, 29%) and obesity as BMI >95th percentile (four children, 19%).

Ramipril was given as a single daily oral dose in the morning or in the evening (one child). The initial dose was 1.5 mg/m²/day. This dose was doubled if all mean BP values were not <95th percentile after 1 month of treatment. The maximal dose was 6 mg/m²/day. Ramipril was given for 6 months as monotherapy. The ABPM and blood tests for serum creatinine, serum potassium, and blood count (by standard methods) were performed 1 month after the initiation of treatment, 1 month after each change of ramipril dose, and at the end of the study. Echocardiography was performed at the end of the study (at 6 months). Patients were monitored at every outpatient visit for the presence of adverse effects of ramipril, such as cough, abdominal pain, fatigue, dizziness, orthostasis, edema, or rash. All parents gave informed consent for their children to participate in the study, which was approved by the local ethics committee.

Statistics

The data are expressed as medians and range. The Wilcoxon signed rank test and McNemar test were used to assess significant changes in follow-up. The correlations between variables (ambulatory BP, office BP, LVMi, BMI, and glomerular filtration rate) were assessed by Spearman correlation analysis (univariate and multivariate analysis). P < .05 was regarded as statistically significant.

Results

Patients

Nineteen children completed the 6-month study. The reasons for the two dropouts were noncompliance with the study medication (n = 1) and missing the echocardiography evaluation at the end of the study (n = 1).
Blood Pressure

After 6 months of ramipril treatment, the mean daytime systolic as well as nighttime diastolic BP decreased in 17 of 19 children, the mean nighttime systolic BP decreased in all children, and the mean daytime diastolic BP decreased in 14 children. The changes in ambulatory and office BP after ramipril treatment are shown in Table 1. Hypertension normalized (ie, all mean ambulatory BP values < 95th percentile) in 53% of children. The initial dose of ramipril had to be increased during the study in 12 children. The median ramipril dose at the end of the study was 2.9 mg/m²/day (range, 1.1 to 5.7 mg/m²/day). The percentage of nighttime dip in systolic BP decreased by 2% (the systolic BP dip changed from 10% at the start of the study to 8% at the end of the study). The percentage of nighttime dip in diastolic BP decreased by 1% (the diastolic BP dip changed from 18% to 17%). These differences were not statistically significant.

Echocardiography

Left-ventricular hypertrophy was present at the start of the study in 42% of the children (8 of 19 children), using the 95th percentile of normative pediatric LVMI data for our definition, and in 5% (one child), using the adult definition. At the end of the 6-month study, the prevalence of LVH decreased significantly to 11% of the children (2 of 19 children), using the 95th percentile of normative pediatric LVMI data as our definition (P < .05), and did not change (5%, one child, other than at the start) using the adult definition. The data are summarized in Fig. 1.

The median LVMI decreased significantly after 6 months of ramipril treatment (data given in Table 2). Individual values of LVMI before and at the end of the study are given in Fig. 2.

Using univariate analysis, there was no significant correlation between LVMI and daytime or nighttime systolic BP. Using univariate analysis, there was no significant correlation between LVMI and daytime or nighttime systolic BP.

### Table 1. Baseline characteristics of patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median (range) or number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>15.0 (3.3–17.8)</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>14/7</td>
</tr>
<tr>
<td>BMI, absolute (g/m²)</td>
<td>21 (14.8–30.5)</td>
</tr>
<tr>
<td>BMI, relative (percentile)</td>
<td>63 (15–99)</td>
</tr>
<tr>
<td>Renal hypertension</td>
<td>17</td>
</tr>
<tr>
<td>Primary hypertension</td>
<td>4</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min/1.73m²)</td>
<td>113 (55–245)</td>
</tr>
<tr>
<td>Serum potassium (mmol/L)</td>
<td>4.4 (3.6–5.0)</td>
</tr>
</tbody>
</table>

BMI = body mass index.

FIG. 1. Effect of ramipril on the prevalence of hypertension (HT) and left-ventricular hypertrophy (LVH), using 95th percentile of normative pediatric left-ventricular mass index (LVMI) data for definition of LVH.
or diastolic BP. No significant correlation was found between LVMI and renal function or BMI. No significant correlation was found between changes in LVMI and changes in daytime or nighttime systolic or diastolic BP, changes in renal function, or changes in BMI during the study. The correlations with a trend toward a significant

Table 2. Change in left-ventricular dimensions and blood pressure in ramipril-treated patients*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>After 6 months</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ambulatory daytime systolic BP (mm Hg)</td>
<td>133.0 (112–154)</td>
<td>124.4 (110–142)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean ambulatory daytime diastolic BP (mm Hg)</td>
<td>80.0 (67–109)</td>
<td>74.3 (65–90)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Mean ambulatory nighttime systolic BP (mm Hg)</td>
<td>120.0 (109–138)</td>
<td>111.0 (97–125)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean ambulatory nighttime diastolic BP (mm Hg)</td>
<td>69.0 (53–89)</td>
<td>61.0 (51–72)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean ambulatory 24-h systolic BP (mm Hg)</td>
<td>125.5 (112–146)</td>
<td>115.5 (106–134)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean ambulatory 24-hr diastolic BP (mm Hg)</td>
<td>74.5 (64–99)</td>
<td>66.5 (60–81)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Office systolic BP (mm Hg)</td>
<td>135.0 (110–160)</td>
<td>130.0 (102–160)</td>
<td>NS</td>
</tr>
<tr>
<td>Office diastolic BP (mm Hg)</td>
<td>86.0 (70–110)</td>
<td>85.0 (60–100)</td>
<td>NS</td>
</tr>
<tr>
<td>LVMI (g/m².7)</td>
<td>37.4 (18.8–55.8), 36.2 ± 8.6</td>
<td>32.5 (19.0–52.1), 33.1 ± 7.2</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>IVS thickness (cm)</td>
<td>0.72 (0.39–1.08)</td>
<td>0.68 (0.54–1.08)</td>
<td>NS</td>
</tr>
<tr>
<td>LVPW thickness (cm)</td>
<td>0.78 (0.57–1.04)</td>
<td>0.78 (0.55–0.96)</td>
<td>NS</td>
</tr>
<tr>
<td>LVID (cm)</td>
<td>4.82 (3.16–5.58)</td>
<td>4.75 (2.69–5.77)</td>
<td>NS</td>
</tr>
<tr>
<td>RWT</td>
<td>0.31 (0.21–0.41)</td>
<td>0.30 (0.21–0.46)</td>
<td>NS</td>
</tr>
</tbody>
</table>

BP = blood pressure; IVS = interventricular septum; LVID = left-ventricular internal dimension; LVMI = left-ventricular mass index; LVPW = left-ventricular posterior wall; NS = not significant; RWT = relative wall thickness.

* Values are median (range), if not given as mean \( \pm \) SD.

FIG. 2. Effect of ramipril on left-ventricular mass index (LVMI) in individual patients.
relationship were correlations between LVMI and nighttime systolic BP ($r = 0.42$, $P = .07$), BMI in percentiles ($r = 0.43$, $P = .06$), daytime systolic BP ($r = 0.37$, $P = .12$), and 24-h systolic BP at the start of the study ($r = 0.32$, $P = .17$), and between the change in LVMI and the change in daytime systolic BP during the study ($r = 0.39$, $P = .10$). Using multivariate analysis, there was a significant correlation only between LVMI and nighttime systolic BP at the start of the study ($r = 0.46$, $P = .048$, Fig. 3).

Renal Function, BMI, and Side Effects

At the end of the study, the glomerular filtration rate did not change significantly. The median glomerular filtration rate decreased from 113 mL/min/1.73 m$^2$ (range, 55 to 245 mL/min/1.73 m$^2$) to 107 mL/min/1.73 m$^2$ (range, 54 to 195 mL/min/1.73 m$^2$). Body mass index did not change significantly; the median relative BMI increased from the 63rd percentile (range, 16th to 99th percentile) to the 67th percentile (range, 6th to 98th percentile); the median absolute BMI was 21.0 kg/m$^2$ (range, 14.8 to 30.5 kg/m$^2$) at the start of the study and 21.2 kg/m$^2$ (range, 14.8 to 30.1 kg/m$^2$) at the end of the study. Ramipril was well tolerated by the children; no child complained of a cough. The median serum potassium level did not change significantly (a decrease by 0.1 mmol/L). However, two children developed mild hyperkalemia (5.3 and 5.6 mmol/L) at the final outpatient check at 6 months, which normalized by adding a diuretic after completing the 6-month study protocol. One child who developed hyperkalemia had moderately decreased renal function (55 mL/min/1.73 m$^2$), and the second already had a high-normal potassium level at baseline (4.7 mmol/L). No significant change in hemoglobin level was noted (a decrease by 1 g/L).

Discussion

In our previous study, we showed that ramipril is a safe and effective drug for the treatment of hypertension and proteinuria in children with chronic kidney diseases. Our current study is the first prospective, interventional trial on the effects of ramipril on LVM and the prevalence of LVH in children with primary and renal hypertension. We were able to demonstrate that 6-month ramipril monotherapy can induce a significant reduction of LVM and a regression of LVH in three-quarters of the hypertensive children treated.

Left-ventricular hypertrophy is an independent predictor of cardiovascular morbidity and mortality in adults. Moreover, regression of LVH is associated with fewer cardiovascular events. Therefore, LVH is becoming an important treatment goal for hypertensive patients. All classes of antihypertensive drugs are able to reduce LVH.
However, drugs blocking the renin-angiotensin systems, such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) (eg, as used in the HOPE and LIFE trials), seem to have some benefits beyond the BP-lowering effects on regression of LVH in comparison to other antihypertensive agents.24

In children, LVH is also a prevalent cardiovascular consequence of hypertension, affecting 8% to 41% of hypertensive children,9–12,26,27 and 33% to 75% of children with chronic renal insufficiency, and children on dialysis or after renal transplantation.28–30 Because most of the children in our study had renal hypertension, it must be emphasized that children with renal hypertension have a higher prevalence of LVH than children with primary hypertension. Therefore, the relatively high LVH prevalence of 42% in our study is due to the great majority of children having chronic kidney disease. Blood pressure and BMI are the most important determinants of LVH in children.31 We found a correlation between nighttime systolic BP and LVMI using multivariate analysis. In contrast, we could not find any correlation between diastolic BP, daytime systolic BP, or BMI and LVMI, which is in accordance with other cross-sectional studies26 but in contrast to other studies showing a correlation between ambulatory BP and LVMI.27 However, a nonsignificant trend for a relationship between daytime and 24-h systolic BP and BMI and LVMI was noted in our study, suggesting that systolic BP and body composition influence LVM in hypertension children.

In children with chronic renal failure (ie, those with predialysis, dialysis, and transplants), several studies demonstrated that the regression of LVH is possible through strict BP treatment and by achieving correct dry weight and avoiding hyperhydration.32,33 However, for children with primary or renal hypertension without chronic renal failure, there are no studies investigating the effects of antihypertensive therapy on LVM and on the prevalence of LVH. Our study clearly demonstrates that BP reduction by ramipril also leads to a reduction of LVH after 6 months in most children with primary hypertension and renal hypertension without chronic renal failure. It must be stated that the regression of LVH in patients with chronic kidney diseases may be equally due to treatment of the primary renal disease. However, in our study, no child received any treatment for primary renal disease other than ramipril (ie, no steroids or immunosuppressive drugs).

Several adult studies such as the HOPE and LIFE trials showed that agents blocking the renin-angiotensin-aldosterone system, such as ACE inhibitors or ARBs, are better than other antihypertensive drugs to induce a regression of LVH.25 The authors hypothesized that ACE inhibitors or ARBs may have more effects on the heart than do drugs that merely lower BP (eg, effects on interstitial fibrous tissue). In agreement with these large studies, we did not find any correlation between the change in BP during the 6-month period of ramipril therapy and the change in LVMI. However, a trend toward a relationship between change in daytime systolic BP and change in LVMI was noted. Furthermore, since no significant correlation with BP was found with other determinants of LVM, such as BMI, renal function, or hemoglobin level, we can speculate that a part of the regression of LVH may be caused by BP-independent mechanisms because of ACE inhibition.34

Despite the beneficial effect on the prevalence of LVH (reduction from 42% to 11%), almost half of the children remained hypertensive at the end of the 6-month period of ramipril monotherapy. To achieve better BP control, about half of the hypertensive children will require a combination of antihypertensive agents. Further studies are warranted to test whether tighter BP control by combination therapy will result in further regression of LVH.

Ramipril was very well tolerated by the children in our study. We did not observe cough in any child. Mild hyperkalemia was detected in only two children: one of them had moderately decreased renal function, which is a known risk factor for the development of hyperkalemia during therapy with ACE inhibitors, and the second child already had a high-normal potassium level at the start of the study. Therefore, children with decreased renal function or high-normal potassium levels should be checked frequently for hyperkalemia during treatment with ACE inhibitors. The hyperkalemia normalized after adding diuretics at the end of the 6-month study period. No significant effects on renal function or hemoglobin level were observed.

The limitations of our study were mainly its uncontrolled and nonblind design and the lack of a comparison drug. However, our study was not designed to compare different drugs but to demonstrate that regression of LVH by antihypertensive therapy with an ACE inhibitor is possible in children with primary hypertension and renal hypertension without chronic renal failure. A further limitation of our study is the small number of patients, which makes the study insufficiently powered to detect differences in several variables. Despite these limitations, this study provides the first prospective, interventional pediatric trial on the effects of ramipril on LVM.

In conclusion, ramipril is an effective and safe drug in children with hypertension that is able to reduce LVM and induce regression of LVH.

References


