Abstract—Primary hypertension is associated with disturbed activity of the sympathetic nervous system and altered blood pressure rhythmicity. We analyzed changes in cardiovascular rhythmicity and its relation with target organ damage during 12 months of antihypertensive treatment in 50 boys with hypertension (median, 15.0 years). The following parameters were obtained before and after 12 months of antihypertensive treatment: 24-hour ambulatory blood pressure, left ventricular mass, carotid intima–media thickness, and MRI for visceral and subcutaneous adipose tissue. Amplitudes and acrophases of mean arterial pressure and heart rate rhythms were obtained for 24-, 12-, and 8-hour periods. After 1 year of treatment, 68% of patients were normotensive, and left ventricular mass and carotid intima–media thickness decreased in 60% and 62% of patients, respectively. Blood pressure and heart rate rhythmicity patterns did not change. Changes in blood pressure amplitude correlated with the decrease of waist circumference ($P=0.035$). Moreover, the decrease of visceral fat correlated with the decrease of 24-hour mean arterial pressure and heart rate acrophases (both $P<0.05$). There were no differences in changes of blood pressure and heart rate rhythms between patients who achieved or did not achieve normotension and regression of left ventricular mass and carotid intima–media thickness. It was concluded that abnormal cardiovascular rhythmicity persists in children with primary hypertension despite effective antihypertensive treatment, which suggests that it may be the primary abnormality. The correlation between changes in cardiovascular rhythmicity and visceral obesity may indicate that the visceral fat plays an important role in the sympathetic activity of adolescents with hypertension. (Hypertension. 2013;62:782-788.)

Key Words: blood pressure • child • obesity, abdominal • primary pulmonary hypertension

Most biological rhythms are driven by an internal biological clock and can be synchronized by different factors. Blood pressure (BP) is modulated in a circadian 24-hour rhythm. This cycle depends on complex internal factors, including neurogenic and endocrine fluctuations, and external factors such as physical activity and diet. Although the genesis of BP rhythmicity is controversial, an increasing amount of evidence suggests that BP rhythm is generated from oscillators within the central nervous system located in the hypothalamic suprachiasmatic nucleus, either located in discrete pacemaker neurons or originating in neuronal networks.1–3 Additionally, activity of the sympathetic nervous system and the genetic components of the circadian clock may play a fundamental role in the regulation of BP.4–5 Finally, humoral factors (angiotensin, endothelin, NO, bradykinines, insulin) participate in the determination of BP rhythms.4

Altered circadian BP rhythmicity has been described in many conditions causing increased cardiovascular risk, such as hypertension, chronic kidney disease, diabetes mellitus, and small birth weight.6–9 Because the main intermediate phenotype of adolescents with primary hypertension (PH) is visceral obesity and metabolic abnormalities, we hypothesized that normalization of BP along with the decrease of visceral fat would correlate with the normalization of altered BP and heart rate (HR) rhythmicity. Therefore, we evaluated the relationship between BP and HR rhythmicity with target organ damage (TOD) and anthropometrical and metabolic variables in adolescent boys with PH, before and after 1 year of antihypertensive therapy.

Patients and Methods
The study was performed according to the Declaration of Helsinki and with the approval of the Children’s Memorial Health Institute Ethics Committee. All patients and parents gave consent to participate in the study.

Fifty boys (age, 15.0 years; range, 8.5–17 years) with newly diagnosed PH who underwent all procedures before and after 12 months of standard antihypertensive therapy were included in the study. The exclusion criteria were the following: the presence of any significant chronic disease (except for PH) including diabetes mellitus and chronic kidney disease, any acute illness including infections in the 6 weeks preceding enrollment, and incomplete data. PH was diagnosed according to the fourth Task Force Report and confirmed by 24-hour ambulatory BP monitoring (ABPM).10
**ABPM Measurements**

All ABPM measurements were assessed oscillometrically using SpaceLabs Monitor 90207, and the most appropriate cuff was applied on the nondominant arm. Readings were taken every 20 minutes during daytime and every 30 minutes at night. Recordings lasting ≥20 hours with ≥80% of readings were considered as valid and were included in the analysis. We used a recently published classification system based on ABPM to classify patients as having normal BP, ambulatory hypertension, and severe ambulatory hypertension.21

Because the mean arterial pressure (MAP) is directly measured during oscillometric measurements (representing the BP value with the greatest oscillations) and systolic and diastolic BPs are mathematically derived with device-specific algorithms, only MAP was used for the rhythmicity analysis. BP nighttime dipping status was analyzed by calculating the ratio of MAP during the day (D) in relation to nighttime (N) MAP (MAP D/N). Dipping was a decrease in MAP of ≥10%, and nondipping was a decrease of <10%.22 Similarly, the HR nighttime dipping was described with the D/N ratio (HR D/N). The night period was defined as 00:00 hours to 06:00 hours, and the daytime period was defined as 08:00 hours to 20:00 hours. MAP, systolic BP, and diastolic BP values are presented as absolute values in mm Hg and as SD score (MAP-SDS, systolic BP-SDS, and diastolic BP-SDS).

**Rhythm Analysis**

Rhythm analysis was performed according to the procedure described elsewhere.15 In short, the 24-, 12-, and 8-hour BP and HR rhythms were analyzed using Fourier analysis. First, the 24-hour circadian rhythm was checked using the least squares analysis and was considered as present if a cosine function within 24 hours was fitted with P<0.05. Then, shorter ultradian rhythms were analyzed in the same manner. The following parameters were calculated for each significant rhythm: (1) the midline estimating statistic of rhythm (MESOR), which is the median value between the lowest and the highest values of the fitted cosine curve, (2) amplitude, which is the difference between MESOR and the highest value, and (3) acrophase, which is the time from midnight to the highest value during the rhythm.

**Fat Tissue Distribution**

Obesity was diagnosed according to International Obesity Task Force recommendations.23 Fat tissue distribution was assessed by the anthropometrical measurements including body mass index (BMI), waist circumference (WC), and waist-to-hip ratio, waist-to-height ratio. MRI with the 1.5 T whole-body scanner was used to quantify visceral adipose tissue (VAT), intraperitoneal VAT, extraperitoneal VAT, subcutaneous adipose tissue (SAT), superficial SAT, and deep SAT. The single slice at the L4–L5 level was done to measure the area of specific fat compartments.15 In short, pharmacological therapy was started according to the guidelines.20 Patients with severe ambulatory hypertension and with TOD (LVMI>95 percentile and cIMT>2 SDS, and WCSA>2 SDS) received pharmacological therapy, BP was assessed after 3 months as home and office BP and after 6 and 12 months by ABPM. If there was still stage 2 and severe ambulatory hypertension, the second drug was prescribed or pharmacotherapy commenced.

Pharmacological therapy was based on the angiotensin-converting enzyme inhibitor (ACEi; ramipril, 6 mg/m² per day). In case of an allergy or ACEi intolerance, there was an angiotensin 2 receptor type 1 blocker (valsartan, 1–4 mg/kg per day) prescribed. A Ca-blocker (amlodipine, 5 mg once daily) was used as the second drug. All patients were advised to use antihypertensive drugs in the morning and, according to parents’ information, all of them received drugs before school, usually before 8.00 am.

**Definition of Metabolic Syndrome**

Metabolic syndrome (MS) was defined according to the International Diabetes Federation Consensus on MS in children.20 WC was referred to Polish reference values.21

**Statistical Analysis**

For assessment of BP rhythms, we used the software Chronos-Fit 1.06 available at http://www.chronopharmacology.de/software.htm (P. Zuther, S. Gorbay, and B. Lemmer, Chronos-Fit 1.06, http://www.ma.uni-heidelberg.de/inst/phar/lehre/chrono.html, 2009). Data from the rhythm analysis were then analyzed in the GraphPad Software, Inc (version 6.0c; La Jolla, CA). The anthropometrical indices, IMT, WCSA, LVMI, and BP values were expressed as absolute values and SDS values. The changes in measured parameters were expressed as a delta value (Δ; ie, the difference between a measurement at the end of the 12-month period and at the beginning of treatment). The homogeneity of variance was checked with the Shapiro–Wilk test. Continuous variables with a normal distribution were compared using the Student t test for independent variables. Continuous values with abnormal distribution were compared using the Wilcoxon test.
Variables with normal distribution were presented as mean and SD values, whereas variables with abnormal distribution were presented as median and range values between the 5th and 95th percentiles. The correlation analysis was performed using Spearman test for abnormal distribution. Variables with significant correlation including changes in anthropometrical parameters, fat tissue distribution, and changes in BP and metabolic parameters were then included in the step-wise multiple regression analysis. $P$ values <0.05 were considered statistically significant, and values between 0.05 and 0.1 were considered as demonstrating trend toward significance.

**Results**

**At Diagnosis**

Of 50 (58%) boys, 29 boys had severe ambulatory hypertension, and 21 (42%) boys had ambulatory hypertension (Figure 1).

As described previously, the baseline rhythmicity data were compared with previously published referential normative values. All patients in the current analysis had reduced amplitudes of the 24-, 12-, and 8-hour BP rhythms and delayed acrophases for all circadian and ultradian rhythms compared with the reference values.

The main intermediate phenotype was truncal obesity, assessed as increased WC (Table 1). Obesity was diagnosed in 28 (56%) and MS in 11 (22%) patients. There were no significant differences in cardiovascular rhythmicity when comparing obese and nonobese subjects.

Throughout the study, 15 (30%) boys who had ambulatory hypertension without TOD received only nonpharmacological therapy. Overall, 35 (70%) boys were treated pharmacologically. Thirty-two boys with severe ambulatory hypertension and with TOD at diagnosis received pharmacotherapy at the beginning. After 3 months, nonpharmacological treatment was ineffective in 3 boys, and they necessitated pharmacological therapy. Overall, 26 boys received monotherapy (ACEi, 9 [18%] patients; angiotensin 2 receptor type 1 blocker, 11 [22%] patients; amlodipine, 6 [12%] patients), 7 boys were prescribed a second drug (amlodipine) after 3 months, and another 2 boys after 6 months (Figure 1).

Twenty-two (44%) boys had LVH including 8 (16%) with severe LVH. cIMT $>2$ SDS was found in 13 (26%) patients, and WCSA $>2$ SDS was found in 12 (24%) patients. Patients with arterial injury did not differ concerning BMI, BP, and HR rhythmicity, but had a greater amount of VAT, lower amount of SAT, greater ratio of VAT to SAT, and greater insulin resistance than patients with normal cIMT and WCSA. In contrast, patients with LVH had a greater BMI and WC but nonsignificantly greater amount of VAT and lower amount of SAT in

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**Figure 1.** Study design. PH indicates primary hypertension; and TOD, target organ damage.
comparison with patients without LVH. There was no correlation between BP and HR rhythmicity and LVH.

Assessment of the Antihypertensive Effect on the Regression of TOD, Metabolic Abnormalities, and BP/HR Rhythmicity After 1 Year of Treatment

After 1 year of treatment (pharmacological and nonpharmacological), there was significant decrease in HR and MAP, systolic BP, and diastolic BP (absolute values and Z scores; Table 1). The prevalence of ambulatory hypertension decreased from 42% to 28% ($P$=0.003), and that of severe ambulatory hypertension decreased from 58% to 4% ($P$=0.001). Normotension was obtained in 68% of boys.

Despite the significant decrease of BP and HR, there were no changes in BP and HR rhythmicity after 1 year of treatment, including changes in the prevalence of 24-, 12-, and 8-hour MAP rhythms or dipping phenomenon before and after treatment. The amplitudes of 24-, 12-, and 8-hour MAP and HR rhythms remained reduced, and acrophases of MAP/HR were still prolonged. There were no significant correlations between changes in BP rhythmicity and changes in BP. Similarly, changes in MAP and HR rhythmicity were not significantly different between children treated pharmacologically and nonpharmacologically.

After 12 months, there were no changes in the level of total cholesterol, triglycerides, high-density lipoprotein, AUC ineligible, AUC ineligible, homeostasis model assessment for insulin resistance, uric acid, high sensitive C reactive protein, homocysteine, and adiponectin, but there were significant decreases of low-density lipoprotein, AUC ineligible, and leptin level ($P$=0.04, $P$=0.01, and $P$=0.002, respectively).

After 1 year of treatment, LVH was still present in 18 (36%) boys (n.s.), severe LVH in 2 (4%) boys (n.s.), cIMT>2 SDS in 12 (24%) boys, and WCSA>2 SDS was present in 11 (22%) boys (n.s.). The prevalence of MS did not change.

No correlation was observed between changes in MAP/HR rhythmicity and changes in LVM, cIMT, BP, BMI, insulin sensitivity/resistance markers, and other metabolic risk factors. The change in 24-hour MAP amplitude correlated with the change in WC ($P$=0.035). Moreover, the decrease of VAT correlated with the decrease of 24-hour MAP and 24-hour HR acrophases (both $P<0.05$; Table 2; Figure 2). Changes of MAP and HR rhythms did not differ between patients who achieved or did not achieve normotension and regression of LVMI or cIMT, and between patients who were obese and nonobese at the beginning and after 12 months.

The step-wise regression analysis revealed that the main predictor of LVMI and cIMT regression was not BP lowering or change in BP and HR rhythmicity, but the decrease of WC ($R^2=0.205$, $\beta=0.481$, $P=0.005$; $R^2=0.183$, $\beta=0.475$, $P=0.003$). The main predictor of WCSA regression was the decrease of intraintraperitoneal VAT/SAT ratio ($R^2=0.472$, $\beta=0.476$, $P=0.004$).

Table 1. Anthropometrical, Metabolic, and Hemodynamic Data Obtained at the Start and After 12 Months of Treatment (N=50 Boys)

<table>
<thead>
<tr>
<th>Variables</th>
<th>At Start</th>
<th>After 12 Mo</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height, cm</td>
<td>174.5 (140 to 186.5)</td>
<td>177.5 (146 to 189)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>75 (38.5 to 129.5)</td>
<td>80.5 (47 to 121)</td>
<td>0.007</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.3±12.6</td>
<td>25.1±10.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>BMI SDS</td>
<td>2.03±1.5</td>
<td>2.12±1.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>WC, cm</td>
<td>85.5±12.5</td>
<td>84.8±8.5</td>
<td>n.s.</td>
</tr>
<tr>
<td>24-h SBP</td>
<td>129±6</td>
<td>128±3</td>
<td>0.08</td>
</tr>
<tr>
<td>24-h SBP-SDS</td>
<td>1.69±1.1</td>
<td>1.28±1.0</td>
<td>0.01</td>
</tr>
<tr>
<td>24-h MAP, mmHg</td>
<td>92±6</td>
<td>89±5</td>
<td>0.02</td>
</tr>
<tr>
<td>24-h MAP-SDS</td>
<td>1.34±1.0</td>
<td>0.86±0.93</td>
<td>0.004</td>
</tr>
<tr>
<td>24-h DBP, mmHg</td>
<td>72±6</td>
<td>69±6</td>
<td>0.02</td>
</tr>
<tr>
<td>24-h DBP-SDS</td>
<td>0.73±1.1</td>
<td>0.24±1.2</td>
<td>0.01</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>77±11</td>
<td>73±12</td>
<td>0.001</td>
</tr>
<tr>
<td>VAT, cm²</td>
<td>27.9 (6.4 to 97.2)</td>
<td>20.9 (0.2 to 50.4)</td>
<td>0.04</td>
</tr>
<tr>
<td>iVAT, cm²</td>
<td>15.2 (9.2 to 18.9)</td>
<td>14.2 (8.1 to 21.3)</td>
<td>n.s.</td>
</tr>
<tr>
<td>SAT, cm²</td>
<td>215.2 (123.4 to 377.4)</td>
<td>230.1 (50.0 to 473.2)</td>
<td>n.s.</td>
</tr>
<tr>
<td>cIMT, mm</td>
<td>0.43 (0.36 to 0.54)</td>
<td>0.42 (0.36 to 0.53)</td>
<td>n.s.</td>
</tr>
<tr>
<td>cIMT-SDS</td>
<td>1.2 (−1.2 to 6.2)</td>
<td>1.1 (−0.8 to 6)</td>
<td>n.s.</td>
</tr>
<tr>
<td>WCSA, mm²</td>
<td>6.5 (5.5 to 8.8)</td>
<td>6.4 (5 to 8.5)</td>
<td>n.s.</td>
</tr>
<tr>
<td>LVMI, g/m²³⁵⁷</td>
<td>35.5 (25.4 to 48.7)</td>
<td>34.2 (23.7 to 48)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>11 patients (22%)</td>
<td>12 patients (24%)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

24-h DBP indicates 24-h diastolic blood pressure; 24-h MAP, 24-h mean arterial pressure; 24-h SBP, 24-h systolic blood pressure; BMI, body mass index; cIMT, carotid intima–media thickness; HR, heart ratio; iVAT, intraperitoneal visceral fat tissue; LVMI, left ventricular mass index; n.s., not significant; SAT, subcutaneous adipose tissue; SDS, SD score; VAT, visceral adipose tissue; WC, waist circumference; and WCSA, wall cross-sectional area.
The main finding of our study is that abnormal cardiovascular rhythmicity persists in most boys with hypertension despite effective antihypertensive therapy and regression of TOD. Because the antihypertensive treatment did not alter the abnormal BP and HR rhythmicity, our results suggest that the abnormal rhythmicity is the primary pathophysiological mechanism, and that the metabolic changes may be secondarily associated with the primary abnormality.

Only few reports indicate the different role of distinct antihypertensive agents on diurnal BP and HR pattern during antihypertensive therapy. It was observed that calcium channel blockers may shorten the ultradian periodicity of BP variation as compared with other antihypertensive agents. On the contrary, ACEi had no effect on the circadian rhythm parameters of BP or HR. β-Blockers reduced the amplitude and MESOR of HR but had no effect on amplitude and acrophase of MAP. It seems that different drug classes exert different effects on the autonomic nervous system and the neurogenic and humoral factors affecting circadian rhythmicity.

The clinical characteristics including intermediary phenotype, severity of hypertension, prevalence of TOD and MS were typical for adolescents with PH. Although we did not find any significant correlation between BP rhythmicity and TOD, it has been shown in several reports that nondipping status and increased morning BP surge were associated with TOD. The lack of correlation between altered BP and HR rhythmicity and TOD in our study may be caused by the fact that absolute BP values in our patients were lower than those reported in studies of adults with hypertension. Second, the exposure to elevated BP is much shorter in adolescents with hypertension than in adults with hypertension. Thus, the relationship between altered cardiovascular rhythms and TOD may develop later in life (ie, be detected at an adult age).

Previously we found that 1 year of nonpharmacological and pharmacological therapy led to BP reduction and TOD regression, and the main predictor of TOD regression was the decrease of visceral obesity expressed as the decrease of WC. In another study, it was demonstrated that obese patients with hypertension displayed similar 24-hour, daytime, and nighttime MAP values as lean patients with hypertension. Nevertheless, the 24-hour MAP amplitudes were lower in nonobese patients with PH in comparison with obese patients with PH. Although the 24-hour MAP acrophases were similarly prolonged in both obese and nonobese children with hypertension in comparison with controls, the 12-hour MAP acrophase was delayed, whereas the 8-hour MAP acrophase was premature in lean patients with PH in comparison with obese patients with PH. Now, we focused on longitudinal changes of body fat in relation with longitudinal changes in BP and HR rhythmicity. We found that decrease of BP and changes in BP and HR rhythmicity were not independent predictors of TOD regression. However, the main independent predictor of TOD regression was decrease of visceral fat. Moreover, the decrease of visceral fat correlated also with the normalization of MAP and HR acrophases. Similarly, the decrease in visceral fat correlated with the decrease of MAP amplitude. This phenomenon may be caused by a concomitant decrease of MAP acrophases and decrease of BP.

Both experimental and clinical studies indicate that obesity is an important regulator of cardiovascular rhythmicity. VAT deposition is an important regulator of cardiovascular rhythmicity. VAT deposition is both the result and the cause of increased sympathetic activity and endocrine disturbances such as hypercortisolism, adipokines secretion, and immune activity. It is also known that insulin resistance is associated with impaired cardiovascular rhythms in humans. The autonomic neurons network innervates fat deposits, and the excess of VAT may disturb the autonomous nervous system activity through local inflammation and secretion of adipocytokines. Windham et al showed that central adiposity was associated with disturbed function of the sympathetic/parasympathetic nervous system. Gupta et al has found a subtle abnormal circadian BP variability in prediabetic and obese patients, and emphasized the hypothesis that an excess of VAT with the accompanying proinflammatory state influenced circadian BP variability and caused increased cardiovascular risk. This is confirmed by our findings that the change in BP and HR rhythmicity correlated with the change in visceral adiposity expressed as the decrease of VAT but not with changes in BMI. Therefore, the decrease of WC may be a marker of treatment efficacy not only in terms of regression of TOD but also normalization of BP rhythmicity. Although the correlations between changes in VAT and changes in BP rhythms were quite strong, as for biological systems, they were only of moderate power with r ranging from 0.22 to 0.45. It suggests that the effects caused by VAT are modulated by other factors both independent of VAT such as diet and activity, and dependent of VAT and caused by cytokines, hormones, and immune activity.

Second, the finding that despite BP normalization, cardiovascular rhythms did not change may explain the fact that antihypertensive treatment (both nonpharmacological and
pharmacological) is difficult to withdraw in PH even after achieving normotension.

Limitations
The major limitation of our study is having only a small number of patients and relatively short period of follow-up. One can assume that longer follow-up of patients who are treated and achieved normotension can allow finding substantial changes in BP rhythms and relation with TOD. The other limitation is complex antihypertensive therapy (both pharmacological and nonpharmacological) and the various antihypertensive agents (ACEi, angiotensin II blocker type 1 blocker) used in our study. It makes it impossible to assess the role of each of them on BP/HR rhythmicity; this was however not the aim of the study. Moreover, patients’ adherence to nonpharmacological and pharmacological treatment were evaluated only by asking patients and their parents. Third, although our data suggest that the abnormal rhythmicity is the primary problem, study design does not allow discerning this hypothesis with certainty.

Conclusions
Our study suggests that disturbed BP and HR rhythmicity is a primary phenomenon in children with hypertension. We found that despite BP lowering, the circadian profile of BP and HR rhythms did not normalize on therapy. However, the decrease of VAT predicted both TOD regression and improved cardiovascular rhythms. These findings underline the importance of disturbed body composition in the pathogenesis of hypertension.

Perspectives
The relationship between altered cardiovascular rhythmicity and visceral adiposity may be important in view of new treatment strategies in PH. The therapy should focus not only on BP lowering or the decrease of BP variability but also on normalization of fat tissue distribution and reduction of VAT. Because this relationship has not been studied in children in the past, it would be interesting to analyze whether this correlation is present in healthy children compared with obese or prehypertensive peers. It is also important to characterize the effects of different antihypertensive medication on BP and HR rhythms. Finally, further studies should be done to analyze whether altered cardiovascular rhythms are a primary or secondary phenomenon in children with hypertension.

Acknowledgments
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Disclosures
None.

References


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**Novelty and Significance**

**What Is New?**

- This study demonstrates that altered blood pressure (BP) rhythmicity may be a primary phenomenon in patients with primary hypertension. However, a complex nature of interactions between cardiovascular rhythmicity and external factors should be considered in predicting cardiovascular outcomes.

**What Is Relevant?**

- Fat tissue distribution modifies BP rhythmicity and influences cardiovascular complications. Decrease of visceral adiposity, regardless of BP lowering, is the main predictor of both normalization of BP rhythmicity and target organ damage regression.

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**Summary**

Disturbed fat tissue distribution plays an important role in both target organ damage and BP rhythmicity in children with primary hypertension. Additionally, the decrease of visceral fat can improve BP rhythmicity and target organ damage. Thus, the normalization/improvement of body composition should become a part of cardiovascular prevention or antihypertensive therapy.
Blood Pressure Rhythmicity and Visceral Fat in Children With Hypertension
Anna Niemirska, Mieczyslaw Litwin, Janusz Feber and Elzbieta Jurkiewicz

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