Possible Correlation Among Echocardiographic Measures, Serum Brain Natriuretic Peptide, and Angiotensin II Levels in Hypertensive Kidney Transplanted Children

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Abstract

Objectives: Ambulatory blood pressure monitoring is the standard for determining patients at risk of hypertension. Left ventricular hypertrophy is common in kidney transplant recipients. We evaluated the correlation between blood pressure measures achieved by ambulatory blood pressure monitoring and conventional (office) methods.

Materials and Methods: This cross-sectional study was done from December 2009 to October 2010 at Alzahra Hospital in Isfahan, Iran. Sixty five participants, 35 kidney transplant recipients under 20 years old, and 30 control subjects of the same age were recruited. Five kidney recipients did not complete the study and were excluded. Blood pressure was measured by ambulatory blood pressure monitoring and conventional methods. Echocardiographic study was done for kidney transplant recipients. Serum brain natriuretic peptide and angiotensin II levels were determined in case and control groups.

Results: Office-recorded systolic and/or diastolic hypertension was observed in 43.4% and 55.3% of patients. According to ambulatory blood pressure monitoring, 86% of kidney transplant recipients had systolic BP load. Left ventricular hypertrophy (defined according to the left ventricular mass index \( \text{left ventricular mass index/height}^2 \)) was seen in 53.3% of the patients. The existence of left ventricular hypertrophy revealed a positive correlation with ambulatory blood pressure monitoring systolic and diastolic night blood pressure and systolic nondipper. Left ventricular mass index showed a positive correlation with brain natriuretic peptide level. Furthermore, the existence of left ventricular hypertrophy was positively correlated with angiotensin II level.

Conclusions: Only ambulatory blood pressure monitoring systolic and diastolic blood pressures (nondippers) were positively correlated with left ventricular hypertrophy and higher left ventricular mass index. Serum levels of brain natriuretic peptide and angiotensin II had a positive relation with left ventricular hypertrophy. Measuring brain natriuretic peptide and angiotensin II in the clinical setting screens patients at risk of left ventricular hypertrophy.

Key words: Ambulatory blood pressure monitoring, Non dipping, Left ventricular mass index, Left ventricular hypertrophy, Children, Nocturnal blood pressure

Introduction

Cardiovascular complications including left ventricular dysfunction and left ventricular hypertrophy (LVH) are considered independent risk factors for mortality in end-stage renal disease and kidney transplant recipients.\(^1\)\(^2\) The nondipping pattern (defined as a nocturnal blood pressure falling less than 10%) is high among kidney transplant recipients.\(^3\)\(^4\) High blood pressure (BP) measures 1 year after kidney transplant is considered a predictor of graft function.\(^5\) Nondipper kidney transplant recipients have been regarded as a high risk for end-organ damage.\(^6\) Ambulatory BP monitoring (ABPM) allows physicians to find nondippers.
Regarding the mechanism of hypertension, plasma aldosterone, and angiotensin levels play a major role in producing LVH.\(^7\) In addition, levels of atrial natriuretic peptide and brain natriuretic peptide (BNP) have been correlated with left ventricular dilatation and dysfunction in chronic kidney diseases.\(^8\)-\(^10\) We compared the BP measurements by ABPM and office-recorded BPs and evaluated their correlation with plasma levels of BNP, angiotensin II, and left ventricular mass index (LVMI) in kidney transplant recipients.

**Materials and Methods**

This cross-sectional study was performed from December 2009 to October 2010 at Alzahra Hospital in Isfahan, Iran. Sixty five participants, 35 kidney transplant recipients younger than 20 years old and 30 control subjects of the same age were recruited into the study. Controls were persons younger than 18 years referred from private pediatric clinics for routine examination.

Inclusion criteria for controls were systolic and diastolic blood pressure between the 25th and 50th percentile for age and height, normal serum creatinine, with no history of kidney diseases and urinary tract infections. Kidney transplant recipients who met the inclusion criteria (aged younger than 20 years, stable renal function, no acute rejection in the last 3 months, and the time since transplant more than 6 months) were recruited.

Blood pressure was measured by sphygmomanometer in the office for all participants. For each participant, BP was measured 3 times using the appropriate cuff. The mean of 3 measures was recorded as “office BP measures.” However, BP was evaluated by ABPM method for the patient group only. An ABPM device (Aspel CR07, ASPEL S.A., Zabierzów, Poland) recorded BP using the spectrophotometry technique. The basis for the definition of hypertension in children was adapted from the report of the Second Task Force on BP Control in Children.\(^11\) Hypertension was defined as an average systolic BP (SBP) and/or diastolic BP (DBP) greater than the 95th percentile for age and height and sex with 10 measurements attained during the day and 3 at night. Nocturnal dipping was considered a drop in mean BP during sleep of 10% or more of the mean arterial pressure when awake. Elevated BP load (systolic or diastolic) was defined as greater than 30% of all BP readings above the 95th percentile for the patient’s age.

Echocardiography was performed using a Medison EKO-7, (Samsung, Seoul, South Korea) with a 2- to 4-MHz transducer probes. Echocardiographic dimensions were reported as the means of at least 3 cardiac cycles, according to the American Society of Echocardiography. Left ventricular mass index was obtained using M-mode echocardiography in the parasternal long axis view. Left ventricular measurements were made at, or just below, the tips of the leaflets of the mitral valve as described by Devereux and associates.\(^12\) Left ventricular mass was calculated from measurements in centimeters by using the thickness of the ventricular septum, the left ventricular internal dimension, and the thickness of the posterior left ventricular wall, all in diastole, by the following regression equation (Penn convention)\(^12\):

\[
\text{LV mass (g)} = 1.04 \times [(\text{LVDd} + \text{IVST} + \text{PWT})^3 - (\text{LVDd})^3] - 13.6
\]

where LVDd is LV end-diastolic dimension, IVST is interventricular septal thickness, and PWT is posterior wall thickness.

As correcting left ventricular mass for height minimizing the effect of sex, race, age, and obesity, the index of left ventricular mass (LVMI) was calculated as left ventricular mass divided by height in meters.\(^13\) The definition of LVH remains in debate. In children, LVH used to be defined as the LVMI value of 38.6 g/m\(^{2.7}\), which defines the 95th percentile of LVMI distribution in healthy children and adolescents from 6 to 17 years of age.\(^11\) Moderate left ventricular hypertrophy was defined as left ventricular mass index more than 51 g/m\(^{2.7}\).\(^14\) To determine mild, moderate, and severe LVH, the following measures were used:

**Male patients** (LV mass/height\(^{2.7}\) (g/m\(^{2.7}\)): mild = 45-51, moderate = 52-58, severe = more than 59.

**Female patients** (LV mass/height\(^{2.7}\) (g/m\(^{2.7}\)): mild = 49-55, moderate = 56-63, severe = more than 64.\(^15\)

Height and weight were measured with the subjects in stocking feet and lightly clothed. Written or oral consent was obtained from all the patients and their parents. The survey was performed in accordance with the ethical standards of the Helsinki Declaration and approved by the Ethics Committee.
of the Research Department of Isfahan University of Medical Sciences.

Serum angiotensin II levels were measured using the enzyme-linked immunosorbent assay ELISA method (Phoenix Kit, Burlingame, CA, USA), and BNP serum levels were determined using the ELISA method (Bachem Americas Kit, Torrance, CA, USA).

Statistical analyses
Statistical analyses were performed with SPSS software (SPSS: An IBM Company, version 18.0, IBM Corporation, Armonk, New York, USA). Differences between groups were assessed by independent t test and 1-way analysis of variance, Pearson product-moment correlation coefficient, and regression analysis were performed to assess any correlation between the variables.

Results
From 65 participants recruited in the study, 5 kidney recipients did not complete the study and were excluded. The case-to-control ratio was 1/1. In the case group, 17 patients of 30 (56.6%) were male and the rest were female. The male:female ratio in the case group was 1.30/1. The mean age in the case and control groups were 176.25 ± 41.02 and 143.12 ± 92.02 months (P > .05) (Table 1).

The means of systolic and diastolic office-recorded BP in the case and control groups were significantly different (P < .05) (Table 1). Approximately, 76% of the patients had received antihypertensive medications. Irrespective of receiving antihypertensive medications, office-recorded systolic and/or diastolic hypertension was observed in 43.4% and 55.3% of the patients. Office-recorded diastolic BP had no correlation with ABPM diastolic BP. While, systolic office-recorded BP had positive correlation with daytime ABPM systolic BP; P = .01, r=0.414 (Table 2). According to ABPM, 86% of the kidney transplant recipients had systolic BP load. The means of office-recorded systolic BP was significantly lower than ABPM day-systolic BP (111.00 ± 3.85 mm Hg vs 129.13 ± 1.97 mm Hg) (P = .03). The same significance was achieved between office-recorded diastolic BP and ABPM day-diastolic BP (P = .025). About 46% and 60% of the patients were either diastolic or systolic nondipper.

The mean AG II in the case group was significantly higher than it was in the control group (0.74 ± 0.07 vs 0.54 ± 0.09; P = .039). Serum AG II levels were positively correlated with both systolic and diastolic nondipper (r=0.579; P = .001, and r=0.554; P = .001). The difference between night and day diastolic BP was significant (74.53 ± 10.86 mm Hg and 85.23 ± 8.93 mm Hg; P = .001). The mean of LVMI/height 2.7 (g/m 2.7 ) was 49.9 ± 23.7 in the case group. Left ventricular hypertrophy (defined according to the LVMI/height 2.7 ) was observed in 53.3% of the patients. Mild, moderate, and severe LVH were observed in 16%, 17.3%, and 20% of the patients. The

### Table 1. Participants’ Blood Pressure Measurements, Demographic, and Laboratory Data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Case Mean ± SE</th>
<th>Control Mean ± SE</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mo)</td>
<td>176.25 ± 41.02</td>
<td>143.12 ± 92.02</td>
<td>.08</td>
</tr>
<tr>
<td>Systolic BP office (mm Hg)</td>
<td>111.00 ± 3.85</td>
<td>100.11 ± 2.53</td>
<td>.02</td>
</tr>
<tr>
<td>Diastolic BP office (mm Hg)</td>
<td>68.33 ± 2.72</td>
<td>60.10 ± 1.01</td>
<td>.035</td>
</tr>
<tr>
<td>Systolic BP night (ABPM) (mm Hg)</td>
<td>117.33 ± 2.22</td>
<td>Not measured</td>
<td></td>
</tr>
<tr>
<td>Systolic day (ABPM) (mm Hg)</td>
<td>129.13 ± 1.97</td>
<td>Not measured</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP night (ABPM) (mm Hg)</td>
<td>74.53 ± 1.98</td>
<td>Not measured</td>
<td></td>
</tr>
<tr>
<td>Diastolic day (ABPM) (mm Hg)</td>
<td>85.23 ± 1.63</td>
<td>Not measured</td>
<td></td>
</tr>
<tr>
<td>Systolic night BP drop (dipping) (mm Hg)</td>
<td>-11.80±1.57</td>
<td>Not measured</td>
<td></td>
</tr>
<tr>
<td>Diastolic night BP drop (dipping) (mm Hg)</td>
<td>-10.70 ± 1.50</td>
<td>Not measured</td>
<td></td>
</tr>
<tr>
<td>Day heart rate (rate/min)</td>
<td>80.23 ± 1.72</td>
<td>Not measured</td>
<td></td>
</tr>
<tr>
<td>Night heart rate (rate/min)</td>
<td>73.63 ± 1.90</td>
<td>Not measured</td>
<td></td>
</tr>
<tr>
<td>Angiotensin II (ng/dL)</td>
<td>167.00 ± 12.88</td>
<td>Not measured</td>
<td></td>
</tr>
<tr>
<td>BNP (ng/dL)</td>
<td>1531.66 ± 31.98</td>
<td>18.25 ± 3.08</td>
<td>.0001</td>
</tr>
</tbody>
</table>

Abbreviations: ABPM, ambulatory blood pressure monitoring; BNP, brain natriuretic peptide; BP, blood pressure; LVM, left ventricular mass

### Table 2. Correlation Between Blood Pressure Measures By Ambulatory Blood Pressure Monitoring and Auscultatory Methods

<table>
<thead>
<tr>
<th>Blood Pressure Measures</th>
<th>Systolic Office Auscultatory Method</th>
<th>Diastolic Office Auscultatory Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABPM systolic day</td>
<td>P = .01</td>
<td>P = .032</td>
</tr>
<tr>
<td>ABPM diastolic day</td>
<td>Not significant</td>
<td>Not significant</td>
</tr>
<tr>
<td>ABPM systolic night</td>
<td>P = .007</td>
<td>r=0.434</td>
</tr>
<tr>
<td>ABPM diastolic night</td>
<td>Not significant</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

Abbreviations: ABPM, ambulatory blood pressure monitoring
mean of LVMI was 167 ± 70.56 grams. The existence of LVH showed a positive correlation with ABPM systolic and diastolic night BP and systolic nondipper \((P = .035, r=0.336; P = .025, r=0.360; \text{and } P = .024, r=0.365)\). Left ventricular mass index had a positive correlation with BNP level \((P = .04, r=0.271)\). Nonetheless, no echocardiographic parameters were correlated with conventional BP measurements (office-recorded). Both ABPM systolic night minus systolic day BP (systolic nondipper) and ABPM night diastolic minus day diastolic BP (diastolic nondipper) were strongly correlated with AG II levels \((P = .0001, r=0.629 \text{ and } P = .001, r=0.554)\). Furthermore, the existence of LVH had a positive correlation with AG II levels \((P = .029, r=0.349)\).

**Discussion**

We evaluated BP measurements achieved by ABPM and conventional methods in kidney transplant recipients younger than 20 years, and we evaluated the correlation between these parameters with LVMI, serum AG II, and BNP levels. To the best of our knowledge, this is the first study in a pediatric transplant setting that has assessed the correlation between BP measures and LVMI, serum AG II, and BNP levels simultaneously. Ambulatory blood pressure monitoring allows physicians to ascertain high BP in patients at risk. The task force IV recommended ABPM can be used not only for confirming white-coat hypertension but also for selecting patients who are candidates for antihypertensive medications.\(^{16}\) \(\text{This method has been accepted as the method of choice in evaluating blood pressure in pediatric patients.}\)

Left ventricular hypertrophy, a feature of hypertensive cardiac remodeling, is a known risk factor for cardiovascular mortality and morbidity.\(^{17}\) Patients with normal glomerular filtration rates but with hypertension and LVH had a 3.3-fold higher risk of cardiac sequelae.\(^{18}\) Groothoff and associates reported LVH in 47% of male and 39% of female children with end-stage renal disease.\(^{19}\) The prevalence of LVH increases with the severity of hypertension and may reach 100% in patients with severe hypertension.\(^{20}\) Left ventricular hypertrophy has been introduced as one of the most common echocardiographic findings after renal transplant.\(^{21}\) It has been reported that pediatric kidney transplant recipients are at continuous risk of developing LVH and cardiovascular complications.\(^{22}\) According to Mitsnefes and associates, 55% of children that underwent kidney transplant had LVH.\(^{23}\) Matteucci and associates reported LVH in 82% of pediatric kidney transplant recipients.\(^{24}\) We observed LVH in 53.3% of patients (mild LVH = 16%; moderate = 17.3%; severe = 20%). The prevalence of severe LVH was unexpectedly high in our patients. Undertreatment of hypertension is responsible for LVH in our patients. Most of the patients with severe LVH had high diastolic BP (office and ABPM recorded).

A survey of 190 patients younger than 19 years revealed a BP-load in approximately 87%.\(^{25}\) A similar BP load (86%) was recorded in our patients. McGregor and associates recorded nondippers in 68% of adult kidney transplant recipients.\(^{26}\) However, nondipping was not related to the degree of autonomic dysfunction.\(^{26}\) Morgan and associates reported 33% hypertension by casual BP monitoring and 40% by ABPM in children after renal transplant. The BP load and nondipping were demonstrated in 44% and 58% of their patients.\(^{27}\) Basiratnia and associates reported hypertension in 57% of kidney transplanted recipients by conventional method. However, ABPM showed that 75.7% of their patients were hypertensive.\(^{28}\) We recorded hypertension in 43.4% and 86% of patients measured by the conventional method and ABPM. The significant difference between the prevalence of hypertension defined by our 2 methods warrant the risk of missed hypertension and consequently, LVH in kidney transplanted recipients. Using ABPM decreases the possibility of white-coat hypertension. Higher amounts of ABPM comparing with office-recorded measures revealed that patients had real hypertension but not white-coat hypertension.

Left ventricular hypertrophy, as a frequent finding in kidney transplant recipients, correlated with LVMI/height\(^2\text{7}\) and BP measures obtained by the ABPM method.\(^{24,29,30}\) Repeat BP measurements by the ABPM method enhanced the chance of finding a correlation between ABPM and LVMI.\(^{31}\) Nonetheless, Morgan and associates found no correlation between LVMI and ABPM data.\(^{27}\) However, Mitsnefes and associates reported that only systolic BP was the predictor of LVMI in pediatric posttransplant.\(^{23}\) Approximately 60% of our patients were systolic nondippers. We showed that ABPM systolic and diastolic night BP and systolic nondipper measurements were more closely
related to LVH than conventional BP readings taken in the office.

Day-night changes in SBP (systolic nondipper) are attributed to cyclosporine dosage and poor kidney function. The role of cyclosporine dosage was not evaluated in our patients.

Atrial natriuretic peptide has several functions. It is known for its inhibitory effect on aldosterone release. Patients with hypertension and LVH have higher atrial natriuretic peptide levels than those with no LVH. In adult kidney recipients, Hestin and associates demonstrated that the high BP had a positive correlation with serum atrial natriuretic peptide levels. Serial measures of atrial natriuretic peptide and BNP in hypertensive adult patients with LVH showed that lowering blood pressure by angiotensin converting enzyme inhibitors results in decreased BNP levels but not in atrial natriuretic peptide levels. Furthermore, atrial natriuretic peptide has an antagonist effect on the renin-angiotensin-aldosterone system by attenuating the vasoconstrictive effect of angiotensin II. The positive correlation between BNP and LVMI has been discussed in hypertensive adults. In addition, BNP has been introduced as a risk marker of cardiovascular events in hypertensive patients. Rinat and associates reported BNP and 76 amino acid N-terminal fragment (NT-Pro BNP) as simple and reliable markers of LVH and systolic and/or diastolic hypertension. In addition to kidney transplant recipients, serum BNP is a good indicator of LVH in children undergoing dialysis. We found a positive correlation between the existence of LVH and BNP. Furthermore, LVMI had a positive correlation with AG II and BNP.

We conclude that BNP has a relation with LVH and increased LVMI. A high percentage of our patients had being receiving antihypertensive medications. However, conventional office-recorded BP did not identify the true incidence of hypertension verified by ABPM. The majority of our patients had hypertension regarding ABPM measures. Neither systolic nor diastolic office-recorded BPs had a correlation with LVH and LVMI. Indeed, only ABPM systolic and diastolic BPs (nondippers) were positively correlated with LVH and higher LVMI. Serum levels of BNP and AG II had an association with LVH. These biochemical substances are useful indicators of LVH and high LVMI in pediatric kidney transplant recipients. Adding measurement of BNP and AG II in clinical setting screens patients at risk of LVH.

References


