Hypertension After Pediatric Heart Transplantation is Primarily Associated With Immunosuppressive Regimen

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Background: Hypertension is recognized as prevalent in pediatric cardiac transplant recipients. This study investigated risk factors for this complication and, in particular, the role of immunosuppression.

Methods: Results of 24-hour ambulatory blood pressure monitoring of children surviving more than 1 year after cardiac transplantation were analyzed retrospectively. Subjects were designated either hypertensive or normotensive by comparison with published normal values. To identify factors associated with hypertension, clinical data contemporaneous with 24-hour ambulatory blood pressure monitoring were collected and compared between the groups.

Results: In the 51 children studied, the incidence of hypertension was 49%. Hypertensive and normotensive recipients were similar for sex, age at transplantation, time between transplantation and 24-hour ambulatory blood pressure results, and choice of calcineurin inhibitor. In contrast, hypertensive patients were taking significantly more immunosuppressive agents (2.92 vs 2.12 $p < 0.01$), had higher tacrolimus levels (10 vs 8.1 μg/liter, $p = 0.03$), and were more likely to be on maintenance prednisone therapy (64% vs 23%, $p < 0.01$) or regimens including sirolimus (40% vs 12%, $p = 0.03$). Multiple regression analysis controlling for tacrolimus level showed a combination of prednisone and sirolimus was more strongly associated with hypertension than either agent alone, with an odds ratio of 7.3 (95% confidence interval, 1.5–36.1) vs 4.1 (95% confidence interval, 0.85–26.3).

Conclusions: Hypertension after pediatric cardiac transplantation is a common problem and primarily associated with immunosuppressive regimen. J Heart Lung Transplant 2008;27:501–7. Copyright © 2008 by the International Society for Heart and Lung Transplantation.

According to the registry of the International Society for Heart and Lung Transplantation (ISHLT), hypertension is present in 47% and 63% of pediatric patients, respectively, at 1 and 5 years after heart transplantation.[1] In adult heart transplant recipients, the etiology of hypertension appears multifactorial, primarily related to the effects of calcineurin inhibitors, but with abnormal neural-hormonal reflexes also implicated.[2–4] Little is known about the cause of this complication in children.

Diminution of the normal nocturnal fall in blood pressure (BP) is recognized in adults and children after heart transplantation,[5,6] and clinic BP measurements consistently under-represent recipients' hypertensive burden.[6,7] Ambulatory blood pressure (ABP) monitoring for 24 hours is therefore preferred when studying hypertension in these populations.

The only previous pediatric study of 24-hour ABP after cardiac transplantation found abnormal recipient BP profiles compared with those of healthy school children. Recipients had elevated mean night and daytime diastolic BPs and a decreased nocturnal systolic BP fall.[6] All the subjects in that study were managed using a steroid-free, cyclosporine-based regimen, whereas worldwide, 40% of pediatric heart transplant recipients remain on corticosteroid therapy 5 years after transplantation and 50% are managed with tacrolimus.[1] It has been suggested that tacrolimus induces less hypertension than cyclosporine.[8,9]

Since 2003, pediatric heart transplant recipients older than age 5 years followed up at the Hospital for Sick Children, Toronto (HSC), have undergone routine 24-hour ABP monitoring. Immunosuppression regimens are individualized and vary. The institutional choice of calcineurin inhibitor is tacrolimus, but patients previously established on cyclosporine are not switched without indication, steroids are weaned from those without history of rejection, use of mycophenolate (MMF) or azathioprine depends on tolerance, and as we have previously reported, sirolimus is used in selected patients.[10]

We wished to establish the incidence, severity, and 24-hour pattern of hypertension in this heterogeneous group of pediatric heart transplant recipients and to

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determine whether any associated factors could be identified. In addition, by considering data from hypertensive subjects with repeated 24-hour ABP recordings, we sought to see how well hypertension was controlled over time.

METHODS

The Institutional Ethics Board approved this study. Data were obtained retrospectively from our pediatric transplant database. All children aged 5 to 18 years who had survived more than 1 year after cardiac transplantation and were followed up at our institution beyond the time when 24-hour ABP monitoring became available were identified. The study population comprised those who had undergone at least one 24-hour ABP recording whilst clinically well. Subjects with 24-hour ABP results of inadequate quality or with incomplete recordings were excluded.

The 24-hour ABP was recorded using an Ultralite 90217 ambulatory BP monitor (SpaceLabs Medical, Inc, Redmond WA). This oscillometric device initially inflates to 165 mm Hg and inflates on subsequent recordings to 30 mm Hg above the previous SBP. It was set to measure BP every 15 minutes during daytime hours and every 30 minutes at night. Before daytime measurements, a beep was sounded and children were asked to stop their activities at this point until the end of the recording. Beeps were not sounded at night. Pressure transducer channels zeroed automatically before each recording, and the machine was calibrated annually in accordance with manufacturer's instructions.

The 24-hour ABP results were compared with published age- and sex-matched normal values in 4 domains: mean daytime systolic BP and diastolic BP, and mean nighttime systolic BP and diastolic BP.[11] The mean pressures in each domain were classified as hypertensive if above the 95th centile for normal.[11] When present, the severity of hypertension was assessed by expressing the number of measurements exceeding the 95th centile as a percentage of the total number of measurements made in that domain. The percentage change in mean systolic and diastolic BPs between daytime and nighttime was also calculated and compared with published normal values.[11]

To facilitate analysis of clinical factors associated with hypertension, subjects were divided into 2 groups according to results of their initial 24-hour ABP: "hypertensive" if their mean BP was high in 1 or more domains and "normotensive" if their mean BP was normal in all 4 domains. In the initial analysis, grouping was only based on hypertension as demonstrated on 24-hour ABP monitoring and not the use of anti-hypertensive medications. Data contemporaneous with 24-hour ABP recordings and details of anti-hypertensive medication in the first 3 months after transplant were extracted from the database.

Glomerular filtration rate (GFR) was used as a marker of renal function. Had a radioisotope study been performed within 1 month of the 24-hour ABP, this was used; otherwise, GFR was estimated using the formula proposed by Schwartz.[12] Plasma creatinine concentrations and height measurements for the formula were made within 1 month of the 24-hour ABP measurement. Measures of cardiac diastolic dysfunction and left ventricular hypertrophy were taken from echocardiographic studies performed within 3 months of the 24-hour ABP study. Data were compared between the groups. A separate analysis was made to identify factors associated with hypertension at night.

The medical records and 24-hour ABP results of hypertensive patients who underwent more than one 24-hour ABP recording were examined to qualitatively assess the effectiveness of our anti-hypertensive interventions.

Statistical Methods

The descriptive statistics of skewed continuous data are presented as the median (interquartile range). Clinical characteristics expressed as means were compared between the groups using a 2-tailed unpaired Student's *t*-test for normally distributed data and a 2-tailed Mann-Whitney test for data that were not normally distributed. Clinical characteristics expressed as percentages of the group were compared using the Fisher exact test. Multiple logistic regression analysis was used to assess the association between hypertension and immunosuppressive agents. The interaction of immunosuppressive agents in combination was also considered.

RESULTS

At the time of data collection and analysis in April 2007, 155 pediatric heart transplants had been performed at HSC during 15 years. There were 53 children aged 5 to 18 years who had been followed up at the hospital, had survived more than 1 year after transplantation, and for whom results of 24-hour ABP recordings were available. Two patients were excluded because their 24-hour ABP recordings were of insufficient quality for further analysis. The remaining 51 children, (25 boys), were the subjects of our study.

Of the 51 subjects, 30 had received a transplant for congenital heart disease and 21 for cardiomyopathy. Before the measurement of 24-hour ABP, 7 subjects underwent retransplantation. The median age at first transplantation was 1.6 years (range, 0.45–7.37 years). The 24-hour ABP monitoring was initially performed at a median of 5.5 years (range, 4.1–7.4 years) after the first transplantation. Follow-up from the initial 24-hour ABP recording to the time of this study was for a median