Research Article



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Is B-type natriuretic peptide clinically useful after pediatric heart transplantation?

Bibhuti B Das*

Department of Pediatric Cardiology, Joe DiMaggio Children's Hospital Heart Institute, Memorial Health Care, Hollywood, FL, USA

Abstract

The evidence for BNP-guided management of pediatric heart transplant recipients is scarce. A search in PubMed with no date or language restriction resulted in 8 studies reporting relation between BNP and rejection, 2 studies on the time course of BNP levels after heart transplantation, one study each reporting relationship of BNP with cardiac allograft vasculopathy and post-transplant mortality. So far, the data available can only support BNP as an adjunctive marker, not a stand-alone test, in the screening of hemodynamically significant cardiac pathology in pediatric heart transplant recipients. A serial intraindividual measurements of BNP level rather than an absolute cut-off value, can be useful in combination with the patient's clinical condition to facilitate management of post-heart transplant care in children.

Abbreviations: BNP: Brian type natriuretic peptide; HT: heart transplant; CAV: cardiac allograft vasculopathy; EMB: endomyocardial biopsy

Introduction

B-type natriuretic peptide (BNP) or the N-terminal segment of pro-BNP (NT-proBNP) is released from ventricular myocardium in response to wall stress due to conditions that lead to increased preload and/or afterload, decreased systolic and/or diastolic ventricular function. The active segment of BNP has natriuretic, vasodilatory, diuretic, anti-proliferative, anti-fibrotic effects and counteracts the renin-angiotensin-aldosterone and sympathetic nervous systems. Over the last decade, a number of small studies have shown that BNP may have potential as a diagnostic and prognostic marker, in which high levels suggest either allograft rejection, cardiac allograft vasculopathy (CAV), or hemodynamic derangement. There is no large scale randomized study to validate the role of BNP as a useful marker of cardiac allograft function and International Society for Heart and Lung Transplantation (ISHLT) guidelines do not recommend BNP for monitoring of acute cardiac allograft rejection [1]. In this brief report, we summarized the published data on the role of BNP as a diagnostic marker after heart transplant (HT) in children.

Time course of BNP level after transplant

Plasma BNP level is universally elevated in children after HT and decrease exponentially in time to 100 pg/ml by 14 weeks after HT was reported in 44 children by Lan, *et al.* [2]. This study showed a return of BNP levels to a relatively normal range unlike adult studies where BNP levels rarely return to normal. The decrease in BNP was not correlated to left ventricular dimension, it appears the mechanism of BNP release in the transplanted heart may be different. Increased BNP level has been found in postoperative period after cardiopulmonary bypass in children [3]. The BNP assay is affected by several other factors including the assay used, age (higher normal values are observed with increasing age), sex (higher values are observed in female), body mass index (lower levels are observed with a higher body mass index), renal dysfunction, inflammatory conditions, steroid therapy, diurnal variation and time

since transplant [4]. These biological variables should be kept in mind as they can influence the reference range for BNP that is often utilized to exclude or confirm a diagnosis.

In healthy children, plasma BNP levels significantly decrease from infancy to adolescence, and then subsequently increase at the onset of puberty to finally reach adult levels [5]. In the acute setting, if there is a clinical suspicion for cardiovascular disease, the currently described discriminatory levels for BNP are: for 1st week of life-cut off of 170 pg/ ml (sensitivity 94%, specificity 73%) and older infants and children up to 19 years-cut off of 41 pg/ml (sensitivity-87% and specificity-70%) [6]. In children with moderately symptomatic HF, BNP \geq 140 pg/ml (sensitivity 71% and specificity 63%) is independently associated with worse outcomes [7]. The interpretation of BNP kinetics in children after HT appears to be more difficult and discrepancies may also be related to the age and sex of the donors.

Relation between BNP and Rejection

The "gold standard" of assessment for cardiac rejection is by histologic examination after endomyocardial biopsy (EMB), using the ISHLT standardized grading system [8]. We found 8 published studies (with a total of patients 422) assessing the relationship between biopsy rejection grade and BNP (or NT-BNP) levels [9-16]. There appears to be a division of opinion over whether there is a consistent relationship between BNP and rejection, with 6 studies [9-14] claiming a relationship, and 2 studies [15-16] refuting such a relationship.

The first report of a significant relationship between BNP levels and cardiac allograft pathology was done by Caludius, *et al.* in 2003 [9]. In 37 consecutive pediatric HT patients who underwent cardiac catheterization, EMB, and echocardiography and BNP levels at the

^{*}*Correspondence to:* Bibhuti B. Das, MD, FAAP, FACC, Joe DiMaggio Children's Hospital Heart Institute Memorial Health Care, 1150 North 35 Avenue, Hollywood, FL 33021, USA, E-mail: bdas99@hotmail.com

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time of catheterization were reviewed. In 9/37 patients who had positive for cardiac pathology had BNP levels ranged from 221 to 1,300 pg/ml, median 614. In the no-pathology group, BNP levels were 20 to 290 pg/ml, median 44 pg/ml. All patients in the pathology group had BNP levels >100 pg/ml and in no-pathology group, only 22% had BNP levels >100 pg/ml. Using BNP threshold of 100 pg/ml as cut-off point for normal allograft, BNP has a high negative predictive value for excluding allograft pathology in pediatric HT recipients.

In 2004, Lindblade, et al. [10], analyzed 211 consecutive plasma BNP measurements in 59 pediatric HT patients along with right ventricular EMB samples. The authors found that patients with a biopsy positive patients had significantly higher level than those with biopsy negative for rejections (p<0.04). This study also showed that a serial BNP titer may be influenced by severe rejection episodes, CAV, and diastolic dysfunction. This study suggested that the cutoff diagnostic value for pediatric allograft rejection may need to be determined for each patient during a clinically stable course proved by normal EMB. The discriminatory capacity of BNP to detect acute rejection was also discussed by Geiger, et al. [11]. In a 53 pediatric HT recipients, BNP value of >700 pg/ml was 100% sensitive and 92% specific for detecting acute rejections (negative predictive value 92%). In a larger study [12] (560 biopsy samples taken from 86 patients), there was a positive association of BNP with acute rejections. After 1 year post-HT, BNP levels <100 pg/ml correlates with a <1% chance of acute rejections. It was therefore suggested that the discriminatory capacity of BNP to detect rejection is high that it may obviate the need for EMB in some cases. Other studies [13,14] also found a significant relationship between BNP and rejection.

Other investigators [15,16] did not detect a significant association between BNP and rejection. As previously stated, the timing of the BNP estimation after transplantation may be an important factor. Hall and colleagues [15] showed no significant difference of BNP levels and acute cellular rejections, however BNP correlates with right-sided pressures, not with other hemodynamic measurements. The authors suggested BNP may have a complimentary role in monitoring of children following HT. Similarly, Sparks, *et al.* [16] have showed that BNP levels correlated modestly with right atrial pressure (r=0.46, p<0.0001) and pulmonary capillary wedge pressure (r=0.26, p<0.001), but poorly with echocardiogram findings of ventricular function. They did not find significant change in BNP without significant rejections with severe hemodynamic compromise.

BNP level and cardiac allograft vasculopathy

A single center retrospective study of transplant recipients <21 years of age, showed that a BNP level >100 pg/ml was correlated with coronary vasculopathy (p=0.006), high right atrial pressure (p=0.024), and hematocrit (p=0.006) [17]. The authors concluded that, BNP may have utility in monitoring of cardiac performance with the caveat that a low hematocrit can also affect its levels. A correlation between diffuse myocardial fibrosis which is considered secondary to microvascular coronary disease after HT and BNP level has been reported [18]. Linear correlations between worsening of global longitudinal strain with high BNP levels, end-diastolic left ventricular volume, and pulmonary capillary wedge pressure have also been reported [19].

BNP level and prediction of survival after transplantation

One study assessed the relationship between BNP level and survival after HT. Bramlet, *et al.* [20] studied 53 pediatric HT recipients and showed that a log fold increase from the median BNP, or a BNP value >250 pg/ml increases the risk of death or re-transplant and suggested a

90-day period of heightened clinical surveillance, perhaps necessitating increased immunosuppression medications.

The BNP levels remain elevated after HT, likely because of increased secretion and/or decreased clearance of the natriuretic peptides. Ationu, *et al.* [21] studied the gene expression of ventricular and atrial natriuretic peptide in patients undergoing HT and found that these peptides may be involved in ventricular remodeling after transplantation. Levels of BNP increases in proportion to the extent of left and right ventricular dysfunction after HT. Clinically complicated cardiac transplantation (cardiac systolic dysfunction, renal failure) is associated with the higher level of circulating BNP, and clinically successful cardiac transplantation (mild cardiac diastolic dysfunction) is associated with moderately increased BNP values. Surprisingly, however, increased BNP has also been found after HT in the absence of hemodynamic perturbations or allograft rejection, raising the possibilities that even subtle modification in the immune system might influence BNP expression.

In conclusion, recent data support the use of BNP as a marker about intravascular volume status and monitoring the serial intraindividual measurements of BNP levels rather than absolute values, which can be used in combination with the patient's clinical condition to facilitate treatment decisions. Further investigation of the intricacies of plasma BNP elevation observed after transplantation will enhance the usefulness of plasma BNP values and will be helpful to elucidate the true prognostic value of BNP in pediatric HT recipients.

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