Influence of Cardiac Diseases on Plasma Brain Natriuretic Peptide Level in Chronic Hemodialysis and Kidney Transplantation Patients

RASHA A. DARWISH, M.D.*; MOHAMED A. HUSSEIN, M.D.*; ALAA M. ABD EL-HAMID, M.D.*;
EMAN F. RAMZY, M.D.** and MOHAMED H. HAFEZ, M.D.*

The Departments of Internal Medicine* and Clinical Pathology**, Faculty of Medicine, Cairo University

Abstract

Background and Objectives: The N Terminal of pro Brain Natriuretic Peptide (NT-pro BNP) is an important biomarker in prognostication and risk stratification of Cardiovascular Disease (CVD) and is significantly associated with decreased Glomerular Filtration Rate (GFR) and Chronic Kidney Disease (CKD) but with insufficient data to establish clear cut off values. In this work, we aimed to find a correlation between plasma NT-pro BNP levels and parameters of echocardiography with establishing of clear cut off values in this setting.

Patients and Methods: Serum NT pro BNP {in pictograms per milliliter (pg/ml)} was measured in 20 patients on Hemodialysis (HD) with cardiac disease, 15 Renal Transplanted (RTx) patients in addition to 10 HD patients with no current or previous cardiac disease as a control group.

All patients in the study were subjected to echocardiography and assessment of fluid status by measuring of Inferior Vena Cava diameter (IVCd) by ultrasonography.

Results: Serum NT pro BNP levels in all included patients were elevated more than 10 folds the upper limit of normal with HD cardiac and RTx patients had 4 folds and 2 folds higher levels than the controls "HD non cardiac patients" respectively. We noticed a higher estimated Left Ventricular Ejection Fraction (LVEF) in RTx compared to HD patients and cut off values of >4.500pg/ml and 3.852pg/ml of the hormone for differentiating cardiac disease in HD and RTx patients respectively. We also found a significant diagnostic value of the hormone in the HD cardiac patients in differentiating cases with Systolic Dysfunction (SD) with cut off value of >5.500pg/ml, Left Ventricular Hypertrophy (LVH) and Coronary Artery Disease (CAD) with cut off value of 4.000-4.500pg/ml with all a high sensitivity of 87-100% and a relatively low specificity of 50%. NT pro BNP cut off value of >4.500pg/ml was helpful for detection of LVH in RTx patients while no value for detection of hydration status, differentiating cases with Diastolic Dysfunction (DD) in HD and Rtx patients or SD and CAD in Rtx patients.

Conclusion: NT pro BNP cut off limits can help in early detection of CVD in HD and RTx patients and renal trans-
plantation may reduce the risk of CVD compared with HD patients.

Key Words: *Cardiac disease – Renal transplantation – Hemodialysis – NT pro BNP.*

Introduction

CVD is the leading cause of death in CKD patients and represents 50% to 60% of posttransplantation mortality [1]. This necessitates its early diagnosis which unfortunately couldn't be achieved by neither echocardiography nor electrocardiogram (ECG). Plasma NT pro BNP levels are elevated in patients with End Stage Renal Disease (ESRD) and renal failure patients in presence or absence of clinically significant heart failure [2] with CAD, diabetes mellitus, dialysis and as yet unidentified other factors like myocarditis, micro infarcts and retained uremic toxins are suggested as possible other mechanisms [3]. But unfortunately until now there are contradictory results in usefulness of this biomarker in identifying high risk patients that allows early treatment institution and better outcome.

Patients and Methods

Thirty patients on regular HD were recruited from King Fahd Renal and Dialysis Unit, Department of Internal Medicine, Cairo University Hospitals; 20 of them with cardiac disease in addition to 10 patients with no prior or current cardiac disease as a control group. The study also included 15 renal transplanted patients who were previously dialyzing and recruited from the same unit in addition to the New Kasr Al-Ainy Teaching Hospital during 2014. Sera of patients were collected and NT pro BNP was measured using a commercially available electro-chemoluminescence immu-

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Correspondence to: Dr. Rasha A. Darwish, The Department of Internal Medicine, Faculty of Medicine, Cairo University

noassay that was performed on a Roche E2010 modularanalytics system, with a measuring range from 5 to 35.000 pg/ml. Transthoracic echocardiography was done for all patients to measure Left Ventricular Enddiastolic diameter (LVDd), Left Ventricular Endsystolic diameter (LVDs), Interventricular Septal Thickness (IVST), Left Atrial Diameter (LAD) and Left Ventricular Posterior Wall Thickness (LVPWT), LVEF calculated by standard techniques and Left Ventricular Mass (LVM) calculated by the regression equation described by Devreux and Reichek [4] according to which, a candidate was considered to have LVH if LVM was >157g in females and 200g in males. SD was diagnosed if EF was <54%. We assessed hydration status of patients by measuring IVCd by ultrasound from a subcostal view during quiet respiration [5].

Statistical analysis:

Data were analyzed with SPSS version 16 Chicago, USA. Data for continuous variables were expressed as means ± SD and median. Categorical variables were expressed as absolute numbers and percentages. Comparison between two groups was analyzed by non parametric test: Mann-Whitney test for continuous variables; and fisher exact test for discrete variables. The student unpaired *t*-test was used to determine significance for numeric variables. Spearman, s rank univariate correlation study was done for correlation between two continuous variables. *p*-value <0.05 is considered statistically significant. Separate Receiver Operating Characteristic curves (ROC) were generated for NT pro BNP and detection of SD, DD, LVH and Segmental Wall Motion Abnormality (SWMA). The best cut off was defined on the basis of analysis of the ROC curves by identifying the value of the biomarker that gave the best combination of sensitivity and specificity that is the value that maximized the sum of the sensitivity and specificity. The ROC curve analysis was performed using the MedCalc software version 7.50 (Mariakerke, Belgium).

Results

The mean age for control group, HD patients with cardiac disease and those with RTx were (35.5±9.812), (46.05±9.944) and (33.9 ± 11.76) years respectively with female to male ratio of (50%:50%), (40%:60%) and (33.3%:66.7%) respectively. The following (Table 1) summarizes the baseline demographic, clinical, biochemical, dialysis and echocardiographic parameters of the studied groups.

The mean serum NT pro BNP levels were (4.995 ±2.324), (17.788±11.718) and (9.991 ±8.207) pg/ml in controls, HD cardiac and RTx patients respectively i.e HD cardiac and RTx patients had 4 folds and 2 folds higher levels than the controls respectively with overall elevation more than 10 folds the upper limit of normal "155pg/ml and 222pg/ml in females aged <50 and between 50-65 years respectively and 84pg/ml and 194pg/ml in males aged <50 and between 50-65 years respectively" Fig. (1) and Table (1).

Our findings revealed no statistical significant differences of serum NT pro BNP levels according to gender in all groups as shown in (Table 2).

In the ANOVA analysis between and within group, significant differences were found in age (*p*:0.003), EF (*p*:0.014) and NT pro BNP levels (*p*:0.002) as shown in (Table 3).

The multiple comparison table showed significant p values on comparing NT pro BNP values in the controls and HD cardiac group (*p* 0.003) as well as in the measured EF between RTx group (mean: 57.15%) and HD cardiac group (mean: 49.75%, *p*:0.035) as shown in (Tables 4,5).

NT pro BNP had a significant diagnostic value for differentiating cardiac cases in HD patients with IVCd <2.5cm as the area under the corresponding ROC curve (AUC) was 0.832 (95%CI, 0.682-0.982; *p*:0.004) and > threshold of diagnostic indifference (50%), cut off value 4.585pg/ml resulted in 84% sensitivity and 50% specificity.

Other valuable cut off values of NT pro BNP in differentiating other echocardiographic parameters among studied groups using ROC curves are shown in (Table 6).
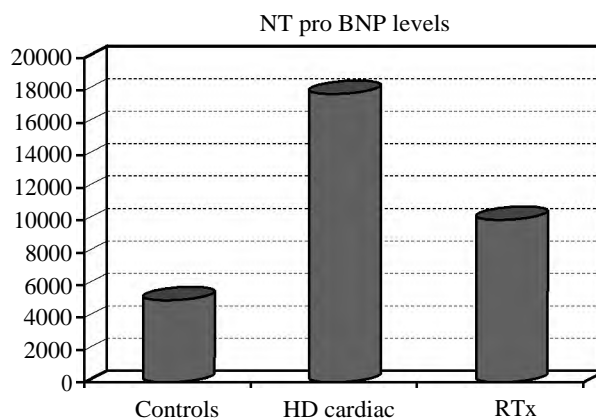

Fig. (1): Mean NT pro BNP among study population.

Table (1): Important demographic, clinical and biochemical parameters.

	Age	HD dura	Creat	Urea	EF%	LVM	IVCd	NT pro BNP
Controls:								
Mean	35.50	22.98	9.110	121.90	57.78	154.30	1.450	4,995.50
SD	9.812	22.751	2.4251	17.910	4.738	41.870	0.4403	2,324.604
HD cardiac:								
Mean	46.05	65.80	9.070	112.30	49.75	168.85	1.416	17,788.23
SD	9.944	57.742	2.3582	20.267	9.391	51.188	0.4858	11,718.492
RTx:								
Mean	33.93	54.80	1.727	62.67	57.13	159.73	1.740	9,991.73
SD	11.768	32.775	0.5725	14.019	8.034	43.234	0.4205	8,207.128
Total:								
Mean	39.67	52.62	6.631	97.89	53.91	162.58	1.532	12,346.57
SD	11.838	46.559	4.0011	30.885	8.886	46.055	0.4693	10,462.665

SD : Standard Deviation.   RTx : Renal Transplantation.   LVM : Left Ventricular Mass.
HD : Hemodialysis.   EF   : Ejection Fraction.   IVCd : IVC diameter.

Table (2): Gender pro BNP in study population variations of NT.

	Gender (N)	Mean (pg/ml)	SD	Test statistics Mann-Whitney U	*p*-value
Controls	F (5)	5,749.80	3,041.918	10.000	0.602
	M (5)	4,241.20	1,217.714		
HD cardiac	F (8)	15,558.38	10,809.899	41.000	0.589
	M (12)	19,274.80	12,522.214		
Rtx	F (5)	8,495.20	3,399.591	24.000	0.903
	M (10)	10,740.00	9,888.104		

Table (3): ANOVA analysis between and within group.

	Sum of square	DF	Mean square	F	*p*-value
Age:					
Between groups	1,481.617	2	740.808	6.642	0.03
Within groups	4,684.383	42	111.533		
Total	6,166.000	44			
HD Dur:					
Between groups	52,263.794	2	26,131.897	1.262	0.294
Within groups	870,006.156	42	20,714.432		
Total	922,269.950	44			
EFL:					
Between groups	636.597	2	318.299	4.730	0.014
Within groups	2,759.039	41	67.294		
Total	3,395.636	43			
LVM:					
Between groups	1,593.394	2	796.697	0.365	0.697
Within groups	91,731.583	42	2,184.085		
Total	93,324.978	44			
IVC d:					
Between groups	0.985	2	0.493	2.377	0.105
Within groups	8.705	42	0.207		
Total	9.691	44			
NT pro BNP:					
Between groups	1,215,793,766.345	2	607,896,883.173	7.091	0.02
Within groups	3,600,769,673.883	42	85,732,611.283		
Total	4,816,563,440.228	44			

Table (4): Multivariate comparisons (clinical and laboratory).

Dependent variable	(I) Group	(J) Group	Mean difference (I-J)	SD. Error	p-value	95% confidence interval Upper Bound	95% confidence interval Lower Bound
Age	Cont	HD car	−10.550 (*)	4.090	0.040	−20.75	−0.35
		RTx	1.567	4.311	1.000	−9.18	12.32
	HDx car	Cont	10.550 (*)	4.090	0.040	0.35	20.75
		RTx	12.117 (*)	3.607	0.005	3.12	21.11
	RTx	Cont	−1.567	4.311	1.000	−12.32	9.18
		HD car	−12.117 (*)	3.607	0.005	−21.11	−3.12
HD Dur	Cont	HD car	−42.825	55.742	1.000	−181.83	96.18
		RTx	−91.825	58.757	0.377	−238.35	54.70
	HDx car	Cont	42.825	55.742	1.000	−96.18	181.83
		RTx	−49.000	49.160	0.974	−171.59	73.59
	RTx	Cont	91.825	58.757	0.377	−54.70	238.35
		HD car	49.000	49.160	0.974	−73.59	171.59
NT proBNP	Cont	HD car	12,792.727 (*)	3,586.069	0.003	21,735.19	−3,850.26
		RTx	−4,996.233	3,780.049	0.580	14,422.42	4,429.95
	HDx car	Cont	12,792.727 (*)	3,58 6.069	0.003	3,850.26	21,735.19
		RTx	7,796.494	3,162.616	0.054	−90.02	1 5,683.01
	RTx	Cont	4,996.233	3,780.049	0.580	−4,429.95	14,422.42
		HD car	−7,796.494	3,162.616	0.054	−15,683.01	90.02

*: The mean difference is significant at the 0.05 level.

Table (5): Multivariate comparisons (echocardiographic parameters).

Dependent variable	(I) Group	(J) Group	Mean difference (I-J)	SD. Error	p-value	95% confidence interval Upper Bound	95% confidence interval Lower Bound
EF	Cont	HD car	8.028	3.293	0.058	−0.19	16.25
		RTx	0.644	3.459	1.000	−7.99	9.28
	HDx car	Cont	−8.028	3.293	0.058	−16.25	0.19
		RTx	−7.383(*)	2.802	0.035	−14.38	−0.39
	RTx	Cont	−0.644	3.459	1.000	−9.28	7.99
		HD car	7.383(*)	2.802	0.035	0.39	14.38
LVM	Cont	HD car	−14.550	18.100	1.000	−59.69	30.59
		RTx	−5.433	19.079	1.000	−53.01	42.14
	HDx car	Cont	14.550	18.100	1.000	−30.59	59.69
		RTx	9.117	15.963	1.000	−30.69	48.92
	RTx	Cont	5.433	19.079	1.000	−42.14	53.01
		HD car	−9.117	15.963	1.000	−48.92	30.69
IVC d	Cont	HD car	0.0340	0.1763	1.000	−0.406	0.474
		RTx	−0.2900	0.1859	0.379	−0.753	0.173
	HDx car	Cont	−0.0340	0.1763	1.000	−0.474	0.406
		RTx	−0.3240	0.1555	0.130	−0.712	0.064
	RTx	Cont	0.2900	0.1859	0.379	−0.173	0.753
		HD car	0.3240	0.1555	0.130	−0.064	0.712

*: The mean difference is significant at the 0.05 level.

Table (6): Important NT pro BNP cut off values in the study.

	NT pro BNP cut off level (pg/ml)	Sensitivity (%)	Specificity (%)	95% CI p-value
Cases with SD in HD group versus controls	4,232.50	100	50	1.000-1.000 0.001
Cases with CAD in HD versus controls	4,195	87	50	0.551-1.024 0.041
Cases with LVH in HD versus controls	4,232.50	90	50	0.654-1.046 0.008
LVH in RTx versus controls	4,991	100	50	0.871-1.063 0.018
Positive SD cases from negative in HD cardiac patients	5,472	100	69	0.590-0.992 0.036
Positive LVH cases from negative in RTx patients	4,642	100	67	0.747-1.087 0.030

SD = Systolic dysfunction.   LVH = Left ventricular hypertrophy.

Discussion

In our study, NT pro BNP levels were higher in females in the control group in agreement with Leowattana et al., [6] who showed that NT pro BNP levels increased with age and female gender. This could be attributed to the premenopausal hormonal changes leading to salt and water retention. On the other hand levels in HD cardiac patients in our work were higher among males that might be explained by the higher age group and percentage of smokers (40%) "predominating in males" in HD group compared to the controls raising the chance for cardiac diseases while in RTx patients, the lower number of included female patients (only 33%) made such comparison less important and necessitates further studies.

In our study, hypertensive patients represented 30%, 85% and 48.9% of control, HD cardiac and RTx patients respectively and the multiple comparison table showed non significant differences among studied groups regarding NT pro BNP levels and pulse pressure in accordance with wieshammer et al., [7] who stated that in the absence of cardiac complications, NT pro BNP wasn't associated with hypertension per se, but in contrary to Rajat et al., [8] who reported such association in absence of cardiac disease.

None of our controls were diabetic versus 25% and 6.7% of HD cardiac and RTx patients respectively. Elevated NT pro BN is not a marker for the presence of diabetes mellitus as such [9] but robustly an independent predictor of heart disease and its consequences in diabetic patients [10].

Neither ANOVA analysis nor multiple comparison tables in our results showed significant relation between NT pro BNP levels and IVC diameter similar to Hebl et al., [11] and Lee et al., [12] who documented that hydration status wasn't reflected adequately by NT pro BNP in contrary to Sommerer et al., [13] who stated that NT pro BNP had a high predictive value for hypervolemia in HD patients as defined by many parameters including respiratory collapse of the IVC. We think that these differences might be related to difference in included patients whether cardiac or renal and also whether the endpoint was the diameter or the functional capacity (respiratory collapse) of the IVC.

High NT pro BNP values in the control group in our study were close to a previous cohort of HD patients without CVD with a mean of 4.524pg/ml versus 4.995±2.324 in our study [13] and even with a higher cut off value (9.084.00±2,316.39) as suggested by Tony et al., [14] that could be explained by lack of exclusion of cardiac cases in the latter study. Racek et al., [15] also clarified elevated NT pro BNP levels in their HD patients even without a diagnosis of heart disease and explained their findings based on chronic volume overload and reduced renal excretion in CKD patients.

Regarding RTx patients, elevated NT pro BNP levels in our results may be related to hypertension (48.9% of patients), CAD (13.3%), SD (6.7%) and/or LVH (20% of patients in this group).

An interesting finding in the ANOVA analysis in our results was the significance difference of NT pro BNP levels between HD cardiac and control patients (p 0.003) which was not the case in RTx

patients (p 0.054) that may be explained by performing the hormonal assessment in the latter group early in the posttransplantation period in the majority of cases; a theory that was previously documented by Zbrog et al., [16] who found that NT pro BNP levels decreased gradually posttransplantation with cut off values after 6 month much lower than those after 3 month.

In our study, ROC curve analysis in HD cardiac patients revealed significant diagnostic value of NT pro BNP in differentiating cardiac cases from controls in general (cut off value >4.500pg/ml) and LVH and CAD cases (cut off value 4.000-4.500pg/ml) in particular with all a high sensitivity of 87-100% but a relatively low specificity of 50%. The highest sensitivity and specificity values were found when ROC curve analysis was done for differentiating positive SD cases from negative (100% and 69% sensitivity and specificity respectively for 5.472 cut off value). These findings were close to the work of David et al., [17] who stated that an NT pro BNP cut off value of 5000pg/ml resulted in as sensitivity of >90% and specificity of 80% for diagnosis of LVD. Sharma et al., [3] results showed also that patients with raised NT pro BNP had a larger LV cavity, reduced systolic function and higher LV filling pressure than those without, they also suggested that CAD, lower GFR and dialysis were associated with higher NT pro BNP levels. In another study by Ronco and Cruz [18], they noticed that levels of BNP were higher in patients with compared to those without CAD. Moreover, Tony et al., [14] reported that CAD wasn't only associated with higher levels of the hormone but also could predict the severity of the disease in ESRD especially in those on HD. This wasn't the case in a study by Madsen et al., [19] who found no statistical significant correlation between NT pro BNP levels and CAD in predialysis patients and this may point to the importance of HD process itself in CAD.

As found in our study, Maoujoud et al., [20] results showed a significant positive correlation between NT pro BNP levels and LVM with a close cut off value 4.002pg/ml while Kadiroglu et al., [21] couldn't find any correlation between the hormone and LVH but again in predialysis stage that also may point to the effect of HD on LVH.

Regarding our RTx patients, their NT pro BNP levels were more than 10 folds the upper limit of normal range, 2 folds higher than control group and almost the half compared to HD cardiac group. This was in agreement with Taskapan et al., [22] who reported that RTx reduces the risk of CVD in

comparison with those on regular HD but still higher than healthy people.

Our results revealed an EF of (57.78±4.738%), (49.7±9.391%) and (57.13±8.034%) in controls, HD cardiac and RTx patients respectively with ANOVA analysis showed significant difference in EF among studied population (p:0.014) and the multiple comparison table suggested a significant difference in comparing EF of the HD cardiac and RTx patients (p:0.035). This improvement of EF up on RTx was in concordance with the findings of Wali et al., [23] who concluded that RTx in ESRD patients with advanced systolic heart failure resulted in an increase in LVEF, improved functional status and increased survival.

According to our findings, NT pro BNP was valuable for the detection of cardiac cases in RTx patients with cut off value of 3.852.50pg/ml resulted in a 80% and 50% sensitivity and specificity respectively with LVH was the only echocardiographic parameter strongly correlated to the hormonal level; a finding that agreed with Zbrog et al., [16] and Slubowska et al., [24] studies with the former study suggested hypertension as a cause of such increase of LVM.

None of our control or RTx groups had DD versus 35% of the HD cardiac group in which NT pro BNP had no significant diagnostic value for differentiating DD cases from controls in agreement with Dubin et al., [25] who concluded the same in their HD patients but unlike John et al., [26] who noticed a positive correlation between the hormone and DD assessed by echocardiography or nuclear medicine scintigraphy in their CKD patients on HD.

Regarding our results, we want to stress on two findings; first we think that it may be relevant to use a cut off value with a higher sensitivity at the expense of low specificity as mentioned above as there is no harm in detecting some false positive patients better than missing them. Second, we concluded that the role of NT pro BNP seems to be more significant regarding SD diagnosis which is of huge clinical importance since SD is an independent CV risk factor in patients on maintenance HD and currently considered one of the strongest predictors of CV and total mortality in the dialysis population as stated by Mallamaci F et al., [27].

Codognotto et al., [28] also mentioned that the increased level of NT pro BNP is the most important prognostic factor even in the absence of severe heart dysfunction and CAD events without any relationship with endothelial dysfunction, inflam-

matory biomarkers or with acute fluid removal. They suggested a cut off value of 10.000pg/ml to identify HD patients with a higher risk of death. Furthermore, Winkler et al., [29] noticed that increased NT pro BNP levels were strongly predictive of an increased risk of CV events and mortality. Unfortunately, follow-up of our cases to assess the mortality wasn't done in the current study and is strongly recommended in further studies.

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الملخص العربى

أثبتت الدراسات العلمية آن الإصابة بأمراض القلب والأوعية الدموية هو أحد آهم آسباب الوفاة فى مرضى القصور الكلوى وكذلك بعد عمليات الزرع الكلوى مما يستوجب تشخيصها المبكر الذى لا يمكن تحقيقه بإستخدام رسم القلب الكهربائى ولا الموجات الصوتية على القلب. معامل الدرار الدماغى بى ان بى هو أحد آهم الهرمونات التى ثبت آهميتها فى تشخيص ومتابعة آمراض القلب ولكن تضاربت الدراسات حول إستخدامها فى مرضى القصور الكلوى ولذا فى هذه الدراسة حاولنا إستخدام قياس مستوى هذه المادة فى الدم كمؤشر للإصابة بأمراض القلب فى مرضى القصور الكلوى فى حالات الاستصفاء الدموى وحالات ما بعد الزرع الكلوى وكذلك دراسة مستوى محدد لهذه المادة بالدم يحدث عنده الاصابة بالآمراض والتغييرات القلبية المختلفة فى هؤلاء المرضى.

تم تقسيم المرضى المشاركين فى الدراسة الى ثلاث مجموعات: الاولى تتكون من عشرين مريضا بالفشل الكلوى المزمن تحت الإستصفاء الدموى المنتظم ويعانون من آمراض قلبية والثانية من خمسة عشرة آخرين من مرضى الزرع الكلوى كانوا تحت الاستصفاء الدموى سابقا بينما المجموعة الثالثة من عشرة مرضى بالفشل الكلوى المزمن تحت الاستصفاء الدموى المنتظم ولا يعانون من آمراض قلبية كمجموعة ضابطة.

تم إجراء موجات صوتية على القلب وآخرى على البطن لقياس قطر الوريد الأجوف السفلى كمعيار لمستوى السوائل بالدم بالإضافة إلى قياس مستوى هرمون بى ان بى بالدم لجميع المرضى المشاركين بالدراسة.

وقد آظهرت الدراسة آن مستوى الهرمون بالدم يزيد عن عشرة آضعاف المعدل الطبيعى فى جميع المرضى المشاركين بالدراسة وآن مستواه فى المجموعة الآولى والثانية يعادل آكثر من ٤ مرات وضعف مستواه بالمجموعة الثالثة الضابطة على الترتيب. آوضحت الدراسة آيضا آن عملية الزرع الكلوى تقلل الإصابة بأمراض القلب والى تحسن القدرة الإنقباضية لعضلة القلب بالمقارنة بمرضى الإستقصاء الدموى كما آظهرت النتائج إمكانية إستخدام هذه المادة كدليل على الإصابة بأمراض القلب عامة وذلك عند مستوى آعلى من ٤.٥٠٠ بيكوجرام/ميلليليتر تقريبا والإصابة بالخلل الإنقباضى بالقلب عند مستوى آعلى من ٥.٥٠٠ بيكوجرام/ميلليليتر، تضخم البطين الآيسر وقصور الشرايين التاجية بالقلب عند مستوى يتراوح بين ٤.٠٠٠ و٤.٥٠٠ بيكوجرام/ميلليليتر خاصة وذلك فى مرضى الإستصفاء الدموى المنتظم بينما فى مرضى الزرع الكلوى يمكن إستخدام هذه المادة كدليل على الإصابة بأمراض القلب علة وذلك عند مستوى ٣.٨٥٢ بيكوجرام/ميلليليتر وتضخم البطين الآيسر خاصة وذلك عند مستوى آعلى من ٤.٥٠٠ بيكوجرام/ميلليليتر تقريبا، بينما لم تثبت الدراسة وجود علاقة بين بى ان بى وكل من قطر الوريد الأجوف السفلى كدليل على إرتفاع مستوى السوائل بالجسم وكذلك الخلل الإنبساطى بالقلب فى كل من مرضى الإستصفاء الدموى والزرع الكلوى وآيضا كل من الخلل الإنبساطى والإصابة بالقصور بالشريان التاجى بالقلب فى مرضى الزرع الكلوى.