Dopamine and Noradrenaline Are Unrelated to Renalase, Heart Rate, and Blood Pressure in Heart Transplant Recipients

G. Wasilewski[a,*], P. Przybyłowski[a], L. Janik[a], E. Nowak[b], J. Sadowski[a], and J. Małyszko[c]

[a]Department of Cardiovascular Surgery and Transplantology, Jagiellonian University, Medical College, John Paul II Hospital, Cracow, Poland; [b]Brothers Hospitallers of St. John of God Hospital, Department of Internal Medicine and Angiology, Cracow, Poland; and [c]2nd Department of Nephrology, Medical University of Bialystok, Bialystok, Poland

ABSTRACT

Introduction. Renalase may degrade catecholamines and regulate sympathetic tone and blood pressure. The aim of this study was to assess dopamine, norepinephrine, and renalase in 80 heart transplant recipients and 22 healthy volunteers and their correlations with heart rate, blood pressure control, type of hypotensive therapy, and renal function.

Patients and Methods. Renalase, dopamine, and norepinephrine were studied by using commercially available assays.

Results. Renalase levels were higher in heart transplant recipients compared with healthy volunteers, and noradrenaline levels were lower in the studied cohort patients than in the healthy volunteers. Noradrenaline was correlated with white blood cell count ($r = -0.21$, $P < .05$), copeptin ($r = 0.41$, $P < .01$), and left ventricular diameter ($r = -0.29$, $P < .05$), whereas dopamine was correlated in univariate analysis with white blood cell count ($r = -0.22$, $P < .05$), posterior wall of left ventricular diameter ($r = 0.58$, $P < .01$), and left atrium diameter ($r = -0.31$, $P < .05$). Neither noradrenaline nor dopamine was correlated with heart rate, blood pressure, kidney function, or New York Heart Association class. Noradrenaline was significantly higher in patients with elevated diastolic blood pressure (>90 mm Hg) compared with those with normal diastolic blood pressure ($P < .05$). Renalase was related to kidney function but was unrelated to catecholamines.

Conclusions. Elevated renalase levels in heart transplant patients were related to kidney function but not linked to the sympathetic nervous system activity in this study population. In heart transplant recipients, these findings might suggest that sympathetic denervation and the modulation of β-receptors persist.

AFTER solid organ transplant (especially heart and kidneys), patients are prone to suffer from hypertension. Elevated blood pressure is an extremely important risk factor for cardiovascular diseases such as coronary artery disease, chronic heart failure, stroke, and chronic kidney failure. Optimal blood pressure in the general population is <140/90 mm Hg; among patients with chronic kidney disease or diabetes, it should be <130/80 mm Hg, according to the European Society of Hypertension/European Society of Cardiology and Joint National Committee 7 guidelines [1,2]. Despite optimal medical therapy, blood pressure control in this group is far from satisfactory. Sometimes even polytherapy does not ensure that target blood pressures will be reached [3]. An immunosuppressive regimen after heart transplantation consists of a calcineurin inhibitor (cyclosporine or tacrolimus) combined with mycophenolate mofetil, azathioprine, or everolimus and prednisone. The adverse effects of immunosuppressive drugs are well known. One of the most significant drawbacks of calcineurin inhibitors is possible damage to the kidneys [4]. The majority of patients in long-term follow-up after heart transplant experience chronic kidney disease.

*Address correspondence to Grzegorz Wasilewski, MD, Department of Cardiovascular Surgery and Transplantology, Jagiellonian University, Medical College, John Paul II Hospital, Pradnicka st. 80, 31-202 Cracow, Poland. E-mail: grzegorz.wa@interia.pl

0041-1345/14
http://dx.doi.org/10.1016/j.transproceed.2014.09.033

Previously, adverse effects of immunosuppression were thought to be responsible for the pathogenesis of hypertension. Recently, authors have studied other metabolic factors such as the abnormalities in the process of circulating catecholamine degradation. Catecholamines are eliminated from circulation by methylation (catechol-O-methyltransferase) or by deamination with monoamine oxidases. In 2005, Xu et al [5] discovered and described a new protein, released by the kidney, which they named renalase. They observed in vitro degradation of catecholamines by renalase and predicted that it may have a significant hemodynamic effect in vivo. Renalase infusion in rats caused a dose-dependent decrease in cardiac contractility, heart rate, and blood pressure and prevented a compensatory increase in peripheral vascular tone. The recent study by Desir et al [6] in 5 of 6 nephrectomized rats, using in vitro enzymatic assays and in vivo administration of recombinant renalase, showed that it acts as NADH-dependent oxidase which lowers blood pressure by degrading plasma epinephrine. They also found that human renalase 1 had low activity against dopamine and did not metabolize norepinephrine. Conversely, it was reported that serum renalase levels were significantly higher in kidney or heart transplant recipients than in healthy volunteers [7]. The genetic studies confirmed the connection between renalase and hypertension [8,9].

Taking into account available data about the relationship between renalase, catecholamines, and blood pressure, we decided to conduct the first (to our knowledge) in vivo study of plasma catecholamines (dopamine and norepinephrine) concentrations and serum renalase levels in heart transplant recipients and to evaluate correlations of those parameters with blood pressure control and heart rate.

PATIENTS AND METHODS

The studies were performed on 80 prevalent heart allograft recipients. All patients were transplanted according to the Shumway-Cooley-Brock technique. Ten patients (13%) had diabetes. The immunosuppressive regimen of prevalent patients consisted of tacrolimus (n = 26 [32%]), cyclosporine (n = 53 [67%]), and rapamycin (n = 1 [1.2%]) in combination with mycophenolate mofetil (n = 66 [82%]) and everolimus (n = 14 [18%]). Thirty patients (38%) were also given prednisone at a dose of 5 to 7.5 mg/d. Drug level monitoring (trough [C0]) was conducted by using the enzyme multiplied immunoassay technique method.

The mean age of patients enrolled in the study was 53.4 years. There were 19 female subjects (24%) and 61 male subjects (76%). The mean time after heart transplantation was 99.8 months (range, 10–210 months). All subjects provided informed consent, and the protocol was approved by the ethics committee. Blood was drawn in the morning when patients arrived for routine office assessment after an overnight fast. Glomerular filtration rate (GFR) was estimated by using the simplified Modification of Diet in Renal Disease formula (estimated GFR = 186.3 × serum creatinine $(mg/dL)^{-1.14}$ × $age^{-0.203}$ × 0.742 if female × 1.21 if African American) [10] and the Chronic Kidney Disease Epidemiology Collaboration equation [11]. Complete blood count and creatinine were assessed by using standard laboratory methods in the central laboratory of the hospital. To obtain the normal ranges, we also studied renalase and catecholamine (dopamine and noradrenaline) levels in 22 healthy volunteers. Renalase was assessed by using commercially available kits from USNC Life Science (Wuhan, China), and catecholamines were assessed by using a noradrenaline and a dopamine enzyme-linked immunoadsorbent assay kit from Labor Diagnostika Nord GmbH & Co. KG (Nordhorn, Germany). Copeptin was studied by using commercially available kits from Phoenix Pharmaceuticals, Inc. (Burlingame, Calif, United States).

Data are expressed as mean ± SD. The data given were analyzed by using Statistica version 10.0 software (StatSoft, Inc., Tulsa, Okla, United States). The examination of the distribution normality of variables was performed by using the Shapiro-Wilk test. The data were also logarithmically transformed to achieve normal distribution, whenever possible. Measurements normally distributed are reported as mean ± SD, and nonnormally distributed data are expressed as a median and minimal–maximal value. The Mann-Whitney rank sum *U* test or Student *t* tests were used in statistical analysis to compare differences between groups, with $P < .05$ considered statistically significant, when appropriate. Multiple regression analysis was used to determine independent factors affecting the dependent variables.

RESULTS

Clinical and biochemical data of heart allograft recipients are given in Table 1. Renalase levels were higher in heart transplant recipients compared with healthy volunteers (8.79 ± 4.85 μg/mL vs 3.86 ± 0.73 μg/mL [$P < .001$],

Table 1. Some Clinical and Biochemical Parameters in Heart Allograft Recipients

Parameter	Control Group	Heart Allograft Recipients
Age, y	49.08 ± 10.76	53.4 ± 13.9
Time after transplantation, mo	NA	97 (54–147)
Hemoglobin, g/dL	13.87 ± 0.89	13.9 ± 2.0
Erythrocyte count, $\times 10^{12}$/μL	4.76 ± 0.98	4.46 ± 0.71
White blood cell count, $\times 10^{3}$/μL	5.69 ± 1.65	6.68 ± 3.20
Creatinine, mg/dL	0 ± 14.09	1.74 ± 1.13
eGFR by MDRD, mL/min/1.72 m^2	96.87 ± 12.98	54 ± 28
eGFR by CKD-EPI, mL/min/1.72 m^2	97.98 ± 14.98	55 ± 29
Creatinine-clearance (Cockcroft-Gault formula), mL/min	102.76 ± 29.76	62 ± 32
NT-proBNP, pg/mL	NA	157 (82–384)
Copeptin, ng/mL	NA	0.97 (0.8–1.16)
IVSd, mm	NA	13.6 ± 3.2
LVIDd, mm	NA	50.5 ± 5.6
Posterior wall of left ventricular diameter, mm	NA	13.4 ± 4.5
Left atrium diameter, mm	NA	47.3 ± 11.6
EF, %	NA	55 ± 10
Renalase, μg/mL	3.86 ± 0.73	8.79 ± 4.85
Dopamine, pg/mL	134.9 ± 92.7	139.6 ± 85.35
Noradrenaline, ng/mL	394 ± 144*	94.4 ± 34.3
Systolic blood pressure, mm Hg	129 ± 15	127 ± 16
Diastolic blood pressure, mm Hg	80 ± 11	83 ± 12

Data are given as mean ± SD or median (interquartile range).

Abbreviations: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; EF, ejection fraction; eGFR, estimated glomerular filtration rate; IVS, interventricular septum diastole dimension; LVIDd, left ventricular internal end-diastolic dimension; MDRD, Modification of Diet in Renal Disease; NA, not applicable; NT-proBNP, N-terminal pro–B-type natriuretic peptide.

*$P < .001$.