Prognostic Value of Normal Dobutamine Stress Echocardiography in Renal Transplant Candidates

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Background: *Renal transplant candidates are at high-risk for cardiovascular events. No definite screening tool has been recommended for the pre-operative evaluation.*
Objective: *The authors studied the prognostic value of normal dobutamine stress echocardiography in this population.*
Material and Method: *Dobutamine stress echocardiography was performed for the pre-operative assessment in 107 renal transplant candidates (age 53.2 ± 6.2 years, 66.4% male). The mean follow-up time was 2.8 ± 1.7 years. The primary end-point was total mortality.*
Results: *During follow-up, 16 (15.0%) died and 26 (24.3%) patients underwent kidney transplantation. The overall survival probabilities at 1, 3 and 5 years were 87, 83 and 79%, respectively. Among those who underwent renal transplantation, the survival probabilities at 1, 3 and 5 years were 100, 100 and 89%, respectively.*
Conclusion: *In renal transplant candidates, normal dobutamine stress echocardiography portends a good long-term prognosis.*

Keywords: *Dobutamine stress echocardiography, Prognosis, Renal transplant*

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Coronary artery disease is the leading cause of morbidity and mortality in patients with chronic kidney disease, especially those with end-stage renal disease both before and after renal transplantation[1-6]. Individuals with chronic kidney disease have been considered as a high-risk population[1,3]. Although survival has been improved after renal transplantation, as compared to patients remaining on dialysis, the principle cause of death remains cardiovascular disease[4,6,7]. Furthermore, the availability of kidneys for transplantation is limited. Therefore, the screening of renal transplant candidates is critically important to identify and treat those at high risk of subsequent cardiovascular events.

Several previous studies have established the diagnostic accuracy and prognostic values of dobutamine stress echocardiography in different subsets of patients, including patients with chronic kidney disease and renal transplant candidates[8-11]. Although coronary angiogram remains the gold standard for detecting or excluding significant coronary artery disease and provides the better prognostic value, it is invasive and expensive. The role of non-invasive cardiac stress imaging for the pre-transplant evaluation of renal transplant candidates has been mentioned in the clinical practice guidelines[12]. Regarding non-invasive stress testing, the abnormal result of dobutamine stress echocardiography led to the detection of significant coronary artery disease and cardiac risk stratification in patients with chronic kidney disease and renal transplant candidates[8,11]. However, little is known about the prognostic value of normal dobutamine stress echocardiography in renal transplant candidates. Therefore, the authors aimed to study the prognostic value of normal dobutamine stress echocardiography in renal transplant candidates.

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Material and Method

Study population

From September 2004 through October 2010, 862 patients were referred for a clinically indicated

dobutamine stress echocardiography. Among these, 137 patients were identified as patients with end-stage renal disease and renal transplant candidates. There were 30 patients with abnormal dobutamine stress echocardiography who were excluded from the analysis. The remaining 107 patients constituted the study population. The study was approved by Siriraj institutional ethics committee. All patients gave informed consent to undergo dobutamine stress echocardiography. Clinical characteristics, indications, stress hemodymanics, results and adverse effects were recorded at the time of dobutamine stress echocardiography.

Hypertension was defined as systolic blood pressure $\geq$ 140 mmHg, diastolic blood pressure $\geq$ 90 mmHg, or the use of anti-hypertensive medication. Patients were diagnosed as having diabetes mellitus if they had 2 fasting blood glucose concentrations $\geq$ 126 mg/dl, or treatment with insulin or oral hypoglycemic agents. Patients were considered to have hypercholesterolemia if their total cholesterol was $\geq$ 200 mg/dL or if they were receiving lipid-lowering medication. History of coronary artery disease was identified if there was a history of myocardial infarction, coronary revascularization or presence of significant coronary artery stenosis on coronary angiogram.

Dobutamine Stress Echocardiography

Dobutamine stress echocardiography was performed and interpreted as previously described[13] by cardiologists (NC, MK). Wall motion was scored according to a 16-segment and 4-point scale model of the left ventricle[14]. Normal dobutamine stress echocardiography was defined if there were no wall motion abnormality at rest or stress. Abnormal dobutamine stress echocardiography was defined if there was inducible ischemia or fixed wall motion abnormality. Target heart rate was defined as 85% of age-predicted maximal heart rate (220-age in years). Ejection fraction was evaluated by visual estimation or a modification of the method of Quinones et al[15]. The change in left ventricular end-systolic volume (LVESV) from rest to peak stress was recorded as normal (decrease in LVESV) or abnormal (increase or absence of a decrease). The stress electrocardiogram was positive for ischemia if there was horizontal or downsloping ST-segment depression of $\geq$ 1 mm at 80 ms after the J-point in the absence of baseline ST-segment deviation.

Follow-up

Follow-up data were collected by review of medical records or telephone calls. All patients were followed from the time of dobutamine stress echocardiography to the occurrence of death. Kidney transplantation during follow-up was also recorded. The primary end point was all-cause mortality.

Statistical analysis

Subject characteristics were described using categorical variables are summarized as numbers and percentages. Continuous variables are presented as mean $\pm$ standard deviation. Comparison between groups was based on independent t-test and Mann-Whitney U test for continuous variables and categorical variables were analyzed using Chi-square and Fisher's exact test. Survival probability was calculated by the Kaplan-Meier method. A p-value of < 0.05 was considered statistically significant. SPSS version 18 was used for the statistical analysis.

Results

Clinical Data

The present study population consisted of 107 consecutive renal transplant candidates [mean age 53.2 $\pm$ 6.2 years (range 38 to 68), 71 male (66.4%)]. Dobutamine stress echocardiography was performed for preoperative assessment before renal transplantation in all patients. All patients were on chronic dialysis and the majority of them (102 patients) were on hemodialysis. The etiology of renal disease was diabetes mellitus in 39 (36.4%) patients. Table 1 summarizes the clinical characteristics of the study population. Only 1 patient had a history of coronary artery disease. Baseline electrocardiogram showed left ventricular hypertrophy and atrial fibrillation in 54 (50.5%) and 4 (3.7%) patients, respectively. Pathologic Q waves were identified in 2 patients.

Hemodynamic and stress echocardiographic data

Hemodynamic and stress echocardiographic data are shown in Table 2. Atropine, mean dose 0.9 $\pm$ 0.8 mg, was used in 76 (71%) patients. The peak heart rate achieved was 79.8 $\pm$ 11.6% of age-predicted maximal heart rate. All patients had normal left-ventricular end-systolic volume response to stress and negative stress electrocardiogram. Among 60 patients who failed to achieve target heart rate, 22 (36.7%) were receiving beta-blockers. The reasons for test termination were achieving target heart rate in 60 (56.1%), completion of the protocol in 39 (36.4%), intolerable symptoms in 5 (4.7%), hypotension in 2 (1.9%) and hypertension in 1 (0.9%) patients. Neither ventricular tachycardia nor

fibrillation was detected during the test.

Outcomes

During a follow-up time of 2.8 ± 1.7 years, 16 (15.0%) patients died (94% non-cardiac death) and 26 (24.3%) patients underwent kidney transplantation. The overall survival probabilities at 1, 3 and 5 years were 87, 83 and 79%, respectively (Fig. 1). Among 26 patients who received a renal transplantation after the test, only 1 patient subsequently died and the survival probabilities at 1, 3 and 5 years were 100, 100 and 89%, respectively. Table 3 shows clinical and echocardiographic characteristics of the patients grouped according to vital status during follow-up. In renal transplant candidates with normal dobutamine stress echocardiography, there was no statistically significant difference in clinical and echocardiographic parameters between those who survived or died during follow-up.

Table 1. Clinical characteristics of the study population

Characteristic	n = 107
Age (years)	53.2 ± 6.2
Male gender	71 (66.4)
Hypertension	101 (94.4)
Diabetes mellitus	45 (42.1)
Current smoker	6 (5.6)
Hypercholesterolemia	58 (54.2)
Diuretic	59 (57.3)
Betablocker	59 (55.1)

Data are expressed as number (percentage) or mean ± stan dard deviation

Discussion

The results of the present study reported the total mortality of 15% and 3.8% in renal transplant candidates and after renal transplantation, respectively. Also, it demonstrates a favorable long-term prognosis of normal dobutamine stress echocardiography in renal transplant candidates. The warranty of normal dobutamine stress echocardiography in patients with chronic kidney disease is in concordance with previously published prognostic studies[8,16]. Therefore, it is reasonable and reliable to use dobutamine stress echocardiography as the screening tool andfor risk stratification in patients with chronic kidney disease and renal transplant candidates.

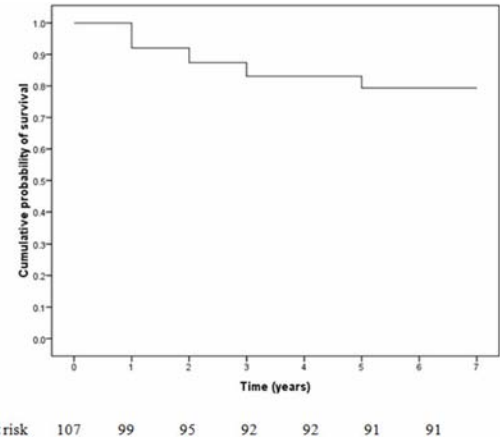

Fig. 1 Kaplan-Meier survival curve of renal transplant candidates with normal result of dobutamine stress echocardiography

Table 2. Hemodynamic and stress echocardiographic data of the study population

Characteristic	n = 107
Rest heart rate (/min)	73.9 ± 13.0
Peak heart rate (/min)	132.8 ± 19.6
Rest systolic blood pressure (mmHg)	156.9 ± 29.9
Peak systolic blood pressure (mmHg)	173.7 ± 40.5
Rest diastolic blood pressure (mmHg)	69.0 ± 18.0
Peak diastolic blood pressure (mmHg)	70.1 ± 19.0
Peak dose of dobutamine (mcg/kg/min)	38.4 ± 5.5
Achieving target heart rate	60 (56.1)
Rate-pressure product	23,030.6 ± 6,275.9
Rest left ventricular ejection fraction (%)	67.4 ± 4.4
Peak left ventricular ejection fraction (%)	76.8 ± 5.2

Data are expressed as number (percentage) or mean ± standard deviation

Table 3. Clinical and echocardiographic characteristics of the patients grouped according to vital status

Characteristic	Survived (n = 91)	Dead (n = 16)	p-value
Age (years)	52.9 ± 5.9	54.4 ± 7.9	0.41
Male gender	60 (65.9)	11 (68.8)	0.83
Hypertension	85 (93.4)	16 (100)	0.59
Diabetes mellitus	37 (40.7)	8 (50)	0.49
Smoking	35 (38.5)	9 (56.2)	0.18
Hypercholesterolemia	49 (53.8)	9 (56.2)	0.86
Beta blocker	49 (53.8)	10 (62.5)	0.52
Diuretic	50 (57.5)	9 (56.2)	0.93
Rest heart rate/(min)	74.4 ± 13.5	71.1 ± 9.7	0.35
%PMHR	80.0 ± 11.9	78.6 ± 10.3	0.65
Rate-pressure product	22,901.5 ± 6,273.3	23,764.9 ± 6,444.6	0.77
Kidney transplant	25 (27.5)	1 (6.2)	0.11

Data are expressed as number (percentage) or mean ± standard deviation. PMHR = peak maximal heart rate

Role of Dobutamine stress echocardiography in the renal transplant candidate

Patients with end stage renal disease, regard less of kidney transplantation, are at high risk of coronary artery disease. The optimal screening tool to detect coronary artery disease in renal transplant candidates is still inconclusive. Current guidelines suggest a practical approach according to the estimation of risk and the result of non-invasive testing[12]. There are 2 main strategies, invasive and non-invasive testing, to employ in the risk assessment before kidney transplantation. Coronary angiography has been proven as the better prognostic and diagnostic tool in renal transplant candidates[11,17]. However, it is invasive, costly and associated with some serious procedural-related complications. Also, the angiographic studies showed that the majority of patients on dialysis had no significant coronaryartery disease[11,18]. Therefore, the non-invasive strategy has become an attractive screening modality before renal transplantation[19]. The results from non-invasive stress testing can subsequently be used to select patients who may benefit from coronary angiogram. There are many different choices of non-invasive modalities, such as exercise stress electrocardiographic testing, myocardial perfusion imaging and stress echocardiography. Exercise testing is a practical tool, but less accurate due to some limitations in patients with chronic kidney disease, such as limited exercise capacity, abnormal resting electrocardiogram and failure to achieve target heart rate[19,20]. Myocardial perfusion imaging and stress echocardiography have become popular in risk stratification and prognostication in patients with chronic kidney disease. The abnormal test results indicate a poor prognosis and are associated with a high risk for cardiovascular events[21]. These modalities provide the high negative predictive value and the warranty of normal result of the test[8,16,21-23]. The present study confirms a favorable prognosis of normal dobutamine stress echocardiography in renal transplant candidates. The clinical implication of a normal stress test result is very important in patients with end stage renal disease as it confidently excludes significant coronary artery disease. Renal transplant candidates without stress-induced myocardial ischemia from noninvasive stress imaging should be placed on the transplant waiting list without the need for further coronary angiography.

Study limitation

The sample size of study population is relatively small and only 1 cardiac death occurred. These represent the potential limitation of the present study. Since clinical decision-making is generally affected by the result of stress echocardiography and the result of dobutamine stress echocardiography in the present study was normal in all patients, none would undergo coronary angiography to determine the presence of coronary artery disease. Therefore, the false negative predictive value could not be ascertained in the present study.

Conclusion

Dobutamine stress echocardiography should be used as an ideal screening tool for the detection of coronary artery disease in renal transplant candidates.

The normal result of dobutamine stress echocardiography provides a favorable prognostic information and warrant a low-risk population without the need for an invasive testing.

Potential conflicts of interest

None.

References

1. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation 2003; 108: 2154-69.
2. Jardine AG, McLaughlin K. Cardiovascular complications of renal disease. Heart 2001; 86: 459-66.
3. Levey AS, Beto JA, Coronado BE, Eknoyan G, Foley RN, Kasiske BL, et al. Controlling the epidemic of cardiovascular disease in chronic renal disease: what do we know? What do we need to learn? Where do we go from here? National Kidney Foundation Task Force on Cardiovascular Disease. Am J Kidney Dis 1998; 32: 853-906.
4. Baigent C, Burbury K, Wheeler D. Premature cardiovascular disease in chronic renal failure. Lancet 2000; 356: 147-52.
5. Hostetter TH. Chronic kidney disease predicts cardiovascular disease. N Engl J Med 2004; 351: 1344-6.
6. Ojo AO, Hanson JA, Wolfe RA, Leichtman AB, Agodoa LY, Port FK. Long-term survival in renal transplant recipients with graft function. Kidney Int 2000; 57: 307-13.
7. Lindholm A, Albrechtsen D, Frodin L, Tufveson G, Persson NH, Lundgren G. Ischemic heart disease—major cause of death and graft loss after renal transplantation in Scandinavia. Transplantation 1995; 60: 451-7.
8. Marwick TH, Lauer MS, Lobo A, Nally J, Braun W. Use of dobutamine echocardiography for cardiac risk stratification of patients with chronic renal failure. J Intern Med 1998; 244: 155-61.
9. Brennan DC, Vedala G, Miller SB, Anstey ME, Singer GG, Kovacs A, et al. Pretransplant dobutamine stress echocardiography is useful and cost-effective in renal transplant candidates. Transplant Proc 1997; 29: 233-4.
10. Reis G, Marcovitz PA, Leichtman AB, Merion RM, Fay WP, Werns SW, et al. Usefulness of dobutamine stress echocardiography in detecting coronary artery disease in end-stage renal disease. Am J Cardiol 1995; 75: 707-10.
11. Herzog CA, Marwick TH, Pheley AM, White CW, Rao VK, Dick CD. Dobutamine stress echocardiography for the detection of significant coronary artery disease in renal transplant candidates. Am J Kidney Dis 1999; 33: 1080-90.
12. Kasiske BL, Cangro CB, Hariharan S, Hricik DE, Kerman RH, Roth D, et al. The evaluation of renal transplantation candidates: clinical practice guidelines. Am J Transplant 2001; 1 (Suppl 2): 3-95.
13. Chuah SC, Pellikka PA, Roger VL, McCully RB, Seward JB. Role of dobutamine stress echocardiography in predicting outcome in 860 patients with known or suspected coronary artery disease. Circulation 1998; 97: 1474-80.
14. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr 1989; 2: 358-67.
15. Quinones MA, Waggoner AD, Reduto LA, Nelson JG, Young JB, Winters WL Jr, et al. A new, simplified and accurate method for determining ejection fraction with two-dimensional echocardiography. Circulation 1981; 64: 744-53.
16. Bergeron S, Hillis GS, Haugen EN, Oh JK, Bailey KR, Pellikka PA. Prognostic value of dobutamine stress echocardiography in patients with chronic kidney disease. Am Heart J 2007; 153: 385-91.
17. De Lima JJ, Sabbaga E, Vieira ML, de Paula FJ, Ianhez LE, Krieger EM, et al. Coronary angiography is the best predictor of events in renal transplant candidates compared with noninvasive testing. Hypertension 2003; 42: 263-8.
18. Manske CL, Wang Y, Rector T, Wilson RF, White CW. Coronary revascularisation in insulin-dependent diabetic patients with chronic renal failure. Lancet 1992; 340: 998-1002.
19. Kasiske BL, Ramos EL, Gaston RS, Bia MJ, Danovitch GM, Bowen PA, et al. The evaluation of renal transplant candidates: clinical practice guidelines. Patient Care and Education Committee of the American Society of Transplant Physicians.

J Am Soc Nephrol 1995; 6: 1-34.
20. Murphy SW, Parfrey PS. Screening for cardiovascular disease in dialysis patients. Curr Opin Nephrol Hypertens 1996; 5: 532-40.
21. Rabbat CG, Treleaven DJ, Russell JD, Ludwin D, Cook DJ. Prognostic value of myocardial perfusion studies in patients with end-stage renal disease assessed for kidney or kidney-pancreas transplantation: a meta-analysis. J Am Soc Nephrol 2003; 14: 431-9.
22. Dahan M, Viron BM, Faraggi M, Himbert DL, Lagallicier BJ, Kolta AM, et al. Diagnostic accuracy and prognostic value of combined dipyridamole-exercise thallium imaging in hemodialysis patients. Kidney Int 1998; 54: 255-62.
23. Patel AD, Abo-Auda WS, Davis JM, Zoghbi GJ, Deierhoi MH, Heo J, et al. Prognostic value of myocardial perfusion imaging in predicting outcome after renal transplantation. Am J Cardiol 2003; 92: 146-51.

การพยากรณ์โรคของผลปกติจากการตรวจคลื่นเสียงสะท้อนหัวใจร่วมกับการใช้สารโดบูทามีนกระตุ้นหัวใจในผู้ป่วยไตวายที่รอผ่าตัดเปลี่ยนไต

นิธิมา เชาวลิต, เมทินี กิตติโพวานนท์, เขมจิรา การเกตกลาง, บุษกร กิจรัตนา, เดโช จักราพานิชกุล, อรรถพงศ์ วงศ์วิวัฒน์, นลินี เปรมัษเฐียร

ภูมิหลัง*: ผู้ป่วยไตวายที่รอผ่าตัดเปลี่ยนไตมีความเสี่ยงสูงที่จะเกิดภาวะไม่พึงประสงค์ทางหัวใจและหลอดเลือด การตรวจคัดกรองมีหลายวิธี แต่ยังไม่มีวิธีการตรวจคัดกรองใดที่ถูกแนะนำจำเพาะให้ใช้ในการประเมินผู้ป่วยกลุ่มนี้ก่อนการผ่าตัด*

วัตถุประสงค์*: การศึกษานี้แสดงบทบาทของผลปกติจาก การตรวจคลื่นเสียงสะท้อนหัวใจร่วมกับการใช้สารโดบูทามีนกระตุ้นหัวใจในการพยากรณ์โรค*

วัสดุและวิธีการ*: การศึกษานี้ได้รวบรวมผู้ป่วยไตวายที่รอผ่าตัดเปลี่ยนไตจำนวน 107 คน (อายุเฉลี่ย 53.2 $\pm$ 6.2 ปี, ผู้ชาย ร้อยละ 66.4) ที่มีผลปกติจากการตรวจคลื่นเสียงสะท้อนหัวใจร่วมกับการใช้สารโดบูทามีนกระตุ้นหัวใจ และได้ติดตามเป็นระยะเวลาเฉลี่ย 2.8 $\pm$ 1.7 ปี ผลลัพธ์ของการศึกษานี้คือการเสียชีวิตจากทุกสาเหตุ*

ผลการศึกษา*: มีผู้ป่วยเสียชีวิต 16 ราย (ร้อยละ 15.0) และได้รับการผ่าตัดเปลี่ยนไต 26 ราย (ร้อยละ 24.3) อัตราการรอดชีวิตโดยรวมที่ 1, 3 และ 5 ปี เท่ากับร้อยละ 87, 83 และ 79 ตามลำดับ ในผู้ป่วยที่ได้รับการผ่าตัดเปลี่ยนไต อัตราการรอดชีวิตโดยรวมที่ 1, 3 และ 5 ปี เท่ากับร้อยละ 100, 100 และ 89 ตามลำดับ*

สรุป*: ในผู้ป่วยไตวายที่รอผ่าตัดเปลี่ยนไต การมีผลตรวจปกติจากการตรวจคลื่นเสียงสะท้อนหัวใจ ร่วมกับการใช้สารโดบูทามีนกระตุ้นหัวใจ เป็นตัวบ่งชี้ถึงการพยากรณ์โรคที่ดี*