

**Communication**

# Dobutamine Stress Echocardiography in Chronic Kidney Disease Patients Candidates for Renal Transplantation

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**Abstract:** *Background:* Dobutamine stress echocardiography (DSE) is used for induction of ischemia in different population. One of those is chronic kidney disease patients before renal transplantation for pre-operative risk assessment. *Aim of the work:* to evaluate the difference in dobutamine stress echocardiography between those with chronic kidney disease (CKD) on regular dialysis and patient with no known history of chronic renal impairment. *Methods:* From February 2016 to January 2017, twenty consecutive chronic kidney disease patients prepared for renal transplantation without history suggestive of ischemic heart disease and 40 consecutive patients with without history of renal impairment. Their heart rate, dobutamine dose, atropine dose and adverse side effects were compared between the two groups. *Results:* Both groups were matched in age and risk factors. Peak heart rate (HR) ( $133.7 \pm 16.99$  vs.  $144.08 \pm 10.99$  b/m,  $P=0.012$ ), time to target heart rate was ( $17.75 \pm 3.29$  vs.  $13.05 \pm 2.95$  min,  $p=0.001$ ) and dobutamine and atropine doses were higher in chronic kidney disease group than other group. Adverse reactions present in both groups but more incidence in CKD group. *Conclusion:* Chronic kidney disease patients response to dobutamine when underwent dobutamine stress echocardiography showed delayed effect of it with more dobutamine and atropine doses needed and more adverse reactions including Bezold-Jarisch reflex.

**Keywords:** Dobutamine Stress Echocardiography, Chronic Kidney Disease, Bezold-Jarisch Reflex

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## 1. Introduction

Chronic kidney disease (CKD) is a worldwide disease affecting more than 20 million adults and with increasing prevalence of obesity, old age and diabetes, this number is expected to be the double by 2030 [1]. Cardiovascular disease is the leading cause of mortality and morbidity in patients with CKD [2]. The cardiovascular mortality is 15-30 times higher than the general population [3]. The prevalence of coronary artery disease (CAD) is high in CKD although less predicted conventional risk factors and low sensitivity of chest pain (65%) [4]. So, stress testing is used for risk stratification in CKD patients prepared for renal transplantation pre-operatively.

There is no agreement in guidelines about the optimal approach of cardiovascular evaluation in renal transplantation candidates. American College of Cardiology (ACC) and American Heart Association (AHA) guidelines on

perioperative cardiovascular evaluation in population undergoing non-cardiac surgery published in 2014 in asymptomatic patients with a functional capacity  $\geq 4$  metabolic equivalents) that no need for further tests. While, noninvasive tests performed for patients at elevated risk regardless of functional status based on the 2012 AHA/ACC scientific statement regarding cardiac evaluation in renal transplantation candidates [5-6]. These risk factors include diabetes mellitus, previous cardiovascular disease,  $>1$  year on dialysis, left ventricular hypertrophy (LVH), age  $>60$  years, smoking, hypertension, and dyslipidemia with presence of  $\geq 3$  risk factors is reasonable threshold for noninvasive testing [6]. The recommendation of American Society of Transplantation is that patients with diabetes, known to be ischemic heart disease or had an abnormal electrocardiogram (ECG), or their age  $\geq 50$  years should be classified as high-risk for CAD and should be referred for a cardiac stress test, if positive result referred for coronary angiography [7].

Dobutamine Stress echocardiography (DSE) is a procedure that evaluate myocardial ischemia in a manner simulating the exercise by increased cardiac output, heart rate and myocardial oxygen demand.

## 2. Patients and Methods

### 2.1. Study Design

In this observational case-control study twenty consecutive patients with chronic kidney disease planned for renal transplantation referred for a pre-operative DSE from February 2016 to January 2017 at Naser Institute for Research and Treatment. Another 40 consecutive patients without history of kidney disease who also referred for DSE. Clinical indications for DSE were the evaluation of patients with chest pain and intermediate pretest probability for CAD. Exclusion criteria were known to be ischemic patients (a recent myocardial infarction, unstable angina), uncontrolled arrhythmia (ventricular tachycardia or atrial fibrillation with the rapid ventricular response) and significant aortic stenosis. No medications were stopped before the procedure. The study was approved by the local ethical committee and an informed consents were obtained from all patients.

### 2.2. Dobutamine Stress Echocardiographic Procedure

Baseline transthoracic echocardiography was done using GE Vivid S6 Ultrasound System with M4S phased array probe (GE Healthcare, Wauwatosa, WI, USA) was performed in all the standard views (apical 4 chamber, apical 2 chamber, parasternal long axis and parasternal short axis views) ECG guided were done and acquired on the vendor archive [8].

### 2.3. Standard Dobutamine-Atropine Infusion Protocol

After IV line was inserted, dobutamine was infused with 3-5 minutes dose increments, starting from 5 µg/kg/min and increasing to 10, 20, 30 and 40 µg/kg/min, then recovery stage with acquiring video loops at baseline, low-dose (20 µg/kg/min), peak when reach target heart rate either with dobutamine alone or with adding atropine. Throughout and after dobutamine infusion the ECG was monitored. Target heart rate (THR) was calculated from the following equation  $THR = (220 - \text{age}) \times 85$ . When THR not reached, atropine was given to the continuing 40 µg/kg/min dobutamine infusion stage if no contraindications such as glaucoma or prostatic enlargement were present. Atropine was given at dose 0.5 mg bolus then 10 ml flush of saline and repeated at dose 0.25 mg for maximum dose 2 mg [9]. The infusion was terminated after reaching the maximal dose or at any of the following points:

- 1) More than 85% of the age-predicted maximal HR
- 2) Marked elevation of hypertension (SBP of >240 mm Hg or diastolic BP of >120 mm Hg)
- 3) Significant cardiac arrhythmias (sustained ventricular tachycardia)
- 4) Severe typical chest pain
- 5) Horizontal or downsloping ECG ST depression of  $\geq 1$

mm (80 ms after the J point) or ST-segment elevation (in the absence of Q wave) more than or equal mm

- 6) New regional wall motion abnormalities in more than two adjacent segments
- 7) On patient request due to intolerable symptoms [10].

### 2.4. Images Interpretation

After the study end off-line assessment of stored digitized echocardiographic loops and displayed in a standard quad-screen digital format that for easy side by side comparison for each patient by the operator. Regional wall motion was assessed according to the recommendations of the American Society of Echocardiography using a 17-segment model and wall motion was graded as follows: 1=normal, 2=hypokinetic, 3=akinetic, and 4=dyskinetic [8]. Wall motion score index were calculated by dividing the sum of wall motion scores by the number of examined segments at baseline and at peak of stress test. The test was considered positive when wall motion in any segment deteriorated >1 grade, as all patients showed baseline normokinetic segments [11]. Studies were identified as non-conclusive if the patient cannot reach 85% age-predicted maximal HR in the absence of inducible ischemia. The baseline heart rate and maximal reached HR was recorded. Offline measurement of EF using biplane modified Simpson's methods for baseline and peak loops were calculated, the time till reach of peak HR was measured using the stop watch on the vendor. The adverse symptoms and arrhythmia was recorded in special sheets. Bezold-Jarisch reflex was considered present when the heart rate decreases with continuous incremental dobutamine infusion. It was transient with spontaneously relieved or 0.5 mg atropine bolus IV if persists more than 1 minute [12].

### 2.5. Statistical Analysis

Data management and statistics were done using IBM statistical package for social sciences, version 22.0 (IBM corporation and others, USA). Numerical data were expressed as mean±standard deviation (SD). Categorical data were expressed as number and percentage. Independent t test was used when comparing between two means. Chi-square ( $\chi^2$ ) test of significance was used in order to compare proportions between categorical parameters. The p-value was considered significant if P-value <0.05 and highly significant if P-value <0.001.

## 3. Results

The patients included in this study were 60 patients with male predominance (49 patient, 80.7%) with their age  $54.45 \pm 8.88$  years. Diabetes mellitus was present in 5 patients (8.3%), hypertension in 24 patients (40%) and smoking in 26 patients (43.3%) while chronic kidney disease was present in one third of cases (20 patients). The average baseline heart rate was  $66.73 \pm 12.05$  b/m while peak HR was  $140.62 \pm 14.04$ . the maximum reached dose of dobutamine was  $37.17 \pm 5.24$  µg/kg/min while the maximum atropine dose was  $0.54 \pm 0.42$

mg. the patients needed  $14.62 \pm 3.77$  minute to reach the target heart rate. The calculated EF was  $58.25 \pm 3.38\%$  at baseline and  $69.35 \pm 5.19\%$  at peak of the test. The resting WMSI was 1 while the peak WMSI was  $1.10 \pm 0.12$ . The adverse reactions of dobutamine were reported in table 2.

**Table 1.** Demographic characters and risk factors of the studied population.

Parameter	mean $\pm$ SD/frequency (%)
Age (years)	54.45 $\pm$ 8.88
Sex (F)	11 (18.3%)
Diabetes mellitus F (%)	5 (8.3%)
Hypertension F (%)	24 (40%)
Smoking F (%)	26 (43.3%)
CKD F (%)	20 (33.3%)

**Table 2.** Baseline and peak parameters.

Parameter	mean $\pm$ SD/frequency (%)
Resting HR (b/m)	66.73 $\pm$ 12.05
Peak HR (b/m)	140.62 $\pm$ 14.04
Dobutamine rate ( $\mu$ /kg/min)	37.17 $\pm$ 5.24
Atropine dose (mg)	0.54 $\pm$ 0.42
Time to THR (minutes)	14.62 $\pm$ 3.77
Baseline EF (%)	58.25 $\pm$ 3.38
Peak EF (%)	69.35 $\pm$ 5.19
Resting WMSI	1.0 $\pm$ 0.0
Peak WMSI	1.10 $\pm$ 0.12
Nausea F (%)	49 (81.7%)
Vomiting F (%)	20 (33.3%)
Palpitation F (%)	31 (51.7%)
Chest pain F (%)	28 (46.7%)
PVCs F (%)	31 (51.7%)
APCs F (%)	40 (66.6%)
Runs of V tach F (%)	3 (5%)
Bezold-Jarisch reflex	7 (11.7%)

When comparing the patients with chronic kidney disease to those without chronic kidney disease the age, sex, diabetes mellitus, hypertension and smoking were matched between both groups (table 3).

**Table 3.** Comparison between demographic parameters and risk factors based on chronic kidney disease presence.

Parameters	No CKD (n=40)	CKD (n=20)	P value
Age (years)	54.48 $\pm$ 8.57	54.40 $\pm$ 9.70	0.47
Sex (F)	5 (12.5%)	6 (30%)	0.09
Diabetes mellitus F (%)	3 (7.25%)	2 (10%)	0.7
Hypertension F (%)	17 (42.5%)	7 (35%)	0.5
Smoking F (%)	18 (45%)	8 (40%)	0.7

The baseline HR was matched while the peak HR was reduced in CKD group which may be explained by higher mean age of them. The dobutamine doses needed to reach the target heart rate and needed atropine dose were higher in CKD group (40 vs  $35.75 \pm 5.94$   $\mu$ /kg/min and  $0.91 \pm 0.1$  vs  $0.36 \pm 0.38$  mg respectively). Also, the time needed to reach THR was higher in CKD ( $17.75 \pm 3.29$  vs  $13.05 \pm 2.95$  minutes) with all these difference is highly statically significant. No significant difference between EF nor WMSI either at baseline or at peak of test. The adverse symptoms was not significant between the two group except nausea which is significantly dominant in CKD. Ventricular ectopics were higher in CKD group with p value 0.04. Bezold-Jarisch reflex was highly significant

present in CKD group (table 4).

**Table 4.** Comparison of baseline and peak parameters between the both groups.

Parameters	No CKD (n=40)	CKD (n=20)	P value
Resting HR (b/m)	65.08 $\pm$ 12.90	70.05 $\pm$ 9.59	0.51
Peak HR (b/m)	144.08 $\pm$ 10.99	133.70 $\pm$ 16.99	0.012
Dobutamine rate ( $\mu$ /kg/min)	35.75 $\pm$ 5.94	40.00 $\pm$ 0	0.001
Atropine dose (mg)	0.36 $\pm$ 0.38	0.91 $\pm$ 0.19	0.001
Time to THR (minutes)	13.05 $\pm$ 2.95	17.75 $\pm$ 3.29	0.001
Baseline EF (%)	57.40 $\pm$ 2.43	59.95 $\pm$ 4.33	0.003
Peak EF (%)	70.10 $\pm$ 4.61	67.85 $\pm$ 6.03	0.123
Resting WMSI	1.00 $\pm$ 0	1.00 $\pm$ 0	1
Peak WMSI	1.09 $\pm$ 0.11	1.12 $\pm$ 0.14	0.405
Nausea F (%)	29 (72.5%)	20 (100%)	0.009
Vomiting F (%)	13 (32.5%)	7 (35%)	0.8
Palpitation F (%)	20 (50%)	11 (55%)	0.7
Chest pain F (%)	20 (50%)	8 (40%)	0.4
PVCs F (%)	17 (42.5%)	14 (70%)	0.04
APCs F (%)	25 (62.5%)	15 (75%)	0.06
Runs of V tach F (%)	2 (5%)	1 (5%)	1
Bezold-Jarisch reflex	2 (5%)	5 (25%)	0.02

## 4. Discussion

Because end stage renal (especially those on regular dialysis) associated with other comorbidities such as hypertension, diabetes mellitus, dyslipidemia, and tobacco so CAD is highly prevalent in those patients (38%, with a relative risk of 5 - to 20 - fold) [13]. There is cardiorenal axis as both atherosclerosis and end stage renal disease (ESRD) are inflammatory state beside uremia accelerate progression of CAD [14]. In CKD and ESRD activated renin-angiotensin-aldosterone system leads to endothelial dysfunction and oxidative stress that predispose to plaque formation, fissuring and extensive heterotopic calcification [13]. In a meta - analysis the accuracy of dobutamine stress echocardiogram and Single-photon emission computed tomography (SPECT) in detecting significant obstructive CAD ( $\geq 70\%$  stenosis) in renal transplantation candidates is not statistically significant beside prognostic value of induced ischemia by dobutamine stress echocardiogram (DSE) and the local availability in many echocardiography machines, short half life of dobutamine (2 minutes) and available beta-blocker intravenous as antidote if arrhythmia is persistent [15].

This study while assessed and evaluated the difference between CKD and non-CKD when both exposed to DSE found that the peak HR was reduced in CKD group which may be explained by higher mean age of them and delayed time to reach the peak HR. The dobutamine doses needed to reach the target heart rate and needed atropine dose were higher in CKD group.

The previous study on DSE including the different meta-analysis [15-19] (studied the prognostic and diagnostic capabilities but not the dose of drugs nor the response to dobutamine.

The delayed response to dobutamine and need to use higher doses of atropine may be related to effect of metabolites in ESRD that may blunt the heart response to dobutamine as dobutamine is metabolized by the liver and no role of kidney

in dobutamine metabolism. Although previous report in pediatrics of delayed clearance of dobutamine in infants with serum creatinine concentrations  $>2$  mg/dl [20]. This observation alerts the alternative protocol of accelerated DSE [21] where atropine is used at dobutamine dose of  $20 \mu\text{g}/\text{kg}/\text{min}$  that could decrease the procedure time and dose of dobutamine used.

In this study no difference in diagnostic capability of DSE between CKD and non-CKD patients as RWMSI in both groups were comparable.

CKD potentiates the arrhythmogenic effect of DSE in the form of ventricular ectopics and this could be explained by the electrolyte disturbance in CKD and the regulation of adrenergic receptors in CKD patients.

Bezold-Jarisch reflex (BJR) was significant present in CKD group and this reminds us of the potential complications and importance of closely monitoring patients during dobutamine infusion. Although Bezold-Jarisch reflex (BJR) is a benign condition that can be abolished by dobutamine infusion cessations or atropine injection, but there were reported severe cases of DSE induced asystole [12]. BJR has been described in patients with heart failure or inferior or posterior wall ischemia. BJR is a cardioprotective reflex through decreasing afterload and mechanical work resulting in reduction of myocardial oxygen demand. In addition, the patients developed BJR were diabetic (all of non-CKD and 2 of 5 in CKD) with predisposition to autonomic dysfunction and dominant vagal tone. But, coronary angiography in those patients may add a value.

## 5. Limitations

The current study limitations are: small sample size and the single-center experience.

## 6. Conclusion

Chronic kidney disease patients response to dobutamine differ than non-CKD patients high doses of dobutamine needed and mandatory need to use atropine. Accelerated DSE is an alternative protocol to be used instead of ordinary DSE. Exaggerated response to dobutamine is present with close monitoring is needed.

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