Frequency of Hypertensive Response to Dobutamine Stress and Diminished Diagnostic Value in Patients with End Stage Renal Disease Awaiting Renal Transplant

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Abstract

Background: Patients with end stage renal disease (ESRD) have a cardiovascular mortality about 15-30 times the general population and this is reduced by about 70% with renal transplant. Dobutamine stress echocardiography (DSE) is commonly performed for preoperative cardiac evaluation before renal transplantation. Hypertensive response during DSE occurs in about 1-5% of DSE studies. However, it seems to be more frequent in patients with ESRD. But its frequency and clinical implications are not known. Methods and Results: Of the 249-consecutive adult ESRD patients undergoing DSE for pre-kidney transplant cardiac risk assessment at our dedicated clinic, 53 (21%) had a hypertensive response. Half of the patients with a hypertensive response, had stress induced segmental wall motion abnormalities, of whom only half had angiographically significant coronary artery disease by quantitative coronary angiography. The hypertensive response was not a predictor of survival. Stress induced segmental wall motion abnormalities predicted poor survival in those with a normotensive response, but not in those with a hypertensive response. The main and independent predictor of a hypertensive response was higher baseline systolic blood pressure ($p< 0.0001$). Conclusions: Hypertensive response to dobutamine stress is common in ESRD patients and is not a predictor of survival. Stress induced segmental wall motion abnormalities occur nearly thrice as frequently with a hypertensive response, but this is a poor predictor of angiographically significant coronary artery disease and does not predict survival.

Introduction

Patients with end stage renal disease (ESRD) have a cardiovascular mortality about 15-30 times the general population and this is dramatically reduced by renal transplantation (1-2). Dobutamine stress echocardiography (DSE) is commonly performed in the preoperative cardiac evaluation of this high-risk population before renal transplantation. Hypertensive response during DSE defined as stress induced systolic blood pressure of >220 mmHg or diastolic blood pressure of >110 mmHg occurs in about 1-5% of DSE studies (3). But this phenomenon seems to be more frequent in patients with renal failure. However, its precise frequency, predictors, diagnostic and clinical implications in ESRD population are unknown. We investigated these questions in a large consecutive series of patients from a tertiary care center undergoing dobutamine stress echocardiography before listing for renal transplantation.

Methods:

Study subjects : We prospectively evaluated 575 consecutive ESRD patients at our dedicated pre-transplant cardiology clinic for potential renal transplant candidates between July 2008 and October 2010. Out of these, 249 consecutive patients who underwent DSE as part of preoperative cardiac risk stratification were included in the present analysis (Figure 1). These patients were managed with very well with regards to hypertension,

diabetes and lipid control. The remaining 316 patients were risk stratified using pharmacological nuclear stress test or dobutamine stress cardiac magnetic resonance imaging (CMR). DSE was performed in between their dialysis days, usually a day after hemodialysis. The study was approved by our Institutional Review Board. Data were recorded as part of our ongoing prospective registry. All had comprehensive history, physical examination and an echocardiogram. Medication data including antihypertensive medications, antiplatelets, diabetic medications and phosphate lowering therapies were entered after medication reconciliation.

2-D echocardiograms: All echocardiograms were performed according to American society of Echocardiography guidelines and interpreted by level III trained echocardiographers (4-6). Left ventricular (LV) ejection fraction was assessed by single or biplane Simpson's method (70%) when possible or by visual assessment when images were suboptimal for quantification (30%). Myocardial contrast was not used for left ventricular opacification. The inter and intra observer correlation was excellent with an r value of 0.93. Elevated left atrial pressure was defined as mitral annular E to E prime (E') ratio> 15 and elevated right atrial pressure was determined by <50% collapse of IVC during deep inspiration or sniffing. Left atrial volume was calculated by biplane Simpson's method in end-systole.

Dobutamine Stress Test: The decision to perform dobutamine stress test was taken after detailed clinical evaluation and analysis of baseline echocardiograms. Patients on beta blockers (BB) and in some cases on high doses of non-dihydropyridine calcium channel blockers (CCB) were asked to hold their medications for 24 hours before the test. Appropriate substitute medications for short term use were prescribed in patients with uncontrolled BP for the time period when BB or CCB were on hold. Standard dobutamine – atropine infusion protocol was used, starting dobutamine at a dose of 10 microgram/kg body weight per minute with incremental increase to 20, 30 or 40 microgram/kg/per min at intervals of 3 minutes. In patients with resting wall motion abnormalities dobutamine was started at 5 micrograms/kilograms/minute to evaluate for contractile reserve. Atropine was used if dobutamine infusion was not able to achieve 85% of maximum age predicted heart rate in the absence of contraindications like glaucoma or symptoms of prostatic obstruction. Vital signs were monitored throughout the test. An electrocardiogram was obtained with each increase in dobutamine dose. Resting and peak stress loop echocardiographic images in 4 views were recorded. Test was terminated if patient had symptoms of chest pain or new wall motion abnormality seen both on electrocardiogram and echocardiogram, or development of significant arrhythmias like atrial fibrillation, or non-sustained ventricular tachycardia. Test was also terminated if patients had markedly elevated BP during stress (7). Not achieving target heart rate was predominantly due to an indication to terminate stress: new wall motion abnormalities (n=78), hypertensive response (n=60), arrhythmias (n=13). In some, the target heart rate was not achieved with dobutamine alone, but there was a contraindication for the use of atropine (37%).Stress test data collected at rest, during peak stress and up to 6 minutes into recovery were critically reviewed by a two-level III trained attending echocardiographers. Information about maximum dosage of dobutamine, atropine and double product of blood pressure and heart rate was entered into the database. Stress test results were considered positive for ischemia if a new wall motion abnormality or worsening occurred compared to the baseline image. Ischemia was defined as per American Society of Echocardiography (ASE) guidelines (7).

Coronary Angiogram: The decision to refer for coronary angiogram was done based upon outcomes of the stress test and overall cardiac risk profile of individual patients. Coronary angiograms were quantitatively analyzed (QCA) using GE software according to AHA's classification and description of coronary segments (8). Positive coronary angiogram was defined as > 70% diameter stenosis in any of the coronary segments. In patients with stenosis ranging between 50-70% which were considered borderline fractional flow reserve (FFR) was used to evaluate physiological significance.

Statistical Analysis: Statistical analysis was performed using Stat View Inc. 2005 software. Student t- test or Chi-square tests were used as appropriate to compare group characteristics. Logistic regression analysis was used to further analyze the predictors of hypertensive response. Survival analysis was performed using Kaplan Meier analysis with log rank test. Mortality data was obtained from clinic records and social security death index and patients were censored on the date of transplant as transplant markedly improves survival.

A p value of < 0.05 was considered significant. In multivariable predictive model for hypertensive response, all predictors with p value of 0.10 or less were included.

Results:

*Baseline characteristics and predictors of hypertensive response:*Tables 1 and 2 summarize the baseline patient characteristics of all patients and as a function of presence or absence of a hypertensive response to dobutamine. The mean age was 59+ 12 years, 45% were women, 71% had diabetes mellitus. Of the 249 patients 53 (21%) had a hypertensive response.

As shown in table 2, hypertensive response was predicted principally by higher baseline systolic blood pressure (p<0.0001). They also had higher estimated left atrial pressure (p=0.02) with similar prevalence of right atrial hypertension by size of inferior vena cava as well as by physical examination. They were more likely to be on angiotensin converting enzyme inhibitor or receptor blocker (p=0.01) and had a trend towards larger number of anti-hypertensive medications (p=0.06). Left atrial enlargement and LV hypertrophy were more frequent in the hypertensive group (p=0.006 and p=0.01 respectively). On multivariable analysis, only pre-stress systolic blood pressure was a predictor of hypertensive response (p<0.0001). A graded relationship between pre-stress systolic blood pressure and hypertensive response was observed (table 3). A pre-stress systolic blood pressure of 160 or more was highly predictive of hypertensive response during dobutamine stress (Table 3). Pre-stress diastolic blood pressure was not predictive of stress induced hypertensive response.

*Stress test positivity and their angiographic correlates:*Hypertensive response resulted in far more peak stress wall motion abnormalities than normotensive group patients (OR 2.75, 95% CI 1.44-5.24, P = 0.002). As shown in figure 1, 25 (47%) of the 53 patients with hypertensive response had stress induced wall motion abnormalities; of these 22 patients underwent coronary angiography and 12 (54%) were abnormal. Additionally, 12 of the 28 patients from hypertensive group without systolic wall motion abnormalities were also referred for coronary angiography and 7 (58%) were positive for significant coronary artery disease. Even though some patients had normal dobutamine stress echo, they underwent coronary angiography because of request by the transplant committee.

In the normotensive response group (n= 196), only 48 (24%) patients had stress induced wall motion abnormalities; of these 42 underwent coronary angiography and 18 (43%) had significant CAD. In addition, 75 patients from normotensive group without stress induced wall motion abnormalities also received coronary angiography on the request of the transplant committee and 22 (29%) had significant CAD. Thus, the sensitivity of dobutamine stress test in normotensive group was 46% and specificity was 66% (table 4).

Prognostic implications: Hypertensive response during stress test was not predictive of mortality over the duration of follow-up (Figure 2). Stress induced wall motion abnormalities were predictive of higher mortality in the normotensive group (p=0.03), but not in the hypertensive group (Figure 3).

Discussion:

To our knowledge, this is the first study to describe the patient characteristics, clinical and echocardiographic predictors and implications of hypertensive dobutamine response in ESRD patients. In the present study, prevalence of hypertensive response was found to be 21% which is strikingly higher than general population, described previously as around 1-7% (3, 9-11).

The major determinant of this abrupt and marked elevation in BP during stress test in ESRD patients appears to be their pre-stress BP of >160 mm Hg. whereas a pre-stress SBP of <140 appears to have protective effect against hypertensive response. Because of high prevalence of LVH and left atrial dilatation in hypertensive response patients, this pre-stress uncontrolled BP appears to be a chronic phenomenon. Higher left atrial pressure despite similar right atrial pressures in patients with hypertensive response suggest possible contribution from excess volume on a back-drop of other abnormalities generally encountered in ESRD patients such heightened sympathetic nervous system activity (12-13), decreased renal clearance and elevated vascular vasoconstrictor endothelin 1 levels (14), hyperactivity of Renin Angiotensin system (15-16) that would increase plasma renin activity and angiotensin II levels, decreased nitric oxide levels (17) and

pathological changes in the arterial system including reduced compliance, medial hypertrophy and vascular calcification (18-22). Before DSE in ESRD populations, it may be prudent to bring systolic blood pressure <140 mmHg and get them euvolumic to reduce the probability of a hypertensive response. LV hypertrophy has also been shown to elicit a hypertensive response to stress (23). Greater use of angiotensin converting enzyme inhibitor or receptor blocker in the group with hypertensive response is likely a marker for need for greater number of antihypertensive agents to control the blood pressure. The strong relationship between pre-stress elevated BP and elevated post stress elevation shown in our study is in accordance with prior studies of hypertensive response with dobutamine (9-11) as well as with exercise stress testing in general population (24).

Reliability of dobutamine echocardiogram to detect significant CAD defined as $> 70\%$ luminal narrowing of an epicardial coronary artery was lower in our ESRD population compared with general population (25-27), with similar performances in both normotensive group and hypertensive groups. It is possible that the definition of significant CAD may not apply to ESRD patients who have heavily calcified coronary arteries and increased myocardial mass which would affect both supply and demand for oxygenated blood. The high false positive rates may possibly be due to underestimation of coronary stenosis because of complex pathology in ESRD, transient stress induced cardiomyopathies from dobutamine (28), just an afterload mismatch in those with a hypertensive response or microvascular disease. Low sensitivity to detect significant CAD is a concern as well. It is possible that a hyperdynamic response to dobutamine in a hypertrophied LV may markedly reduce end systolic wall stress (as radius to wall thickness ratio is low) and may result in false negative testing. Hyperdynamic response with LV cavity obliteration was very common in our subjects. LV cavity obliteration with DSE has been associated with false negative DSE results (28).

Neither the hypertensive response nor stress induced wall motion abnormalities in the hypertensive group was associated with reduced survival during the limited follow-up. But stress induced wall motion abnormalities predicted reduced survival in the normotensive group. The latter findings are not surprising but have important practical implications as neither the extent of CAD nor coronary calcium burden were predictors of survival in our ESRD cohort. Hence, DSE in the normotensive group seems to be a better prognostic marker than any measures of angiographic CAD burden.

There are practical implications of our findings. We believe that an excess volume reflected by left atrial hypertension may have a role not only in causing resting hypertension, but a hypertensive response as well. Achieving euvolemic status may help achieve better blood pressure control. We have observed this in our dedicated pre-renal transplant cardiac clinic. As left atrial hypertension may exist without right atrial hypertension, focused Doppler studies may be helpful to achieve dry weights (31). Coronary angiography for detecting significant lesions may not be a good tool in ESRD patients who have severely calcified, diffusely diseased vessels. Coronary anatomic-physiological relationship warrants further investigations in ESRD patients. Validity of DSE in ESRD patients perhaps should be tested against direct measures of myocardial perfusion and metabolism rather than coronary angiography which may not be a perfect tool. One should also be vary of false negative DSE in the presence of cavity obliteration which reduces wall stress and may mask or attenuate ischemia.

Study Limitations: The main study limitations include its observational nature. In view of severely calcified diffusely diseased vessels, a better measure of significant lesion may be needed in patients with ESRD. Blood pressure measurements were by sphygmomanometer on an available limb. This may not be a very accurate reflection of central aortic pressure because of stiff calcified arteries as well as because of possibly undiagnosed peripheral vascular stenosis.

Conclusions: ESRD patient have high prevalence of hypertensive response to dobutamine stress (21%) compared to general population and this was predicted mainly by higher resting systolic and pulse pressures. Stress induced wall motion abnormalities are common in patients with a hypertensive response and half of these are false positive compared to quantitative coronary angiography. Stress induced wall motion abnormality in patients with a normotensive response predicts higher mortality irrespective of angiographic findings.

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Figure Legends:

Figure 1: Showing Schemata of patients with abnormal stress wall motion and relationship to positive angiograms

Figure 2: Prognostic value of stress induced segmental wall motion abnormalities (SWA) in patients with hypertensive response

Figure 3: Prognostic value of stress induced segmental wall motion abnormalities (SWA) in patients with normotensive response to dobutamine stress.

Table1: Clinical and pharmacological characteristics of normotensive and hypertensive groups:

Variable	All Patients (n= 249)	Normotensive Response (n= 196)	Hypertensive Response (n= 53)	P Value
Age (years)	58 + 11	58+ 11	59 + 12	0.45
Male gender	**55%**	**52%**	**66%**	**0.07**

Variable	All Patients (n= 249)	Normotensive Response (n= 196)	Hypertensive Response (n= 53)	P Value
Hypertension	96%	98%	96%	0.49
Diabetes mellitus	71%	70%	79%	0.19
Body mass index (Kg/m^2)	28 + 5	28 + 5	29 + 5	0.29
Smoking	40%	42%	36%	0.44
Alcohol use	18%	30%	35%	0.64
History of heart failure	12%	12%	15%	0.49
History of Atrial fibrillation	3%	2%	4%	0.48
History of coronary artery disease	23%	22%	25%	0.70
History of peripheral vascular disease	4%	3%	6%	0.37
History of Stroke	9%	11%	6%	0.28
Hemodialysis	82%	84%	90%	0.29
Peritoneal Dialysis	2%	6%	2%	0.23
Duration of dialysis (months)	48 + 45	47 + 44	51+ 53	0.67
High jugular venous pressures	12%	13%	10%	0.51
Peripheral Edema	13%	14%	10%	0.36
Hemoglobin (g/dl)	12.0+ 1.5	12.0 + 1.5	12 + 1.6	0.50
Treatment with ACEI/ ARB	**57%**	**53%**	**72%**	**0.01**
Treatment with calcium channel blocker	62%	67 %	58%	0.24
Treatment with beta blocker	70%	69%	76%	0.34
Treatment with Antiplatelet agents	67%	70%	58%	0.13
Treatment with Statin	75%	77%	68%	0.20

Abbreviations : ACEI = Angiotensin converting enzyme inhibitor, ARB = Angiotensin receptor blocker

Table. 2 Echocardiographic and stress variables in normotensive and hypertensive groups:

Variable	All Patients	Normotensive response	Hypertensive response	P Value

Variable	All Patients	Normotensive response	Hypertensive response	P Value

Base line heart rate (beats/min)	70 + 11	71 + 11	68 + 9	0.12
Base line systolic BP (mmHg)	**156 + 25**	**150 + 22**	179 + 24	**< 0.0001**
Baseline diastolic BP (mmHg)	74 + 16	73 + 16	77 + 15	0.06
Maximum Dobutamine dose (mcg/kg/min)	27 + 11	28 + 11	25 + 10	0.12
Atropine dose (mg)	1.20 + 0.88	1.09 + 0.92	1.1 + 0.86	0.94
Peak stress heart rate (beats/min)	137 + 19	138 + 20	136 + 14	0.40
Base Line LV ejection fraction (%)	62 + 10	63 + 10	61 + 11	0.15
Post Stress LV ejection fraction (%)	**71 + 19**	**74 + 17**	60 + 21	**< 0.0001**
Pre Stress Wall motion abnormality	7%	7%	10%	0.42
Peak stress wall motion abnormality	**30%**	**27%**	**50%**	**0.002**
85% of MPHR achieved	70%	71%	70%	0.92
LVH on baseline echo	**81%**	**79%**	94%	**0.01**
Mitral lateral E prime (cm/s)	5.90 + 1.79	5.96+ 1.86	5.54+ 1.38	0.15
Mitral E wave deceleration time (ms)	244 + 68	228+ 65	212 + 59	0.12
E/A velocity ratio	1.10 +0.50	1.09 + 0.45	1.08 + 0.42	0.87
High LAP E/E'> 15	**43%**	**45 %**	**65%**	**0.02**
LAVI (ml/m2) > 28	**71%**	**70%**	90%	**0.006**
High RAP by echo	28%	26%	36%	0.17

Abbreviations: DBP= Diastolic blood pressure, HR = Heart Rate, LAP = Left atrial pressure, LAVI=

Left atrial volume index, LVH = Left ventricular hypertrophy, LVEF = Left Ventricular Ejection Fraction, MPHR= Maximum Predicted Heart Rate, SBP = Systolic blood pressure.

Table. 3 Graded relationship between pre-stress blood pressures and hypertensive response

Pre-stress systolic blood pressures (mmHg)	OR	95% CI	P value
< 140 (25%)	0.14	0.04-0.46	0.001
140-160 (28%)	0.37	0.17-0.77	0.008
>160 (45%)	6.90	3.43-13.86	< 0.0001

Abbreviations: OR= Odds Ratio,

Table. 4 Sensitivity and specificity of dobutamine stress echocardiography

Patient Groups	Sensitivity	Specificity
All patients	47%	60%
Patients with a hypertensive response	52%	41%
Patients with a normotensive response	46%	66%

Figure 1

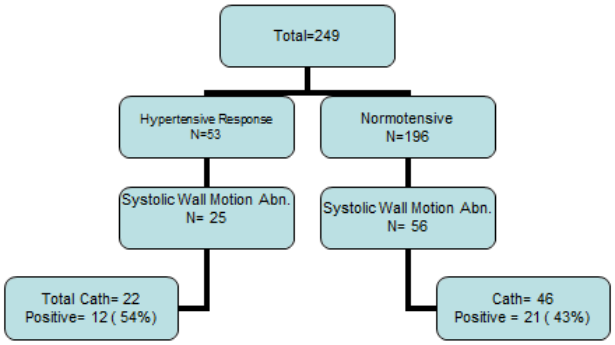

Figure 2

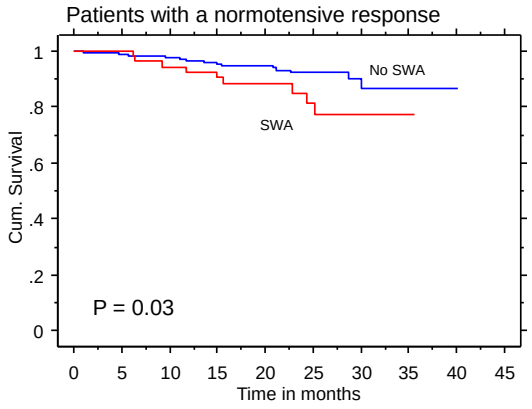

Figure 3