# Feasibility, Safety and Accuracy of Dobutamine/Atropine Stress Echocardiography for the Detection of Coronary Artery Disease in Renal Transplant Candidates

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**Objective:** To evaluate the feasibility, safety and accuracy of dobutamine/atropine stress echocardiography (DASE) for the detection of coronary artery disease (CAD) in renal transplant candidates.

**Methods:** Patients candidates to renal transplant were submitted consecutively to DASE and coronary angiography. The adopted angiographic criteria for (CAD) were an obstructive lesion of ≥ 50% and ≥ 70%.

**Results:** 148 patients underwent the DASE and the coronary angiography. Mean age was 52 ± 9 years, and 69% of the patients were males; 27% had diabetic nephropathy and 73% had LVH; 63% were asymptomatic; 36% and 22% presented coronary obstructions ≥ 50% and 70%, respectively. The DASE performance was 91% and major complication rate was 2.7%. The sensibility, specificity and accuracy for the diagnosis of coronary obstruction ≥ 50% were 53% (CI:45-61), 87% (CI:81-93), and 75% (CI:63-83) respectively. For coronary obstruction ≥ 70% these values were, respectively, 71% (CI:64-92), 85% (CI:79-91) and 81% (CI:75-87). The sensibility to detect univessel and multivessel disease was 41% (CI:19-63) and 78% (CI:64-92), respectively.

**Conclusion:** The DASE was practical and safe; however, it presented a poor result for the detection of CAD regarding obstructions ≥ 50%. It can be a useful screening for the detection of CAD in candidates with obstructions ≥ 70% and multivessel disease.

**Key words:** Stress echocardiography, coronary artery disease, chronic renal failure.

Renal transplant is increasingly becoming the ideal therapy for patients with chronic renal failure undergoing dialysis. As a consequence, there has been an increase in the number of receptors, which is disproportional to number of donated organs, resulting in the need for rigorous receptor's selection criteria.

In the last decades, with the great advances in immunosuppressive therapy and the introduction of more potent antibiotic drugs for infection control after the renal transplant, coronary artery disease (CAD) became one of the main causes of death in this population. Considering that, the researchers have emphasized the pre-existence of DAC as one of the most important factors associated to coronary events after renal transplant[1]. Moreover, prophylactic myocardial revascularization in renal transplant candidates has determined a longer survival when compared to the group undergoing clinical treatment alone[2].

The clinical identification of CAD in this population, as well as its early detection through non-invasive techniques, presents practical difficulties in addition to the usual ones. These methods have shown to be insufficient regarding their diagnostic performance for surveillance, and therefore, some institutions prefer to use a systematic invasive investigation, although approximately two-thirds of these patients present unobstructed coronary arteries or with just non-significant lesions[3]. The ergometric analysis presents some limitations that hinder its use, such as: the degree of physical incapacity that prevents them from exercising normally[4], the elevated prevalence of alterations in the ST[5] segment at rest and the marked presence of LVH[6]. There is much controversy regarding the diagnosis sensitivity of the scintigraphy associated to dipiridamol in renal transplant candidates; Marwick et al[7] found a sensitivity of 37%, whereas Boudreau et al[8], found a sensitivity of 86%.

The dobutamine/atropine stress echocardiography (DASE) is a feasible and safe method in non-selected patients. However, despite the accumulated experience in this population, the method has not been sufficiently evaluated regarding these

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aspects in patients with chronic renal failure (CRF). The DASE is an accurate method to detect CAD, locating and estimating with precision the disease extension[9], but there have been few studies in renal transplant candidates.

## Methods

From 2000 to 2003, patients that were renal transplant candidates, followed at the Renal Transplant Unit, were referred to evaluation at the Laboratory of Echocardiography and the Laboratory of Hemodynamics of the same Institution. The echocardiogram images were obtained from an ATL equipment, model Ultramark 9 HDI and the coronary angiographies were performed in a Phillips equipment. The examinations were carried out one day after the hemodialysis session. The inclusion criteria included the following: diabetic nephropathy or other causes of CRF and age older than 40 yrs, who presented 2 or more risk factors for DAC. Exclusion criteria included: previous history of myocardial infarction or surgical or percutaneous myocardial revascularization; unstable angina; decompensated congestive heart failure (CHF); significant aortic stenosis; pulmonary hypertension; hypertrophic cardiomyopathy; non-controlled arterial hypertension (systolic blood pressure - SBP - ≥ 180mmHg after 30 min at rest); non-controlled atrial fibrillation or complex ventricular cardiac arrhythmia (non-sustained ventricular tachycardia, frequent, polymorphic bigeminated ventricular extrasystoles); inadequate echocardiographic window; atropine use restrictions (glaucoma and obstructive uropathy); irregular dialysis regimen and lack of patent's informed consent.

Venous access was attained through venipuncture with a JELCO catheter. A solution containing 230 ml of 0.9% saline solution, to which 20 ml of a solution with 250 mg of dobutamine was added, resulting in a concentration of 1 mg of dobutamine per ml was used. Administration of the solution was carried out by a peripheral vein, through an infusion pump, with progressive doses of 5, 10, 20 , 30 and 40 $\mu$g/kg/min, with an increment every 3 min. In cases when the final objective of the evaluation had not been reached, the atropine was added, simultaneously, after the third minute of the infusion of 40 $\mu$g/kg/min of dobutamine, at a dose of 0.25 mg every minute, up to a total maximum cumulative dose of 1 mg[10]. Alternatively, isometric hand-grip exercise was used to attain slight increases in cardiac frequency.

Intravenous metroprolol at a dose of 5 mg, was used when one of the following symptoms appeared: significant side effect, myocardial ischemia, or persistence of the dobutamine effects after the end of the protocol.

The reasons for test interruption were: end of the dobutamine infusion protocol; attaining 85% of the maximum cardiac frequency (CF) for age (220-age); new reversible alterations of segmental contraction and limiting side effects (angina, supraventricular tachycardia or sustained ventricular tachycardia), complex ventricular extrasystoles, atrial fibrillation, significant symptomatic hypotension, systolic arterial pressure ≥ 240 mmHg or diastolic arterial pressure ≥ 120 mmHg and unbearable discomfort.

The test was considered diagnostic when at least one of these aims was reached: 85% of the maximum CF for age and echocardiographic signs of myocardial ischemia. The test was considered non-diagnostic when at least one of these situations came up: inadequate images for the analysis (lack of definition of at least 2 myocardial segments); end of the protocol of dobutamine infusion without reaching the target CF with no manifested signs of myocardial ischemia and premature test withdrawal due to limiting side effects without attaining one of the test aims.

Major test complications included: death, sustained ventricular tachycardia, ventricular fibrillation, acute pulmonary edema and acute ischemic syndrome (acute myocardial infarction or unstable angina).

The images at each stage were recorded in VHS tapes for all patients. When the quadruple screen system was available, the standard rest images were digitized and placed side by side to the corresponding images after each dobutamine infusion stage.

The recorded images were later interpreted by two members of the Stress Echocardiography team who were blinded to the patients' clinical data, as independent observers. The discordance was solved by consensus between the two observers. The interpretation of the DASE was carried out according to the following criteria: Normal result defined as uniform increase of systolic movement and thickening of the left ventricular wall and consequent reduction of its final systolic volume (global hyperdynamic response). Positive result for myocardial ischemia was defined as a new alteration of the reversible segmental contractility or worsening of a pre-existing segmental alteration, in 2 or more contiguous myocardial segments.

The echocardiographic measurements were carried out according to the criteria established by the American Society of Echocardiography[11]. The calculation of the LVM was carried out by the M-mode measurement, using the formula of Devereux et al[12]; the LVM was obtained by the correction of the mass by the body surface area. The coronary angiography was carried out at the Outpatient Clinic one day after the hemodialysis for those who were undergoing such treatment. The Judkins technique was employed and the contrast used was non-ionic with low osmolarity. The angiographic studies were interpreted by two hemodynamicists who were blinded to the patients' clinical data and DASE findings. The interpretation was carried out by visual estimation, using the following criteria for the quantification of degree of stenosis: absence of obstruction or obstruction < 50% of a main epicardic coronary artery lumen; obstruction ≥ 50% and obstruction ≥ 70%. The time interval between the DASE and the coronary angiography was not longer than 2 months. The study protocol was reviewed and approved by the Medical Ethical Committee of the Institution. Sensitivity was defined as the number of true positive tests divided by the total number of patients with angiographic stenosis at two obstruction levels, ≥ 50% and ≥ 70%. Specificity was defined as the number of true negative tests divided by the total number of patients with angiographic stenosis < 50% and < 70%.

The positive predictive value was defined as the number of true positive tests divided by the total number of positive stress echocardiograms. The negative predictive value was defined as the number of true negative tests divided by the total number of negative stress echocardiograms. Accuracy

was defined as the number of true positive and true negative tests divided by the total number of patients.

The measurement bias was controlled through the "blind" interpretation of the test regarding the coronary angiography, which was considered the reference standard. The continuous variables were expressed by means and SD. To analyze the differences between continuous variables, student's t test was employed. The Chi-square test or Fisher's exact test were used to compare differences between ratios. Statistical significance was set at $p < 0.05$.

## Results

During the study period, 170 patients were referred for evaluation. According to the selection criteria, 12 patients were excluded and 158 consecutive patients who were candidates to renal transplant underwent DASE. Of these, 6 patients underwent the renal transplant before undergoing the coronary angiography, and 4 patients gave up participating in the study after undergoing DASE, remaining in the waiting list for the transplant. The remaining 148 patients who underwent DASE and the coronary angiography comprised the study group. Mean age was 52 ± 9 yrs (ranging from 23 to 78 yrs) with 101 male patients (69%) and 47 female ones (31%). The causes of CRF established by clinical and anatomopathological criteria were: SAH in 59 patients (40%), diabetic nephropathy in 40 (27%), chronic glomerulonephritis in 16 (4%) and other causes in 33 (22%). The mean time of dialysis was 40 ± 37 months (ranging from 1 to 216 months) with a median of 24 months. There were 134 patients (91%) undergoing a regular hemodialysis regimen at different Nephrology Services and 14 (9%) undergoing continuous outpatient peritoneal dialysis. Of the total, 93 (63%) of the patients were asymptomatic, 17 (12%) had a history of typical angina pectoris, 21 (14%) referred at least one episode of angina during the dialysis sessions and 39 (27%) had manifested signs and symptoms of congestive heart failure (CHF) at some point during their clinical evolution.

The prevalence of CAD was established by the coronary angiography, considering two degrees of obstruction: ≥ 50%, 36% and ≥ 70%, 22%, respectively.

The prevalence of typical angina pectoris, atypical angina and angina during the dialysis, in the absence of significant obstruction of the coronary artery (< 50% of the vessel lumen) was 29%. Asymptomatic patients, but who presented significant obstruction of the coronary artery (≥ 50% of the vessel lumen) corresponded to 56% of the sample.

The diastolic diameters of the left ventricle varied from 35 mm to 73 mm, with a mean value of 51 ± 7 mm. The left ventricular mass index (LVMI) varied from 71g/m² to 349g/m², with a mean value of 182 ± 61g/m². The ejection fraction (EF) of the left ventricle varied from 23% to 84%, with a mean value of 67 ±12%; 108 patients (73%) presented left ventricle hypertrophy (LVH). Diastolic dysfunction of the LV was present in 24 patients (16%). The duration of DASE was on average 12 ± 3 minutes (2-19 min) and the mean dose of dobutamine infused during the examinations was 36 ± 7 μg/Kg/min (10μg/kg/min to 40μg/kg/min). Of the total number of examinations, 22 patients (18%) needed atropine to attain submaximum cardiac frequency or to conclude the protocol and 17 (14%) were submitted to the isometric hand grip when the maximum dose of dobutamine had been reached and there were only a few heart beats left to reach the target CF.

The hemodynamic test data are shown in Table 1.

| | REST | PEAK | p |
|---|---|---|---|
| CF | 78 + 11 | 139 + 19 | < 0.05 |
| DBP | 92 + 12 | 81 + 20 | < 0.05 |
| SBP | 155 + 22 | 165 + 44 | 0.222 |
| DP | 12,192 + 2,685 | 22,549 + 5,168 | < 0.05 |

*CF= cardiac frequency; DBP= diastolic blood pressure; SBP= systolic blood pressure; DP (CF x SBP) = double product*

**Table 1 - Hemodynamic data of DASE in patients with CRF being evaluated for renal transplant.**

Of 148 patients submitted to the test, 135 finished the protocol, which corresponds to a feasibility of 91%. The reasons that led to test interruption were: attaining 85% of maximum CF for age: 121 (81%); limiting side effects: 13 (9%); echocardiographic signs of ischemia: 10 (7%) and end of the protocol: 4 (3%).

Thirteen patients presented an early withdrawal of the protocol due to limiting side effects: 12 (8.5%) due to hypertensive response and 1 (0.5%) due to severe angina. Most of these situations were promptly reverted with test withdrawal and 5 patients needed metropolol administration. Mean systolic arterial pressure at rest was significantly higher in the group that developed a hypertensive response (170±26mmHg) than in the group that did not (152±27), p=0.009.

The complications observed during DASE are shown in Table 2.

| Major complications | Number | Percentage (%) |
|---|---|---|
| Death, AMI, UA and Acute Pulmonary Edema | 0 | 0 |
| Prolonged angina | 1 | 0.7 |
| Complex ventricular Arrhythmia (NSVT) | 3 | 2 |
| Total | 4 | 2.7 |
| Minor complications | | |
| Significant SAH | 12 | 8.5 |
| Marked hypotension | 11 | 8 |
| V or SV extra-systole | 22 | 15 |
| Atrial fibrillation | 1 | 0.7 |
| Headache, nausea, palpitation, tremors | 16 | 12 |
| Total | 62 | 44 |

*SAH=systemic arterial hypertension; AMI=acute myocardial infarction; V=ventricular; SV=supraventricular; UA= Unstable Angina; NSVT=non-sustained ventricular tachycardia.*

**Table 2 - Complications observed during DASE in renal transplant candidates**

The DASE induced arterial hypotension in 38 patients (27%); of these, 11 patients (8%) developed a more accentuated degree of arterial hypotension (SBP decrease ≥ 40mmhg). None of these patients had to be prematurely withdrawn from the study due to the arterial hypotension. Neither the extension nor the severity of the lesion were associated to the hypotension: P= 0.458 and CAD > 70%: p=0.667. Groups with and without LV dysfunction presented similar results (p=0.180).

One hundred and twenty-six tests (85%) were considered diagnostic. In 22 patients (15%), the test was not considered diagnostic due to the following reasons: 5 (4%) due to inadequate image (considered by at least 1 observer); 13 (10%) due to limiting side effects and 4 (3%) for not attaining the target cardiac frequency at the end of the protocol without presenting echocardiographic signs of myocardial ischemia.

The results of the DASE regarding the presence or absence of CAD ≥ 50% or ≥ 70% in the 126 patients with conclusive diagnostic tests are shown in Tables 3 and 4.

Table 5 shows the diagnostic DASE indexes, with their respective confidence intervals, for both degrees of coronary obstruction considered in the study.

The correlation between DASE results and the severity of CAD was analyzed. The data shown as mean values are depicted in Table 6.

## Discussion

The present study evaluated the dynamic response, feasibility, safety and performance of DASE in the largest cohort available in the current Literature to date, of patients who were candidates to renal transplant, systematically submitted to coronary angiography.

When comparing the data of the present study with other DASE series carried out in the general population, we observe a similarity regarding the test feasibility. The percentage of non-diagnostic tests due to the inadequate acoustic window was, on the whole, 5% in the general series[13,14], which corresponds to the value of 4% of this study. Tests considered as non-diagnostic occurred in 10% in the series by Poldermans et al[14] and Picano et al[15], close to the 13% of cases in the present series. Regarding particularly the studies that analyzed DASE in patients with pre-renal transplant CRF, only Reis et al[16] defined data regarding the feasibility. These authors obtained 80% of diagnostic tests.

The non-cardiac side effects observed in this study occurred at a frequency that was similar to those described by Mathias et al[17] in an extensive series of 4,033 non-chronic renal failure patients. However, they were slightly higher than those observed by Secknus et al[18], in 3,011 general population patients. Among the studies performed in patients

| | CAD>50%n (%) | CAD< 50% n (%) | Total |
|---|---|---|---|
| DASE (+) | 26(20%) | 10(8%) | 36(29%) |
| DASE (-) | 23(18%) | 67(54%) | 90(71%) |
| Total | 49(38%) | 77(62%) | 126(100%) |

*DASE= dobutamine/atropine stress echocardiography.*

**Table 3 - DASE results considering coronary artery obstructions ≥ 50%, in renal transplant candidates.**

| | CAD≥ 70% n (%) | CAD< 70% n (%) | Total |
|---|---|---|---|
| DASE (+) | 24(19%) | 14(11%) | 38(30%) |
| DASE (-) | 10(8%) | 78(62%) | 88(70)% |
| Total | 34(27%) | 92(73%) | 126(100%) |

*DASE= dobutamine/atropine stress echocardiography.*

**Table 4 - DASE results considering coronary artery obstructions ≥ 70%, in renal transplant candidates.**

| Obstruction | Se (%) | Sp (%) | PPV (%) | NPV(%) | Accuracy |
|---|---|---|---|---|---|
| ≥ 50 | 53 (45-61)* | 87 (81-93) | 72 (65-81) | 74 (67-82)* | 74 (63-83) |
| ≥ 70 | 71 (63-79)* | 85 (79-91) | 63 (56-72) | 89 (83-95)* | 81 (75-87) |

*( ) = 95% Confidence Interval; Se = sensitivity; Sp = specificity; PPV = positive predictive value; NPV = negative predictive value; A= accuracy*
** p<0.05*

**Table 5 - Sensitivity , specificity , positive predictive value, negative predictive value, and accuracy of DASE for the diagnosis of CAD in patients with CRF, at both levels of coronary obstruction (≥ 50% and ≥ 70%).**

| | S(%) | E(%) | VPP (%) | VPN(%) | A(%) |
|---|---|---|---|---|---|
| UNI | 41(19-63)* | 72(52-92) | 33(12-54) | 81(63-99) | 64(42-86)# |
| MULTI | 78(64-92)* | 76(62-90) | 31(16-46) | 96( 90-99)* | 76(61-89)# |

*Se = sensitivity; Sp = specificity; PPV = positive predictive value; NPV = negative predictive value; A= accuracy; UNI = univessel; MULTI = multivessel. * p= 0.032; # p=0.05*

**Table 6 - Sensitivity, specificity, Positive predictive value, negative predictive value, and accuracy of DASE for the diagnosis of univessel and multivessel CAD in renal transplant candidates (coronary obstruction >50%).**

with pre-transplant CRF, Bates et al[19] found elevated side effect rates (36%).

The systemic arterial hypotension observed in studies with DASE in the general population has varied from 5% to 37%[20,21]. In the present series, we found a prevalence of 27% of arterial hypotension, with 8% being the most severe form, a situation that did not cause test withdrawal. Reis et al[16], evaluating CRF patients, reported 26% of arterial hypotension prevalence, which was not a cause for DASE interruption, either.

The hypertensive response was the most important cause of DASE interruption in the present study (8.5%), which a higher rate than those seen in series involving the general population (1%)[18,17]. In the studies carried out in patients with CRF, this complication caused the interruption of the test in 2% to 6% of the cases[16,19,22]. In the present study, this fact can be attributed to the elevated mean of the systemic arterial pressure at rest.

Previous DASE studies[23,14], carried out in the general population, reported similar rates of ventricular or supraventricular extra-systoles, similar to those detected in the present study. Higher frequencies of ventricular extra-systoles were reported by Mathias et al[17]. The present series showed only 1 case of atrial fibrillation (0.7%), similar to that reported by Mathias et al[17], but 3-fold lower than the series by Herzog et al[22], who studied patients with CRF.

Therefore, the presence of CRF was not a difficulty factor for performing DASE, and was not an additional risk factor to this kind of patient, except for the marked hypertensive response, which could have been prevented with better ambulatory control of hypertension.

In this series, the mean test duration was 12 ± 3 minutes and the mean dose of dobutamine infused at the test peak was 36 ± 7$\mu$g/kg/min. This dose was similar to those utilized in standard protocols in the general population[24] and also in pre-transplant patients with CRF.

In the present study, at the peak of the pharmacological infusion, the mean double product (DP) found was 22,549 ± 5,168 mmHg/min. This value is higher than those reported by Rallids et al[25], for the DASE (19,339 ± 3,923), as well as for the echocardiogram associated with physical stress (24,577 ± 5,680). There were also similarities between the hemodynamic response found in this study when compared to other studies carried out in patients with CRF[22,19].

In this study, the following sensitivity, specificity and accuracy means were obtained, considering a coronary obstruction ≥ 50%: 53%, 87% and 74%, respectively. The same indexes, considering a coronary stenosis ≥ 70% were: 71%, 85% and 81%. Although a low sensitivity to diagnose univessel disease was observed (41%), the sensitivity for the diagnosis of patients with multivessel disease was considered good and was significantly higher (78%; $P < 0.05$) than that of the univessel disease.

These results have been also observed in the population of patients with normal renal function[25-28].

In a recent review de 28 DASE studies involving 2,246 patients from the general population, mean sensitivity values of 80% have been described[9]. However, this analysis has shown a broad sensitivity variation among the studies, varying from 40% to 97%. This ample variation might be related to the applied methodology, such as: percentage of male patients included; inclusion of patients with myocardial infarction; patients with high pre-test probability of CAD; number of patients with multivessel disease; specific analysis of patients with univessel disease; use of beta-blockers and use of different criteria of coronary obstruction.

When comparing this study with others carried out in patients that were candidates to renal transplant, one can observe differences among them. Initially, three of the four studies had as the main objective to evaluate the prognostic value of DASE[16,19,29]. Regarding the sample size, no study reported a number > 100 patients, varying from 47 to 97 cases, with a mean of 62 cases[16,19,29,22]. In the first series, the number of patients who underwent DASE and coronary angiography varied from 25%[29] to 35%[16,19]. More recently, Herzog et al[22] performed a coronary angiography in 50 (100%) of the studied patients. The patients studied by those authors had a pre-test probability of CAD that was higher than this series. The prevalence of CAD varied from 54%[22] to 77%[16]. The reference bias was well characterized in some studies[16,19], as for these authors, the positive DASE was the most important indication for coronary angiography and only a small number of patients with normal DASE underwent the invasive procedure.

As a consequence, the sensitivities in those studies, considering the 95% CI, presented a broad variation that ranged from 38% to 95%[16,19,29,22]. There was also a broad variation regarding specificity, as low as 14%[19] and as good as 86%[16], differences that can be attributed to the methodology employed in each study.

Recently, de Lima et al[30] evaluated the accuracy and the prognostic value of DASE and the scintigraphy, comparing the results with those by angiography in renal transplant candidates. The authors found low sensitivity of DASE (43%) in the detection of CAD with obstruction ≥75%, in 89 patients.

The extension of the area at risk can influence the accuracy of tests to evaluate ischemia. The present study showed a significant difference regarding DASE sensitivity in patients with multivessel disease when compared to those with univessel disease. These data are in accordance with several investigators who evaluated the performance of DASE, regarding this aspect, in the general population[28, 31-33]. Therefore, the predominance of univessel lesions, affecting 2/3 of patients with obstructions ≥ 50%, was one of the determinants of the test's low sensitivity in the studied group.

Another factors associated to the DASE false-negative response was the degree of coronary obstruction < 70%. Patients with intermediary coronary stenosis (obstruction between 40% and 70%) frequently do not present a reduction in the coronary flow reserve[34], and thus the sensitivity of ischemic tests can be compromised. In the present study, 78% of the patients had coronary artery disease with obstruction < 70%, also contributing to the reduction in sensitivity.

The reduced prevalence of relevant coronary stenosis in the present study was due to the main study aim. The surveillance studies involve the use of a test in a predominantly

asymptomatic population, in which the prevalence of the disease is not high and the spectrum of the disease focus on milder and earlier cases. In these situations, the test sensitivity tends to be lower and the specificity tends to be higher in comparison to when the same test is applied to patients suspected of having the disease, as these frequently present the more advanced stages of CAD.

In summary, the results of the present study showed that DASE was safe, as it did not present severe complications and feasible in most patients, as there was a low incidence of limiting side effects during the test performance. However, the test was inefficient for CAD detection, considering obstructions ≥ 50%, but it was useful to detect CAD in patients with obstructions ≥ 70% and multivessel disease.

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