Coronary Angiography Is the Best Predictor of Events in Renal Transplant Candidates Compared With Noninvasive Testing

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Abstract—Guidelines for the detection of coronary artery disease (CAD) and assess of risk in renal transplant candidates are based on the results of noninvasive testing, according to data originated in the nonuremic population. We evaluated prospectively the accuracy of 2 noninvasive tests and risk stratification in detecting CAD ($\geq$70% obstruction) and assessing cardiac risk by using coronary angiography (CA). One hundred twenty-six renal transplant candidates who were classified as at moderate ($\geq$50 years) or high (diabetes, extracardiac atherosclerosis, or clinical coronary artery disease) coronary risk underwent myocardial scintigraphy (SPECT), dobutamine stress echocardiography, and CA and were followed for 6 to 48 months. The prevalence of CAD was 42%. The sensitivities and negative predictive values for the 2 noninvasive tests and risk stratification were <75%. After 6 to 48 months, there were 18 cardiac events, 9 fatal. Risk stratification (P=0.007) and CA (P=0.0002) predicted the crude probability of surviving free of cardiac events. The probability of event-free survival at 6, 12, 24, 36, and 48 months were 98%, 98%, 94%, 94%, and 94% in patients with <70% stenosis on CA and 97%, 87%, 61%, 56%, and 54% in patients with $\geq$70% stenosis. Multivariate analysis showed that the sole predictor of cardiac events was critical coronary lesions (P=0.003). Coronary angiography may still be necessary for detecting CAD and determining cardiac risk in renal transplant candidates. The data suggest that current algorithms based on noninvasive testing in this population should be revised. (*Hypertension*. 2003;42:263-268.)

Key Words: transplantation ■ risk factors ■ coronary artery disease ■ hypertension, essential ■ kidney failure

Coronary artery disease (CAD) is a major cause of death among renal transplant patients.[1] Therefore, evaluation for the presence of CAD is part of the routine pretransplant workup. Coronary angiography (CA) remains the most effective method for detecting CAD, but it is expensive, carries its own risks, and may be refused by some individuals. Consequently, most centers initially perform noninvasive evaluation, restricting the use of CA to subjects with clinical or laboratory evidence of CAD.

Several strategies have been devised to identify patients with kidney disease who are more likely to benefit from invasive evaluation. Initially, patients were selected on the basis of their symptoms. This approach, however, proved to be unreliable, because of the poor correlation between clinical signs and significant coronary disease in individuals with renal failure.[2,3] Superior stratification, separating low- from high-risk individuals, was achieved by combining symptoms with age and the excessive accumulation of CAD risk factors.[4]

Next, it was necessary to determine whether CA should be performed in all high-risk individuals or whether noninvasive testing could reliably identify patients with critical coronary lesions. Dobutamine stress echocardiography (DSE)[5–7] and radionuclide dipyridamole stress testing[4,8–10] have been used to help select high-risk patients for invasive investigation. However, controversy still exists regarding the accuracy of these tests in patients with end-stage renal disease.[6,8,10,11] One reason is that the sensitivity and specificity of neither test have been validated by CA in most studies, with CA being performed only in individuals with positive tests. Moreover, no study has compared the clinical accuracy of DSE and myocardial scintigraphy for detecting CAD in renal transplant candidates (RTC). Finally, the value of noninvasive evaluation compared with CA for predicting cardiac events has not been clearly established, again because angiographic investigation has usually been limited to patients with positive noninvasive test results. In this prospective study, we submitted a group of RTC to CA, clinical risk stratification (RS), and 2 different noninvasive tests for myocardial ischemia, performed before cardiac catheterization. The individuals were subsequently followed up for a maximum of 4 years to evaluate the value of these tests as predictors of cardiac events.

Methods

Study Population

The study was approved by the institutional ethics committee and conducted according to the Declaration of Helsinki (version 2000). Patients gave their written informed consent. Between January 1998

and January 2002, 380 RTC were evaluated. One hundred fifty patients were selected to undergo CA, based on the presence of at least one of the following characteristics: age ≥50 years, diabetes, angina, previous myocardial infarction or stroke, left ventricular (LV) dysfunction, and extracardiac atherosclerosis. Subjects without these characteristics were not studied because they have a low frequency of coronary events.[4,10] Twenty-four individuals were excluded because they were lost to follow up (n=5) or refused to continue the protocol (n=19).

One hundred twenty-six individuals completed at least one coronary test (myocardial scintigraphy, 122 patients; CA, 106 patients; DSE, 93 patients; and all 3 tests, 88 patients) and were further stratified into 2 groups: high-risk, who presented with diabetes or cardiovascular alterations, and moderate-risk RTC, whose sole reason for protocol inclusion was age ≥50 years. The mean age for the whole group was 55±7.8 years, and the mean duration of dialysis was 53±35.2 months (median, 46 months). There were 97 men, 85 whites, 120 hypertensive patients, 42 smokers, 38 with diabetes, 47 with serum total cholesterol and/or serum triglycerides >200 mg/100 mL, 31 with angina, 13 with previous myocardial infarction, 11 with stroke, 6 with LV systolic dysfunction, and 27 with arteriopathy. Fifty-one patients were taking calcium antagonists (40.4%); 48, ACE inhibitors (38.1%); 38, β-blockers (30.2%); and 59, other antihypertensive drugs (46.8%).

Echocardiograms
Echocardiograms were performed according to the recommendations of the American Society of Echocardiography, with the use of an HDI 5000 apparatus (Advanced Technological Laboratories Inc), as reported.[12]

Dobutamine Stress Echocardiography
Stepwise infusion of dobutamine was started at 5 μg/kg per minute and increased up to 40 μg/kg per minute in 3-minute stages. Inducible ischemia was defined as hypokinesis or as accentuation of the degree of baseline hypokinesis during the infusion. The test was interrupted if systolic or diastolic blood pressure surpassed 220 and 120 mm Hg, respectively, or when systolic blood pressure fell below 90 mm Hg.

Dipyridamole Stress Testing (Single Photon Emission-Computed Tomography With Technecium-99m Methoxyisobutylisonitrite)
Stress was induced by dipyridamole (0.5 mg/kg IV). Fixed perfusion defects were interpreted as evidence of fibrosis; transient hypoperfusion was interpreted as ischemia.

Coronary Arteriography
Significant CAD was defined as ≥70% stenosis in one or more of the epicardial arteries by visual estimation.

Invasive and noninvasive testing were analyzed independently by two experts in the respective methods without previous knowledge of the experimental hypothesis. Disagreement was arbitrated by a third expert. Interobserver and intraobserver variability of all the tests was <10%.

Follow-Up
Minimum and mean follow-up periods were 6 and 26 months, respectively. The outcome measure was cardiac events, predefined as sudden death, myocardial infarction, life-threatening arrhythmia, heart failure, pulmonary edema, unstable angina, and myocardial revascularization.

Statistics
Values are expressed as mean±SD. A probability value of <0.05 was considered significant. Comparisons between groups were performed by using the unpaired t test or the χ^2 test, as required. The sensitivity, specificity, and positive and negative predictive values of the noninvasive testing and RS for detecting significant CAD and

TABLE 1.　Clinical Characteristics of Patients With and Without CAD

Variable	Degree of Coronary Obstruction		P
	≥70%	<70%/nil	
n	44	62	
Age, y	55.1±7.6	56.4±8.3	NS
Males, n (%)	36 (84)	45 (73)	NS
White race, n (%)	33 (77)	41 (66)	NS
Body mass index, kg/m^2	26.6±4.1	25.4±4.3	NS
Systolic blood pressure, mm Hg	175±34	178±32	NS
Diastolic blood pressure, mm Hg	101±18	103±17	NS
First degree relatives with CVD, n (%)	17 (37)	20 (32)	NS
High clinical risk, n (%)	27 (63)	21 (34)	0.005
Diabetes, n (%)	17 (37)	12 (19)	0.03
Dyslipidemia, n (%)	16 (37)	31 (34)	NS
Hypertension, n (%)	42 (98)	58 (94)	NS
Time on dialysis, mo	53.5±37.8	54.8±36.9	NS
Smoking, n (%)	14 (33)	19 (31)	NS
Angina, n (%)	12 (28)	17 (27)	NS
Myocardial infarction, n (%)	8 (19)	3 (5)	0.03
Arteriopathy, n (%)	17 (37)	10 (16)	0.006
Stroke, n (%)	7 (16)	3 (5)	0.04
Left ventricular dysfunction, n (%)	3 (7)	3 (5)	NS

CAD indicates coronary artery disease; CVD, cardiovascular disease; NS, not significant.

cardiac events were calculated.[13] The adjusted risk ratio was estimated by using the Cox multivariate model, including age, gender, race, smoking, diabetes, dyslipidemia, time on dialysis, systolic and diastolic blood pressures, use of ACE inhibitor or β-blockers, LV mass index, LV ejection fraction, RS, and results of noninvasive and invasive testing. Survival curves were calculated by means of the Kaplan-Meier method, and the curves were compared by means of the log-rank method. All statistical analysis was performed with the use of a SAS statistical package, version 6.11.

Results
Risk Stratification
Sixty-one patients had at least one significant cardiovascular condition, had a history of a previous cardiovascular event, or were diabetic (high-risk group); 65 other subjects were considered to be at moderate risk for CAD, since age was the only reason they were included in the protocol.

Coronary Angiography
Significant CAD was detected by angiography in 44 of 106 patients (42%), involving 1 vessel in 20 patients, 2 vessels in 17, and 3 vessels in 7. Tables 1 and 2 compare the most important characteristics of the patients with and without significant CAD. CAD was associated with a higher frequency of diabetes (P=0.03), peripheral artery disease (P=0.06), previous myocardial infarction (P=0.03), and stroke (P=0.04). Consequently, subjects with CAD were also more often classified as high-risk patients (P=0.005). Patients with and without significant CAD did not differ in terms of other clinical or resting echocardiographic charac-

TABLE 2.   Laboratory Data, Echocardiographic Characteristics, and Use of Antihypertensive Medication in Patients With and Without CAD*

| Variable | Degree of Coronary Obstruction | | P |
	≥70%	<70 %/nil	
n	44	62	
LV mass index, g/m^2	179±36	192±41	NS
LV posterior wall thickness, mm	11.9±1.2	12.2±1.2	NS
LV end-diastolic diameter, mm	54±5.1	54.3±4.5	NS
Ejection fraction	0.66±0.10	0.65±0.08	NS
Serum creatinine, mmol/L	769.1±221	804.4±247.5	NS
Total cholesterol, mmol/L	4.81±1.16	4.68±1.32	NS
Triglycerides, mmol/L	2.16±2.38	1.51±0.82	NS
Glucose, mmol/L	6.05±2.20	6.16±3.44	NS
Hematocrit	0.35±0.6	0.35±0.5	NS
Use of medication, n (%)†			
Diuretics	8 (19)	7 (11)	NS
ACE inhibitors	14 (33)	25 (40)	NS
Beta blockers	11 (26)	23 (37)	NS
Calcium channel blockers	23 (54)	20 (32)	0.04
Sympatholytics	8 (19)	17 (27)	NS
Vasodilators	7 (16)	8 (13)	NS

*CAD is defined as coronary lumen obstruction ≥70% on coronary angiography.

†Some patients were taking more the one medication.

teristics. Patients with CAD were more like to receive calcium blockers.

Dipyridamole Stress Testing (SPECT)

Sixty-seven patients had normal SPECT. Transient (ischemic) defects were observed in 18 of 122 individuals (14.7%), alone or in association with fixed defects. Isolated fixed defects, interpreted as fibrosis, were seen in 37 subjects (30.3%).

Dobutamine Stress Echocardiography

Although DSE was attempted in 118 subjects, only 89 completed the examination. In 19 patients (16.1%), the test could not be completed because of hypertension. The test was negative in 67 of 89 (75.3%) and positive in 22 of 89 patients (24.7%).

Distribution of LV Hypertrophy, CAD, and Use of β-Blocker Drugs Among Patients Evaluated by SPECT or DSE

LV hypertrophy (LVH) (LV mass index >125 g/m^2) was present in 95.7% of patients submitted to SPECT and in 94.6% of those evaluated by DSE. Among patients submitted to SPECT, the frequency of 1, 2, or 3 compromised coronary vessels were 16.1%, 16.1%, and 3.2%, respectively; for those who underwent DSE, the same frequencies were 14.6%, 16.4%, and 3.3%, respectively. β-Blockers were used by 31.1% of the individuals examined by SPECT and in 35.5% of those evaluated by DSE. These differences were not significant.

TABLE 3.   Comparison of SPECT, DSE, and RS as Predictors of CAD in Renal Transplant Candidates

| Evaluation Method | Coronary Obstruction ≥70% | | P |
	n	%	
SPECT transient defect			NS
Positive (n=18)	8	44.4	
Negative (n=47)	15	31.9	
SPECT fixed defect			0.02
Positive (n=37)	21	56.8	
Negative (n=47)	15	31.9	
SPECT transient/fixed defect			0.02
Positive (n=55)	27	49.1	
Negative (n=47)	15	31.9	
DSE			0.003
Positive (n=22)	15	68.2	
Negative (n=67)	19	28.4	
High clinical risk (by RS)			0.004
Yes (n=48)	27	58.3	
No (n=58)	17	29.3	

CA indicates coronary angiography; DSE, dobutamine stress echocardiography; RS, risk stratification; SPECT, Thallium/SESTAMIBI dipyridamole stress testing.

Utility of Noninvasive Testing and RS in Predicting CAD

Tables 3 and 4 show the abilities of the noninvasive testing and RS to predict the presence of significant CAD. Only 102 of the 122 patients who underwent SPECT also underwent CA. Of these, 47 (46.1%) had normal results, 18 had transient defects (17.6%), and 37 (36.3%) showed persistent defects on the SPECT. Results from CA were available in all 89 patients who completed DSE. DSE was negative in 67 (75.3%) and altered in 22 (24.7%) of these patients. Except for the transient defects on SPECT, the results from the noninvasive tests and RS correlated significantly with the degree of coronary artery obstruction (Table 3). However, the noninvasive testing and RS failed to identify ≈30% of the patients with CAD (false-negative). This phenomenon was reflected by the relatively low sensitivity of the noninvasive investigation (Table 4). The negative predictive values of SPECT, DSE, and RS were similar and <75%.

TABLE 4.   Sensitivity, Specificity, and Positive and Negative Predictive Values of SPECT, DSE, and RS as Predictors of CAD* in Renal Transplant Candidates

Evaluation Method	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
SPECT transient defect	35	76	53	60
SPECT fixed defect	58	67	58	67
SPECT transient or fixed defect	64	53	53	66
DSE	44	87	72	68
RS	61	66	59	69

Data are expressed as percentages.

*The assumed prevalence of CAD is 42%.

TABLE 5.   Comparison of SPECT, DSE, RS, and CA as Predictors of Cardiac Events* in Renal Transplant Candidates

Evaluation Method	Cardiac Events		P
	n	%	
SPECT transient defect			NS
Positive (n=18)	4	22.2	
Negative (n=67)	12	17.9	
SPECT fixed defect			NS
Positive (n=37)	8	21.5	
Negative (n=67)	8	11.9	
SPECT transient/fixed defect			NS
Positive (n=55)	10	18.2	
Negative (n=67)	6	9.0	
DSE			NS
Positive (n=24)	4	16.7	
Negative (n=69)	9	13.0	
High clinical risk (by RS)			0.008
Yes (n=61)	13	21.3	
No (n=65)	4	6.2	
Coronary angiography			0.0004
Positive (n=44)	12	27.3	
Negative (n=62)	2	3.2	

*The assumed prevalence of cardiac events is 15%.

Cardiac Events

A total of 18 cardiac events were observed in the 126 study subjects (18/126; 14.3%). Nine (50%) were fatal, consisting of 3 myocardial infarctions, 3 cases of pulmonary edema, and 3 sudden deaths. Nonfatal cardiac events occurred in an additional 9 patients, consisting of myocardial infarction (n=1), life-threatening arrhythmia requiring pacemaker implantation (n=1), and unstable angina treated by myocardium revascularization (angioplasty, n=3 and surgery, n=4). Twenty-five patients (19.8%) died of the following noncardiac causes: infection (n=12), cerebrovascular accident (n=3), malnutrition (n=2), arterial femoral thrombosis with gangrene (n=2), arterial mesenteric thrombosis (n=1), cancer (n=1), trauma (n=1), and undetermined (n=3). Therefore, there were a total of 34 deaths (27%), including the 9 caused by cardiac events.

Utility of Noninvasive Testing, RS, and CA in Predicting Cardiac Events

Univariate analysis showed that results from RS (high-risk, 21.3% versus moderate-risk, 6.2%, P=0.008) and CA (≥70% stenosis, 27.3% versus <70% stenosis, 3.2%, P=0.0004) were related to cardiac events (Table 5). Only 4 of 65 patients classified as being at moderate risk for CAD had events; 2 of 62 subjects with nonsignificant coronary lesions had events (Table 5). Table 6 depicts the sensitivity, specificity, and predictive values of RS of all tests. RS (78%) and CA (80%) displayed good sensitivity. Conversely, the sensitivity of SPECT and DSE was <60%. The negative predictive values of SPECT and DSE were >85% but still lower than those of RS and CA. Analysis of the Kaplan-Meier

TABLE 6.   Sensitivity, Specificity, and Positive and Negative Predictive Values of SPECT, DSE, and RS as Predictors of Cardiac Events* in Renal Transplant Candidates.

Evaluation Method	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
SPECT transient defect	25	80	18	86
SPECT fixed defect	50	67	21	88
SPECT transient or fixed defect	63	58	21	90
DSE	31	75	18	86
RS	76	56	23	93
CA	86	65	30	96

*The assumed prevalence of cardiac events is 15%.

curves indicated that RS (risk ratio, 4.2; P=0.007) and CA (risk ratio, 9.9; P=0.0002) reliably predicted the probability of event-free survival. Probabilities of event-free survival at 6, 12, 24, 36, and 48 months were 100%, 98%, 87%, 87%, and 87% (moderate-risk patients); 95%, 83%, 71%, 71%, and 67% (high-risk patients); 98%, 98%, 94%, 94%, and 94% (CA <70% stenosis); and 97%, 87%, 61%, 56%, and 54% (CA ≥70% stenosis) (Figure). Multivariate analysis (Cox model) showed that CAD was the only significant factor associated with cardiac events (P<0.003). SPECT and DSE did not discriminate patients with a low and high probability of having cardiac events (Figure).

Discussion

The incidence of cardiac events is 4 times higher in renal transplant patients compared with that in the general population,[14] suggesting that the present strategies used to detect and prevent CAD in this patient population are not ideal. Previous studies[4,10] have demonstrated that RTC younger than 40 years without excessive risk factors or clinical evidence of CAD are at low risk for development of posttransplantation cardiac complications and therefore do not require extensive coronary evaluation. What remains unclear is whether all patients classified as moderate- or high-risk patients should undergo CA or whether a screening test could identify a group not needing invasive investigation. The purpose of our study was to answer this question.

Prevalence of CAD

In our patients, significant coronary artery stenosis (≥70%) was detected in 42%, a prevalence slightly higher than values reported for similar populations.[8,15,16] This probably reflects the fact that we relied on coronary angiography for detecting CAD. Clinical evidence of cardiac and extracardiac atherosclerosis and diabetes were useful in identifying patients more likely to have CAD. Interestingly, demographic, biochemical, and resting echocardiographic data were not helpful in distinguishing patients with and without significant CAD.

Usefulness of Noninvasive Testing and RS in Identifying CAD

Epidemiological studies have indicated that a useful diagnostic test for CAD would have to attain a sensitivity and
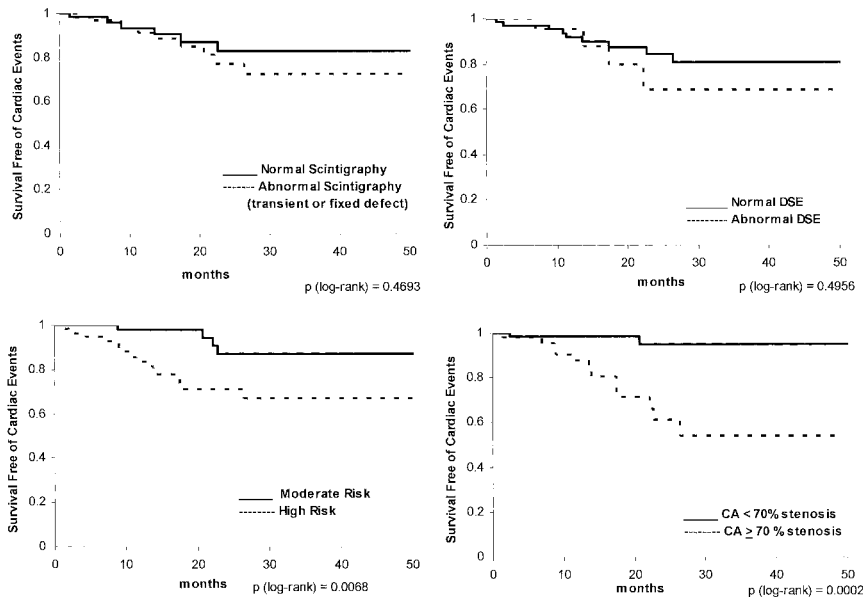
Kaplan-Meier curves depicting probability of survival, free of cardiac events, for renal transplant recipients based on (clockwise) results from myocardial scintigraphy, DSE, CA, and risk stratification.

specificity of close to 80%.[17] Ideally, in cases in which the prevalence of a serious condition is elevated, as in the present situation, the sensitivity and particularly the negative predictive value (which incorporates the disease prevalence into its formula) would be even higher.[13] Otherwise, a negative test is likely to represent a false-negative result. Previous investigations have shown that the sensitivity and/or specificity of myocardial perfusion imaging for detecting CAD in patients with chronic renal failure are highly variable and often <60%.[4,8,18,19] In most of these studies, CA was limited to select patients with altered scintigraphy. In perhaps the only reported study that used a control group, Marwick et al[8] showed that the sensitivity of dipyridamole thallium scintigraphy for detecting CAD was 95% in control subjects but only 37% in dialysis patients, a figure close to that reported here. The reason for this important disparity is unclear, but it may reflect the increased resting levels of adenosine, reduced coronary flow reserve, or concurrent LV hypertrophy frequently observed in these patients.[8,20] Less frequently, others[9,21,22] have reported higher sensitivity of myocardial scintigraphy but still with a low negative predictive value.[22] DSE has been associated with better and more consistent results, with a sensitivity and negative predictive value for significant (≥70% stenosis) CAD >75%.[5–7] In the present study, we tried to determine the true sensitivity and specificity of the most frequently used screening test, using CA as the gold standard. We found that although the specificities of DSE and SPECT were acceptable, their sensitivities and predictive values were not. The large number of patients (30%) who had negative test results with both tests but had critical coronary lesions reflects this finding. Indeed, the noninvasive tests were not significantly better than the simple application of clinical criteria in that regard. Therefore, we conclude that at least in this particular population of RTC, CA is still necessary to rule out significant CAD.

Usefulness of Noninvasive Testing and RS as Predictors of Cardiac Events

The clinical relevance of coronary obstruction is related to the degree of ischemic damage to the myocardium. Consequently, a test with relatively low sensitivity for detecting anatomic evidence of CAD may still be useful clinically, provided that it helps to identify patients at high risk for future cardiac events. Some authors have reported a good correlation between the results of myocardial scitigraphy[4,9,10,16,23–26] and DSE[5,6,27–29] and the cardiac prognosis of uremic subjects, although other authors have failed to confirm this result.[18,30] Our data indicate that CA, and, to some extent, RS, were the best prognostic predictors, as both had a sensitivity close to 80% and a negative predictive value of 95%. The adjusted relative risk of cardiac events in patients with ≥70% coronary stenosis was almost 10 times higher than that of individuals with normal or less serious lesions. Patients classified as being at high risk presented with an adjusted relative risk of 4.2. In contrast, the sensitivity of both SPECT and DSE in predicting cardiac events was inadequate, although both tests provided good negative predictive values of close to 85%. However, the latter were not better than that observed with RS. These results suggest that SPECT and DSE do not offer any special advantage over clinical evaluation in assessing cardiac risk in RTC.

Comparison of Accuracy of DSE and SPECT in RTC

To the best of our knowledge, ours is the first study to compare the diagnostic and prognostic accuracy of DSE and SPECT in uremic patients. We found no consistent difference between the 2 tests in the detection of CAD, an observation that agrees with that reported in the general population,[31] nor in the assessment of cardiac risk. In our study, the frequencies of 1-, 2-, or 3-vessel disease, LVH and use of β-blockers, which could interfere with the sensitivity and/or specificity, were similar among patients evaluated by either test. From the data at hand, it is not possible

to determine why 2 tests based on different mechanisms should perform similarly, with both consistently offering a reduced degree of sensitivity. It may be that compromised coronary flow reserve, which is associated with chronic uremia,[8,20] plays a role, since the effects of pharmacological and inotropic stress involve an increase in coronary flow.

Perspective

In conclusion, CA is still necessary for the detection of CAD and represents the best method for determining cardiac risk in patients with end-stage renal failure who are ≥50 years or have a high number of coronary risk factors. Ideally, all patients with the characteristics displayed in our sample should undergo CA before transplant. Alternatively, such invasive investigation may be restricted to high-risk individuals, because RS proved to be a good predictor of cardiac events. SPECT and DSE are no better than RS in that regard. The data suggest that current algorithms based on the use of radionuclide imaging and/or stress echocardiography for the detection of CAD and evaluation of cardiac risk in patients with chronic renal failure should be revised.

Acknowledgments

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