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Original Article

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Ischaemia imaging in type 2 diabetic kidney transplant candidates—is coronary angiography essential?

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Abstract

Background. Coronary artery disease (CAD) remains the leading cause of death in type 2 diabetes mellitus (DM) patients undergoing renal transplantation. There is a high prevalence of silent CAD in these patients. Controversy exists regarding the role of dobutamine stress echocardiography (DSE) in detection of CAD. Our purpose was to compare DSE with coronary angiography (CA) for the detection of CAD in type 2 diabetic patients undergoing evaluation for renal transplantation.

Methods. Forty (36 male, four female) type 2 diabetic patients with end-stage renal disease (ESRD) were subjected to DSE followed by CA as a part of their pre-renal transplant evaluation. The ability of DSE to predict 70% stenosis in one or more coronary arteries as determined by CA was evaluated. Mean age of the patients was 49.2 ± 5 years (range 39–60 years).

Results. DSE was positive in 10 (25%) patients, while 19 patients (48%) had a more than 70% lesion in at least one epicardial vessel on CA (six patients had single vessel, three had double vessel and 10 had triple vessel disease). The sensitivity and specificity in identifying CAD was 47.3 and 95.2%, respectively, while positive predictive value and negative predictive value was 90% and 66%. Accuracy of DSE was 72.5%. All four patients with diffuse diabetic coronary artery disease had negative DSE.

Conclusion. DSE is a poor predictor of coronary artery disease in type 2 DM patients being evaluated for renal transplantation. CA should be included in evaluation of type 2 diabetic patients who are renal transplant candidates.

Keywords: coronary angiography; dobutamine stress echocardiography; kidney trnsplant; Type 2 diabetes mellitus

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Introduction

Type 2 DM is now the single most common cause of patients requiring renal replacement therapy. They constitute about 20% of renal transplants performed annually [1–3]. Coronary artery disease (CAD) is the major cause of death in diabetic patients following renal transplantation [4]. Pre-transplant detection and treatment might reduce these risks. Clinical practice guidelines and reviews have recommended that non-invasive screening tests or coronary angiography be performed on the basis of the individual's estimated risk of CAD [5]. However, controversy exists regarding the accuracy of myocardial perfusion studies such as thallium scintigraphy or dobutamine stress echocardiography (DSE) in type 2 diabetes mellitus (DM) patients awaiting renal transplantation [6–9].

The Manske group evaluated type I diabetic patients and recommended routine coronary angiography only in the high-risk group [10]. Similar study in a limited number of type 2 DM patients has produced mixed recommendation [9–13].

The purpose of our study was to compare DSE and coronary angiography (CA) in predicting significant coronary artery disease in type 2 DM patients awaiting renal transplantation.

Subjects and methods

Patient selection

The present study was undertaken from January 2002 to June 2004 in Muljibhai Patel Institute for research in Nephro-Urology (Nadiad, Gujarat, India). Patients who were referred for renal transplantation were eligible for enrolment prospectively by the following inclusion criteria: end stage renal disease (ESRD) from type 2 diabetic nephropathy with or without history of symptoms referable to CAD or past history of CAD defined as history of angina, prior myocardial infarction or history of coronary intervention.

Exclusion criteria were inability to give consent, presence of unstable angina and not able to undergo any of the two studies i.e. DSE and CA.

At study entry, all patients underwent a history, physical examination and baseline investigations including resting electrocardiography (ECG) and screening echocardiography (M-mode, 2D and Doppler). All patients underwent DSE and CA preferably on the same interdialytic day when they were most likely to be euvolaemic. Antihypertensive medications including β-blockers were continued to prevent sudden rise in blood pressure.

Dobutamine stress echocardiography

DSE was performed by recording images in standard parasternal long and short axis and apical four chamber and two chamber views at baseline, and during stepwise infusion of dobutamine in 3 min stages at 5, 10, 20, 30 and 40 μg/kg/min. Atropine was administered whenever needed. End points of DSE were target heart rate achieved ([220-age] × 0.85), maximum drug dose, intolerable angina, new provocable regional wall motion abnormalities in two or more coronary vascular territories, ventricular tachycardia, supraventricular tachycardia, hypotension and systolic blood pressure >240 mmHg [14].

Coronary angiography

All coronary angiograms were performed after DSE. Since all our patients were dialysis dependent there was no issue of contrast-induced nephropathy. All lesions occurring in the major coronary artery segments or their proximal branches [i.e. left anterior descending (LAD), circumflex (CX), and right coronary artery (RCA) and their major branches diagonal (D1), obtuse marginal (OM), posterior descending (PDA) and posterior lateral (PL)], were visually identified and recorded. Significant stenosis was considered if it involved >70% of the lumen.

Data analysis

All continuous variables are expressed as mean value ± SD. All statistical analysis was performed using SPSS 6.0 for Windows software (SPSS, Inc, Chicago, IL, USA, 1994) Sensitivity, specificity, accuracy and the positive and negative predictive values of DSE were calculated against >70% stenosis on CA. DSE was classified as positive if there was presence of inducible ischaemia.

Results

Baseline characteristics

Forty-four consecutive patients were screened out of which 40 patients were enrolled. All the patients were type 2 diabetic. All 40 patients completed the protocol. Table 1 shows the demographic and clinical characteristics.

Patients were predominantly middle-aged males. Half of the patients were smokers and nearly 70% had positive family history of cardiovascular disease.

Table 1. Clinical characteristics

Variables	$n = 40$ (%)
Age (year)	49.2 ± 11.4 (range 39–60)
Sex	36 males, 4 females
Smoking	18 (45)
Dialysis modalities (haemodialysis)	40 (100)
Dialysis duration (months)	6.8 ± 6.9 (range 1–36)
Diabetes duration (years)	11.5 ± 6.8 (range 1–25)
Laser therapy for retinopathy	23 (57.5)
Peripheral vascular disease	10 (25)
Cardiac symptoms	
Previous angina	2 (5)
Congestive heart failure	6 (15)
Prior myocardial infarction	0
Systolic blood pressure (mmHg)	151 ± 21
Diastolic blood pressure (mmHg)	82 ± 14
LDL cholesterol (mg/dl)	127.3 ± 30.3
HDL cholesterol (mg/dl)	41.7 ± 7.7
Drugs	
Nifedepine	30 (75)
Diltiazem	1 (4)
ACE inhibitors	2 (8)
β-Blockers	5 (12.5)
Aspirin	7 (17.5)
Statins	8 (20)
>2 Antihypertensives	23 (57.5)
Insulin	32 (80)
Oral hypoglycaemic agents	8 (20)

Results are expressed as number (%) of patients or as mean ± SD. LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Most patients (92%) were hypertensive and on medications. All these patients were on haemodialysis and the average duration on dialysis was 6.8 months with the range being from 1 to 36 months.

Resting electrocardiography

Twelve patients out of 40 (30%) had baseline ECG evidence of left ventricular hypertrophy (LVH) by voltage criteria, eight patients (20%) had evidence of underlying ischaemia, while one patient (4%) had left bundle branch block. Nineteen patients had normal ECG. Out of 21 patients with abnormal ECG, nine patients had significant coronary artery disease on angiography.

Doppler echocardiography

All patients underwent baseline Doppler echocardiography before DSE, the findings of which were listed in Table 2. None of the patients had significant valvular involvement. A resting regional wall motion abnormality (RWMA) was present in five out of 40 patients. When it was compared with a CAD definition of 70% or greater stenosis, the specificity of a baseline RWMA for diagnosis of CAD was 95%. When the ejection fraction (EF) was compared in CAD and non-CAD patients it was 46 and 49%, respectively, which was not significant.

Table 2. Doppler echocardiography

Variables	Patients ($n=40$) (%)
RWMA	5 (12.5)
LVH	24 (60)
Ejection fraction (%)	
>60	4 (10)
45–60	25 (62.5)
30–45	10 (25)
<30	1 (2.5)

Results are expressed as number (%) of patients.
RWMA, regional wall motion abnormality; LVH, left ventricular hypertrophy.

Table 3. DSE data

Variables	Events ($n=40$) (%)
Positive DSE	10 (25)
Angina during DSE	1 (2.5)
Multi-vessel ischaemia	9 (22.5)
Reasons for termination of DSE	
Target HR achieved	27 (67.5)
Maximum drug dose	3 (7.5)
Intolerable angina	1 (2.5)
Multi-vessel ischaemia	9 (17.5)
Average max. dobutamine dose (μg/kg/min)	27.7 ± 8.3
Number of patients given atropine	3 (7.5)

Results are expressed as number (%) of patients and mean ± SD.
DSE, dobutamine stress echocardiography; HR, heart rate.

Dobutamine stress echocardiography

Table 3 lists DSE findings. During DSE, one patient developed angina, which recovered after termination of test. No episodes of arrhythmias, hypotension or severe hypertension were noted. Ten patients out of 40 were positive for inducible ischaemia.

Coronary angiography

Angiograhic findings are reported using visually estimated severity of lesions in the LAD, left circumflex (LCX), and RCA and their major branches D1, OM, PDA, and PL. Seventy percent or greater stenosis was considered as significant lesion. Nineteen of 40 patients (47.5%) had at least one stenosis of >70% in a coronary or major branch (single vessel-6, double vessels-3, triple vessels-6, while four patients had evidence of diffuse disease). Out of 21 patients who were classified as having normal angiograms (according to definition of significant lesion), two had 50% lesion in single vessel. DSE was negative in all four patients who had diffuse disease.

Comparison of resting ECG, DSE and coronary angiography

Table 4 lists the sensitivity, specificity, positive and negative predictive value and accuracy of resting ECG and DSE compared with CA. For detecting ≥70% stenosis in coronary arteries the sensitivity and specificity of resting ECG was 47.5 and 43%, whereas for DSE it was 47.3 and 95.2%, respectively. The positive and negative predictive value for DSE was 90 and 66%, respectively.

Table 4. Accuracy of resting ECG and DSE *vs* CA for detection of CAD

Parameters	Resting ECG (%)	DSE (%)
Sensitivity	47.5	47.3
Specificity	43	95.2
Positive predictive value	43	90
Negative predictive value	47.5	66
Accuracy of test	45	72.5

ECG, electrocardiogram; DSE, dobutamine stress echocardiography; CA, coronary angiography; CAD, coronary artery disease.

Symptomatic CAD

Out of 40 patients, 19 had significant CAD as defined by CA. Out of these only five were symptomatic. Thus, >70% of patients had asymptomatic significant CAD.

Discussion

Our study compared the use of non-invasive test DSE with CA for detecting significant CAD in type 2 diabetic patients undergoing evaluation for renal transplantation. We found that DSE is not a suitable screening test for detecting CAD in this population.

Previous evidence supporting the use of CA is limited and current guidelines recommended it in only high-risk patients [5]. It is important to select this high-risk group and apply the test. We chose type 2 diabetic patients because they are at the highest risk of CAD and moreover, they constitute a large part of present patients undergoing renal transplantation.

Previous studies using non-invasive tests like resting ECG, DSE and myocardial scintigraphy for predicting CAD have produced variable results [9–13,15–20]. Herzog *et al.* [9], in their study of the role of DSE in detecting significant CAD in renal transplant candidates, concluded that DSE is a useful but imperfect screening technique for angiographicaly-defined CAD, though Sharma *et al.* [13] have shown better prediction of CAD using resting ECG and DSE. Bates *et al.* [19] and Rabbat *et al.* [20] showed in their study that DSE may be a good predictor of subsequent cardiac events. More recently, De Lima *et al.* [11] and Okhate *et al.* [21] reported better prediction of CAD in ESRD patients using CA.

In the present study, we found that the sensitivity of the DSE in detecting >70% coronary artery stenosis using CA as the gold standard is only 45%. This makes DSE a poor screening test for predicting CAD in type 2 diabetic patients awaiting renal transplantation.

One of the major determinants of a screening test to be useful in predicting an event is the pretest probability. The higher the pretest disease probability the lower the negative predictive value [22]. Patients with type 2 diabetes with chronic kidney disease have the highest risk of CAD, hence the performance of the screening test as shown in this study is likely to be poor.

We are aware of the limitations of the accuracy of DSE other than its observer dependent nature. We did not stop antihypertensive medications, which are potentially anti-ischaemic [23]. Five patients were on β-blocker therapy, of which three patients had CAD on CA. Amongst these three patients, two had a positive DSE. Further, 60% of patients had underlying LVH, which can confound the detection of wall motion abnormalities [14]. DSE was negative in all four patients who had diffuse disease. This is so because the ability of DSE to detect inducible ischaemia is dependent on the reference diameter of the vessel supplying the ischaemic bed [24,25]. However, RWMA on DSE was a good predictor of underlying CAD. We did not look at the relationship between DSE and future cardiac event. DSE has been used to predict long-term outcome in patients with diabetes mellitus [26], however the same authors in another paper [27] have concluded that normal DSE does not preclude significant cardiac events especially in high-risk patients.

Further, CA does carry the risk of radiocontrast-induced nephropathy, but for patients on dialysis it may not be significant. Other complications like athero-embolism and puncture site complication were not observed in this study.

In conclusion, this study found that DSE is a poor predictor of significant CAD in type 2 diabetic patients being evaluated for renal transplantation and that CA should be included in the pre-transplant work-up.

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Conflict of interest statement. None declared.

References

1. United States Renal Disease System: USRDS 1996 Annual Data Report. National Institute of Health, Bethesda, MD. National Institute of Diabetes and Digestive and Kidney Disease.1996, pp. 85–94.
2. US Department of Health and Human Services: Morbidity and Mortality: Chartbook on Cardiovascular, Lung and Blood Disease. Department of Health and Human Services, Bethesda, MD, US, 1996.
3. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 1998; 32 [Suppl 3]: S112–S119
4. Kasiske W, Guijarro C, Massy ZA, Wiederkehr MR, Ma JZ. Cardiovascular disease after renal transplantation. *J Am Soc Nephrol* 1996; 7: 158–165
5. Kasiske LB, Cangro BC, Hariharan S, Hricik DE, Kerman HR *et al*. The evaluation of renal transplant candidates. Clinical practice guidelines. *Am J Transplant* 2001; 2 [Suppl 1]: S44–52
6. Schmidt A, Stefenelli T, Schuster E *et al*. Informational contribution of noninvasive screening tests for coronary artery disease in patients on chronic renal replacement therapy. *Am J Kidney Dis* 2001; 37: 56–63
7. Koch M, Gradaus F, Schoebel FC *et al*. Relevance of conventional cardiovascular risk factors for prediction of coronary artery disease in diabetic patients on renal replacement therapy. *Nephrol Dial Transplant* 1997; 12: 1187–1191
8. Vanderberg BF, Rossen JD, Grover-McKay M *et al*. Evaluation of diabetic patients for renal and pancreas transplantation: non-invasive screening for coronary disease using radionuclide methods. *Transplantation* 1996; 62: 1230–1235
9. Herzog CA, Marwick TH, Pheley AM, White WC, Rao VK, Dick CD. Dobutamine stress echocardiography for the detection of significant coronary artery disease in renal transplant candidates. *Am J Kidney Dis* 1999; 33: 1080–1090
10. Manske CL, Thomas W, Wang Y, Wilson RF. Screening diabetic transplant candidates for coronary artery disease: identification of a low risk subgroup. *Kidney Int* 1993; 44: 617–621
11. De Lima JJ, Sabbaga E, Vieira ML *et al*. Coronary angiography is the best predictor of events in renal transplant candidates compared with noninvasive testing. *Hypertension* 2003; 42: 263–268
12. Ramanathan V, Goaral Simin, Helderman HJ *et al*. Screening asymptomatic diabetic patients for coronary artery disease prior to renal transplantation. *Transplantation* 2005; 79: 1453–1458
13. Sharma R, Pellerin D, Gaze DC *et al*. Dobutamine stress echocardiography and the resting but not exercise electrocardiograph predict severe coronary artery disease in renal transplant candidates. *Nephrol Dial Transplant* 2005; 20: 2207–2214
14. Secknus MA, Neiedermaier ON, Lauer MS, Marwick TH. Diagnostic and prognostic implications of left ventricular cavity obliteration response to dobutamine echocardiography. *Am J Cardiol* 1998; 81: 1318–1322
15. Vanderberg BF, Rossen JD, Grover-McKay M *et al*. Evaluation of diabetic patients for renal and pancreas transplantation: non-invasive screening for coronary disease using radionuclide methods. *Transplantation* 1996; 62: 1230–1235
16. Marwick TH, Steinmuller DR, Underwood DA, Hobes RE, Go RT, Swift C, Braun WE. Ineffectiveness of dipyridamole SPECT thallium imaging as a screening technique for coronary artery disease in patients with end stage renal disease. *Transplantation* 1990; 49: 100–103
17. Bourdeau RJ, Strony JT, Du cret RP *et al*. Perfusion thallium imaging of type I diabetes patients with end stage renal disease. Comparison of oral and intravenous dipyridamole administration. *Radiology* 1990; 175: 1459–1463
18. Fuster D, Margina J, Ricart MJ *et al*. Noninvasive assessment of cardiac risk in type I diabetic patients being evaluated for combined pancreas-kidney transplantation using dipyridamole-MIBI perfusion tomographic scintigraphy. *Transplant Int* 2000; 13: 327–332
19. Bates JR, Sawada SJ, Segar DS *et al*. Evaluation using dobutamine stress echocardiography in patients with insulin dependent diabetes mellitus before kidney and/or pancreas transplantation. *Am J Cardiol* 1996; 77: 175–179
20. Rabbat CG, Treleaven DJ, Russell JD *et al*. Prognostic value of myocardial perfusion studies in patients with end-stage renal disease assessed for kidney or kidney-pancreas transplantation: a meta-analysis. *J Am Soc Nephrol* 2003; 14: 431–439
21. Ohtake T, Kobayashi S, Moriya Hidekazu *et al*. High Prevalence of occult coronary artery stenosis in patients with chronic kidney disease at the initiation of renal replacement

therapy: an angiographic examination. *J Am Soc Nephrol* 2005; 16: 1141–1148
22. Fishbane S. Cardiovascular risk evaluation before kidney transplantation. *J Am Soc Nephrol* 2005; 16: 843–845
23. Sicari R, Cortigiani L, Bigi R *et al*. Prognostic value of pharmacological stress echocardiography is affected by concomitant antiischemic therapy at the time of testing. *Circulation* 2004; 109: 2428–2431
24. Bartunek J, Marwick TH, Rodrigues AC *et al*. Dobutamine induced wall motion abnormalities: correlation with myocardial fractional flow reserve and quantitative coronary angiography. *JACC* 1996; 27: 1429–1436
25. Sawada SG, Segar DS, Ryan T *et al*. Echocardiographic detection of coronary artery disease during dobutamine infusion. *Circulation* 1991; 83: 1605–1614
26. Chaowalit N, Arruda AL, McCully RB *et al*. Dobutamine stress echocardiography in patients with diabetes mellitus: enhanced prognostic prediction using a simple risk score. *JACC* 2006; 47: 1029–1036
27. Chaowalit N, McCully RB, Callahan MJ *et al*. Outcomes after normal dobutamine stress echocardiography and predictors of adverse events: long-term follow-up of 3014 patients. *European Heart Journal* 2006; 27: 3039–3044

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