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The value of myocardial perfusion imaging in screening coronary artery disease before kidney transplantation

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Running head: Myocardial SPECT before kidney transplantation

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Abstract

The value of myocardial single-photon emission computed tomography (SPECT) in pre-transplant evaluation of kidney transplant recipients is controversial. We assessed whether myocardial SPECT predicts major adverse cardiac events (MACE) and determined whether SPECT findings affected transplant recipients' medical and invasive treatment.

We analyzed 301 patients referred for myocardial SPECT before kidney transplantation and combined the results with information from patient files and the Transplantation registry.

During the median follow-up time of 96 months (IQR 70.75-118.25 months), the incidence of MACE was higher in patients (n=37) with severely abnormal SPECT (>10 % reversible perfusion defect) than in patients (n=35) with mildly abnormal or normal SPECT (51.4%, 29.4% and 27.0%, respectively, p=0.011). Severely abnormal SPECT findings predicted long-term MACE in a univariable analysis but not after adjusting for other risk factors. Following SPECT, 29 patients (9.6%) underwent coronary angiography and 14 (4.6%) were revascularized. New antithrombotic or statin medication was prescribed to 7.3% of patients with ischemia in SPECT.

Kidney transplantation patients are at high long-term risk of MACE even with normal preoperative myocardial SPECT. Abnormal SPECT did not predict MACE when adjusted for other risk factors. Minority of the patients underwent coronary revascularization or had changes in preventive medication before transplantation.

Keywords: kidney transplantation, cardiovascular disease, myocardial perfusion imaging

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Introduction

Myocardial perfusion imaging with single-photon emission computed tomography (SPECT) is a non-invasive method for assessing the function, ischemia and viability of myocardium. There is broad evidence for its value in evaluating the diagnosis and prognosis of coronary artery disease (CAD). [1,2] Therefore, SPECT has an important role in diagnosis and management of cardiovascular (CV) diseases in international guidelines.

CV diseases are the main causes of death in kidney transplant recipients [3-5]. In addition to high prevalence of traditional CV risk factors in patients with chronic kidney disease, renal dysfunction itself is an independent risk factor for CAD. Scarcity of transplant organs is a part of the rationale in the recommendations to evaluate kidney transplant candidates for CV disease before transplantation to avoid premature deaths with functioning grafts. SPECT plays an important role in the pre-transplant cardiac evaluation of kidney transplant candidates. Reversible perfusion defects in SPECT have been linked with higher risk of CV events and mortality in kidney transplant candidates [6-8]. However, other studies have found SPECT inadequate for the diagnosis of CAD [9] or as a prognostic factor [10]. In our previous study, even mild perfusion defects (1.0-9.9% area of ischemic myocardium) in SPECT predicted mortality in patients evaluated for kidney transplantation [11].

Cardiac evaluation before kidney transplantation is widely performed but there are few studies about whether SPECT is useful in risk stratification or clinical decision-making. Previous observational studies have demonstrated that very few patients have proceeded to coronary revascularization after non-invasive stress testing (such as SPECT) [12,13]. Moreover, very little is known about the physician adherence to guidelines in prescribing appropriate medication for CAD based on the findings in pre-transplant cardiac evaluation. Furthermore, there is limited data on whether pre-transplant cardiac evaluation predicts CV complications associated with kidney transplantation.

The objective of this study was to determine if the pre-transplant SPECT finding predicted CV complications during the perioperative period of kidney transplantation or in the long-term. Another focus was to assess whether the result of the SPECT affected the clinical decision-making in a real-life scenario, i.e., whether kidney transplant candidates underwent coronary

revascularization or had appropriate medication for CAD after an ischemic finding in SPECT imaging.

Patients and methods

Patients and data collection

The SPECT data were collected in the Helsinki University Hospital in 2004-2013. The dataset contains all the 301 kidney transplant patients who underwent pre-transplant cardiac screening with SPECT during 2004-2013 and received a kidney transplant before the end of the follow-up period in October 2017. During the follow-up period, a total of 761 patients from the Helsinki University Hospital area underwent kidney transplantation. Patient selection to screening with SPECT was made according to the local guidelines. Some patients (22.8%) underwent SPECT multiple times because of a long time on the waiting list. For these cases we only chose the most recent SPECT preceding transplantation. The average time on the waiting list for transplantation in Finland is less than 18 months (Scandiarttransplant Activities, annual report 2018) and patients who must wait for the transplantation for a longer time are often referred to another cardiac screening. Additional clinical information was obtained from the Transplantation Registry which is a follow-up registry obliged by law; and patient files. Baseline immunosuppression was a combination of cyclosporine or tacrolimus, mycophenolate and steroids. Induction with basiliximab or ATG was used in patients with higher immunological risk. The study was performed in accordance with the Declaration of Helsinki. We received the institutional review board approval for the study from our institution. The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul.

Guidelines for cardiac screening of kidney transplant candidates

European renal best practice transplantation guidelines and local Helsinki University Hospital guidelines recommend SPECT as a screening method for CV disease before kidney transplantation if the patient has any known risk factors (age > 50 years, diabetes, previous CV disease) or if a

low-risk patient has abnormalities in ECG, thorax x-ray or echocardiography. Angiography is only performed to patients with clear symptoms, previous myocardial infarction or with ischemic results from non-invasive cardiac investigations. [14]

Follow-up and endpoints

The patients were followed until death or the end of the follow-up period on October 31, 2017. The primary endpoint in this study was major adverse cardiac event (MACE) within 30 days of transplantation and the secondary endpoint was long-term MACE. MACE was defined as CV death, acute myocardial infarction, stroke, hospitalization because of heart failure, coronary revascularization with percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG).

Imaging and stress protocol

The stress protocol was performed as a symptom-limited exercise stress test (69.9%) or, if the patient was unable to exercise according to the standard protocol, pharmacological stress test (17.9%) or combination of exercise and pharmacological stress (5.6%). Thallium was used as the isotope in 77% and technetium in 23% of the cases. A Toshiba dual-head gamma camera was used for SPECT imaging from 2004 to 2010, after which the scans were operated with a Siemens C-Clear dual-head gamma camera. A gated scan was performed in 97.0% of the cases and non-gated in 2.6%. Attenuation correction was used in 7.0% of the cases.

Imaging interpretation

The SPECT images were first examined in a clinical setting by an experienced cardiologist. If the SPECT finding was abnormal or ambiguous, two other experienced cardiologists, blinded to the outcomes, analyzed them again for the purposes of the study. Patients with technically insufficient images were excluded.

In the quantitative analysis, the threshold for significant perfusion defect was > 40% reduction in the regional thallium (or technetium) uptake in the inferior segment and > 30% in any of the other segments [15]. We calculated the area of the perfusion defect in the washout image by using the ImageJ software (National Institutes of Health, Bethesda, MD) to obtain the percentage of ischemic myocardium. Because previous studies have suggested that revascularization improves the survival only in patients with > 10% are of ischemic myocardium in SPECT [16], we used the 10% threshold to separate mild and severe ischemia. The bull's eye display was used to analyze the relative difference between stress and rest images.

Statistical analysis

Median with interquartile range (IQR) was used to present continuous data and percentages for categorical data. The between-group differences in the distributions of continuous and categorical variables were calculated with the Kruskal-Wallis and χ^2 tests, respectively. The value of levels of ischemia in SPECT to predict MACE was evaluated in Cox regression models. Common risk factors for CAD (age, sex, diabetic nephropathy and smoking) were included as covariates in the multivariate Cox regression analyses. In addition, longer duration of dialysis and haemodialysis as the modality of dialysis before transplantation have been suggested to increase the risk of death after transplantation [17, 18] and thus these factors were also included in the multivariate models. Statistical analyses were performed with SPSS release 24.0 for Windows (SPSS Inc, Chicago, Illinois, USA). A P-value of < 0.05 was considered statistically significant.

Results

Baseline characteristics

Almost one quarter of the patients, 23.6%, had an abnormal finding in the pre-transplant SPECT. Mild defect in myocardial perfusion was found in 11.3% of the patients while 12.3% had severe ischemia. There were only few significant differences in the distribution of baseline characteristics between the patient groups with different levels of ischemia in SPECT (Table 1). Normal left

ventricular ejection fraction was most common in patients with normal SPECT findings, while patients with mild ischemia were oldest and patients with severe perfusion defects had all antihypertensive medication and were more often male. The follow-up time was 96 months (median, with IQR 70-118 months).

Cardiovascular complications and long-term MACE

There were 8 MACE (1 CV death, 1 stroke, 1 heart failure and 5 myocardial infarctions) within 30 days of transplantation and there was no difference in the incidence between patients with normal (2.6%), mildly (2.9%) or severely (2.7%) abnormal SPECT findings. Reversible perfusion defect in SPECT was not associated with higher risk of 30-day MACE in either adjusted or non-adjusted Cox-regression analysis.

In the long-term, the number of CV events increased and occurred significantly more often in patients with severely abnormal SPECT (Table 2). In a univariable Cox analysis severe perfusion defect was linked with higher risk of long-term MACE while mild ischemia was not (Table 3). However, adjusting for other risk factors (age, sex and diabetes) eliminated the prognostic value of SPECT-detected severe ischemia (Table 3, Figure 1). Perfusion defects in SPECT were not linked to higher risk of graft loss (Table 2). Regarding mortality, the results were similar. Neither mild or severe perfusion defects in SPECT predicted mortality in an adjusted Cox regression analysis (HR 1.35, $p=0.44$ and HR 1.45, $p=0.28$, respectively). In an unadjusted Cox regression analysis severe perfusion defects were associated with a higher risk of mortality (HR 2.27, $p=0.008$) but mild defects were not (HR 1.93, $p=0.078$). There was no significant difference in the time from SPECT to death in patients with normal, mild or severe SPECT findings (medians 48, 67 and 48 months, respectively). In addition, there was no significant difference in the time from SPECT to death in SPECT positive patients who had an invasive or medical intervention compared to those who did not (medians 72, 74 and 86 months, respectively).

In patients who underwent kidney transplantation and SPECT testing, only a few invasive or medical interventions were done after the SPECT imaging (Table 4, Figure 2). Just under 10% of the whole study population underwent angiography after SPECT and 27% of them had symptoms of possible CAD before screening. Patients with large perfusion defects in SPECT proceeded to angiography or coronary revascularization significantly more often but still almost half of them underwent no further post-SPECT cardiac studies. The only statistically significant difference between patients who did or did not undergo angiography or revascularization was that patients with PCI had diabetes more frequently. None of the patients who underwent revascularization with PCI or CABG smoked but a majority of them had diabetes or were over 50 years old. Of the 10 patients who underwent PCI based on the SPECT result, 9 had at least one MACE (1 CV death, 6 myocardial infarctions, 3 strokes, 5 hospitalization because of heart failure). In addition, two of the four post-SPECT CABG patients had at least one MACE (2 myocardial infarctions and hospitalization because of heart failure). As SPECT-based revascularizations could have affected the risk of MACE, we did a further analysis where we divided the SPECT results into four groups: normal, mild, severe and needed an invasive intervention. A majority of the patients who needed an invasive intervention based on the SPECT finding had a MACE (78.6%). Also, in an unadjusted Cox regression analysis the need for a coronary revascularization after SPECT was associated with a higher risk of long-term MACE (HR 2.95, $p=0.001$). However, this association was not seen in an adjusted Cox regression analysis (HR 1.44, $p=0.32$). Only one 30-day MACE occurred in this patient group and there was no statistical difference compared to other SPECT groups. In addition, post-SPECT revascularization did not predict 30-day MACE in either unadjusted or adjusted Cox regression analysis.

Most of the patients were already taking antiplatelet or anticoagulative medication or statins before the pre-transplant screening (Figure 2). New antithrombotic (ASA or P2Y₁₂ inhibitors) or statin medication was initiated after SPECT imaging to 11.8% of the patients with mild perfusion defects in SPECT and 18.9% of the patients with severe perfusion defects. Even though new prescription for CAD medication was significantly more frequent for patients with ischemia in SPECT, as many as 24% did not get antithrombotic and 27% statin medication after abnormal SPECT finding.

The result of the SPECT imaging was more often abnormal in patients older than 60 years (33.0% vs. 19.5%, $p=0.01$). However, there was no significant difference in the treatment after SPECT imaging in patients older or younger than 60 years. There was no statistically significant difference in the incidence of an abnormal SPECT scan in patients with or without diabetes (23.4% vs. 23.7%, $p=0.54$).

We also assessed whether the risk profile of the patients (diabetic nephropathy or age over 60 years) affected the treatment strategies. Patients with diabetic nephropathy underwent PCI after SPECT more often than patients with other causes for kidney disease (6.3% vs. 1.6%, $p=0.03$) and MACE also occurred more often in patients with diabetes (36.9% vs. 26.7%, $p=0.04$).

Discussion

Abnormal perfusion results and cardiovascular events

Kidney transplantation is a surgical operation with possible complications. Risk for related cardiovascular events is highest during the first three months after the transplantation [19,20]. That itself is a strong indication to evaluate cardiac health of patients undergoing kidney transplantation. However, we found out that CV events within 30 days of transplantation were uncommon, only 2.6% for the whole study population, and abnormal findings in SPECT did not predict them. Over time the cumulative number of CV events increased, which is not surprising as the risk of CV events is high in kidney transplant recipients and we had a relatively long follow-up time. Patients with severe ischemia in SPECT had significantly more long-term CV events. However, SPECT finding offered no incremental prognostic value when adjusting for other known risk factors. Patients with diabetic nephropathy had more CV events than patients without diabetes. In comparison to our previous study with all kidney transplant candidates screened with SPECT [11], perfusion defects in SPECT did not predict mortality in the present study. The explanation for this difference is probably the more low-risk population of this study as we included only kidney transplant recipients.

Our results are in line with previous studies. A recent study with 401 patients screened with myocardial SPECT before kidney transplantation demonstrated that the SPECT result did not

predict post-operative CV events [21]. In addition, SPECT finding has been reported to add incremental long-term prognostic value only for patients with intermediate risk profile [21,22].

Medical and invasive treatment strategies after myocardial SPECT

The main rationale for screening asymptomatic patients is to find stable CAD before kidney transplantation. However, there are no randomized controlled trials (RCT) from the current era about the treatment of stable CAD in kidney transplant candidates. Two RCTs, without consideration of the renal function, have concluded that prophylactic coronary revascularization does not improve the long-term outcome of patients undergoing major vascular surgery [23,24] but we cannot draw direct conclusions from non-kidney transplant patients and a RCT should be made also in this patient population to determine the impact of coronary revascularizations before kidney transplantation. In addition, previous studies suggest that PCI does not improve event-free survival when added to optimal medical therapy in patients with CAD and chronic kidney disease [25]. In our study, very few patients underwent revascularization based on the SPECT finding and most of them were asymptomatic. Nevertheless, almost half of the patients referred to angiography based on the SPECT result needed an intervention, so patient selection to angiography was quite effective. However, based on the local guidelines, patients with very high CV risk or symptomatic CAD are referred straight to angiography without SPECT and were not included in the present study. Patients with diabetic nephropathy underwent PCI after SPECT more often than patients without diabetes. Still, only 6% of these high-risk patients underwent PCI. Age did not affect the treatment strategies although older patients had more often abnormal results in the SPECT imaging. In our results, it seems that pre-transplant revascularization did not protect the patients from long-term MACE as almost 80% of these patients had at least one MACE during the follow-up period. These were probably very high-risk patients and not even invasive interventions could decrease their risk of MACE. There was no difference in the incidence of 30-day MACE in patients who needed an invasive intervention based on the SPECT result compared to other SPECT groups so perhaps some perioperative CV complications were avoided with pre-transplant cardiac evaluation and interventions.

Previous studies have reported that patients in high versus low CV risk have reduced survival after kidney transplantation but still the survival of high-risk patients is improved by transplantation

compared to dialysis [26]. Although even the high-risk patients would benefit from transplantation, cardiac evaluation with SPECT is used as a part of the process to select the patients for transplantation to minimize the risk of losing functioning grafts with patients dying of cardiovascular causes. We included only patients who received a kidney transplantation to this study, and therefore conclusions about who to deny transplantation based on SPECT findings are not justified. The overall risk of early MACE was low, suggesting that the predictive value of SPECT is limited. Another essential value of pre-transplant cardiac evaluation could be to identify patients with CAD to ensure they have optimal medication for CV prevention perioperatively and in the long run [25,27,28]. Our results show that most of the kidney transplant candidates are already taking statins and antithrombotic medication. Still, more than 20% of the patients with an abnormal SPECT finding did not get appropriate medication for CAD. However, the data lacked information on patients potentially not taking these new medications due to toleration issues. There was no significant difference in the changes made to the medical therapy after SPECT in younger or older patients or in patients with or without diabetic nephropathy. Clearly, the medical treatment of stable CAD should be more active in patients waiting for kidney transplantation.

Strengths and limitations

Our data contain all the kidney transplant recipients who underwent SPECT as routine pre-transplant cardiac evaluation during the study period in Helsinki University Hospital. The follow-up time is quite long for the long-term CV events. Our study is prone to the common limitations of an observational study. Our results are limited to patients from a single center, characterized by almost exclusively deceased donor transplantation with relatively short waiting times and high frequency of diabetic nephropathy as the cause of end-stage renal disease, and our results may not be applicable to other patient cohorts. The reasons why new medication was not started on some patients could not be accounted for due to data not containing this information.

Conclusion

Screening for coronary artery disease with myocardial SPECT before kidney transplantation yields abnormal findings in about a quarter of the patients. Perioperative CV complications are

infrequent, and risk stratification with SPECT does not add incremental prognostic value to predicting them in addition to traditional risk factors. Minority of the patients underwent coronary revascularization before kidney transplantation or had changes in the preventive medication. Our results suggest that kidney transplantation patients are at high long-term risk of MACE even if the preoperative myocardial SPECT is normal.

Author contributions

Concept/design: SH, TN, IH, PF, ML. Data collection: SH, IH, PF. Data analysis: SH, JS, HR. Drafting article: SH. Critical revision and approval of article: TN, IH, PF, JS, HR, ML

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Table 1. Baseline characteristics based on the ischemic finding in SPECT.

	SPECT normal n=230	SPECT mild n=34	SPECT severe n=37	p
Age, years, median (IQR)	52 (44-60)	59 (54.5-64)	56 (47.5-64)	0.002
Male sex	56.5	73.5	75.7	0.02
Diabetic nephropathy	37.0	23.5	48.6	0.09
BMI, kg/m ² , median (IQR)	25.4 (22.7-28.7)	26.5 (23.9-30.4)	25.0 (24.3-29.4)	0.38
Previous AMI	4.4	11.5	10.3	0.18
Previous CABG	5.8	11.1	14.3	0.20
ASO	2.0	3.7	0.0	0.61
Previous stroke	6.4	15.4	0.0	0.08
Medication for dyslipidemia	57.4	55.9	64.9	0.67
Antithrombotic medication	68.3	61.8	73.0	0.60
Medication for hypertension	89.7	77.8	100.0	0.02
Present smoker	20.0	17.6	5.4	0.10
Ejection fraction > 50%	97.2	84.8	88.9	0.003
Hemodialysis	62.2	55.9	54.1	0.54
Duration of dialysis, months, median (IQR)	21 (12-43)	26 (17-64)	23.5 (14-59)	0.17
Deceased donor	95.2	97.1	97.3	0.32

Values are percentages with the exception of age, BMI, and duration of dialysis. AMI, acute myocardial infarction; ASO, arteriosclerosis obliterans; BMI, body mass index; CABG, coronary artery bypass graft; SPECT, single-photon emission tomography.

Table 2. Cardiovascular events in patients with different levels of ischemia in SPECT (median follow-up time 96 months, IQR 70-118 months)

	SPECT finding			p
	Normal (<1.0%)	Mild (1.0-9.9%)	Severe (≥10.0%)	
	n= 230	n = 34	n = 37	
Death, n (%)	41 (17.8)	9 (26.5)	14 (37.8)	0.02
MACE, n (%)	62 (27.0)	10 (29.4)	19 (51.4)	0.01
CV death, n (%)	11 (4.9)	6 (17.6)	2 (5.9)	0.02
Non-fatal MACE, n (%)	57 (24.8)	9 (26.5)	18 (48.6)	0.01
AMI, n (%)	18 (7.8)	1 (2.9%)	8 (21.6)	0.008
Stroke, n (%)	20 (8.7)	1 (2.9)	5 (13.5)	0.29
Heart failure, n (%)	31 (13.5)	8 (23.5)	8 (21.6)	0.18
PCI, n (%)	14 (6.1)	0 (0.0)	8 (21.6)	<0.001
CABG, n (%)	6 (2.6)	1 (2.9)	4 (10.8)	0.001
Graft loss, n (%)	34 (14.8)	3 (9.1)	4 (10.8)	0.58

AMI, acute myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; MACE, major adverse cardiovascular event; Heart failure, hospitalization because of heart failure; PCI or CABG at any time during the follow-up period.

Table 3. Unadjusted and adjusted Cox regression analysis of long-term MACE

		95% CI		
	RR	Lower	Upper	p
<i>Unadjusted analysis</i>				
SPECT mild	1.827	0.922	3.620	0.084
SPECT severe	2.295	1.360	8.871	0.002
<i>Adjusted analysis</i>				
SPECT mild	1.352	0.664	2.756	0.41
SPECT severe	1.466	0.829	2.591	0.19
Age	1.052	1.026	1.079	<0.001
Sex	1.707	1.052	2.771	0.03
Diabetic nephropathy	2.408	1.521	3.812	<0.001
Hemodialysis	1.609	1.013	2.555	0.04
Duration of dialysis	1.003	0.999	1.006	0.10
Present smoker	1.357	0.769	2.395	0.29

Table 4. Invasive treatment after SPECT

	SPECT finding			p
	Normal (<1.0%)	Mild (1.0-9.9%)	Severe (≥10.0%)	
	n= 230	n = 34	n = 37	
Angio, n (%)	2 (0.9)	7 (20.6)	20 (54.1)	<0.001
PCI, n (%)	3 (1.3)	0 (0.0)	7 (18.9)	<0.001
CABG, n (%)	0 (0.0)	1 (2.9)	3 (8.1)	<0.001

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