Gated SPECT myocardial perfusion imaging in patients with end stage renal disease - comparison with clinical data

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SUMMARY

Abbreviations	2
Abstract	3
Resumo	5
Introduction	7
Material and Methods	8
A. Patient population	8
B. Protocol	9
C. Interpretation of images	9
D. Statistical analysis	10
Results	11
Discussion	20
Conclusions	24
Acknowledgements	25
References	26

ABBREVIATIONS

CAD: coronary artery disease
CKD: chronic kidney disease
DM: diabetes mellitus
ECG: electrocardiogram / electrocardiographic
ESRD: end-stage renal disease
HTN: hypertension
LV: left ventricle
LVEF: left ventricular ejection fraction
RS: reversible score
SD: standard deviation
SPECT-MPI: single-photon emission computed tomography myocardial perfusion imaging
SRS: summed rest score
SSS: summed stress score

ABSTRACT

Background: The patients with end stage renal disease (ESRD) represent a particularly challenging population as coronary artery disease (CAD) remains a leading cause of mortality, limiting the long term success of renal transplantation. Thus cardiovascular risk stratification is essential in the pre-transplant screening and may be performed non-invasively by modalities including single-photon emission computed tomography myocardial perfusion imaging (SPECT-MPI). The goal of this study was to evaluate the prevalence of changes in the SPECT-MPI and its relationship with cardiovascular risk factors, clinical manifestations of ischemia, electrocardiographic pattern and heart rate response to adenosine in patients with ESRD.

Methods: We included 112 cases of consecutive patients with ESRD on dialysis, who were referred to our institution between October 2011 and April 2013, to perform SPECT-MPI for pre-operative risk stratification before renal transplant. Data was collected, including gender, age, the presence of risk factors for atherosclerosis (diabetes (DM), hypertension (HTN), dyslipidemia and smoking habits), rest heart rate, presence of previous angina and baseline ECG pattern. Gated SPECT-MPI was performed according to the protocol stress followed by rest images with Tc 99m-tetrafosmin. A 17 segment score system was used to semi-quantify the perfusion defects. A LVEF \leq 45% was considered abnormal. *Emory Toolbox Software* was used for phase analysis and a standard deviation (SD) \geq 43° was considered significant for mechanical dyssynchrony.

Results: The mean age was 51.8 ± 10.8 and the majority of patients were male. Myocardial perfusion abnormalities were presented in 22.3%. The QRS width (OR = 1.0, *P* value < 0.005) and the rest heart rate (OR = 1.1, *P* value < 0.05) were independent predictors of an abnormal perfusion. An LVEF $\leq 45\%$ was present in 13.4 % of the patients. The evidence of an ECG suggestive of myocardial hypertrophy (OR = 8.2, *P* value < 0.05), the baseline QRS

width (OR = 1.0, *P* value < 0.05) and the reference to previous angina (OR = 5.4, *P* value < 0.05) were independent predictors of a LVEF \leq 45%. Left ventricular dyssynchrony was observed in 16.1% of the studied population. The age (OR = 0.9, *P* value < 0.05) and the SRS (OR = 1.3, *P* value < 0.001) were independent predictors of mechanical dyssynchrony.

Conclusions: An abnormal gated SPECT-MPI in this group of patients was not associated with the presence of cardiovascular risk factors. The changes on the ECG pattern were predictors of an abnormal perfusion and along with the electrocardiographical evidence of myocardial hypertrophy were also predictors of an impaired left ventricle function, with no relationship between them and the presence of mechanical dyssynchrony. The low frequency of perfusion abnormalities found in gated SPECT-MPI, which was also very heterogeneous in what concerns to age, justifies further studies to define the optimal population, protocol and image acquisition of gated SPECT-MPI when evaluating patients with ESRD.

Key words: end stage renal disease • coronary artery disease • cardiovascular risk factors • myocardial perfusion imaging • ECG • left ventricular ejection fraction • ventricular dyssynchrony.

RESUMO

Introdução: Os doentes com doença renal terminal (DRT) representam uma população particularmente desafiante dado que a doença arterial coronária (DAC) continua a ser uma das principais causas de morte nesta população, o que limita o sucesso a longo prazo do transplante renal. Deste modo, a estratificação do risco cardiovascular é fundamental na seleção de doentes para transplante e pode ser realizada de forma não invasiva pela CPM. O objetivo deste estudo foi avaliar a prevalência de alterações na cintigrafia de perfusão do miocárdio (CPM) e a sua relação com fatores de risco cardiovascular, manifestações clínicas de isquémia, padrão electrocardiográfico (ECG) e frequência cardíaca após a administração de adenosina em pacientes com DRT.

Métodos: Foram incluídos 112 doentes consecutivos com DRT em diálise, que foram encaminhados para a nossa instituição entre Outubro de 2011 e Abril de 2013, para realizar CPM, de forma a estratificar o risco cardiovascular pré-operatório do transplante renal. Os dados colhidos incluíram o género, a idade, a presença de fatores de risco para aterosclerose (diabetes *mellitus*, hipertensão arterial, dislipidémia e tabagismo), a frequência cardíaca em repouso, a presença de angina prévia e o padrão eletrocardiográfico basal. A CPM foi realizada de acordo com o protocolo de esforço seguido pela obtenção de imagens em repouso, com o uso de Tc 99m-tetrafosmina. Um sistema de pontuação de 17 segmentos foi usado para semi-quantificar os defeitos de perfusão miocárdica. Uma FEVE $\leq 45\%$ foi considerada anormal. O histograma de fase foi obtido pelo *Emory Toolbox Software* e um desvio padrão (SD) $\geq 43^{\circ}$ foi considerado significativo para dessincronia mecânica.

Resultados: A idade média foi de 51.8 ± 10.8 anos e a maioria dos pacientes eram do género masculino. Alterações da perfusão miocárdica estavam presentes em 22.3% dos pacientes. A duração do intervalo QRS (OR = 1.0, P < 0.005) e a frequência cardíaca em repouso (OR =

1.1, P < 0.05) foram preditores independentes de uma perfusão anormal. Uma FEVE \leq 45 % estava presente em 13.4% dos doentes. A evidência de um ECG sugestivo de hipertrofia do miocárdio (OR = 8.2, P < 0.05), a duração do intervalo QRS (OR = 1.0, P < 0.05) e a referência a história prévia de angina (OR = 5.4, P < 0.05) foram preditores independentes de uma FEVE \leq 45%. A dessincronia ventricular esquerda foi observada em 16.1% da população estudada. A idade (OR = 0.9, P < 0.05) e o SRS (OR = 1.3, P < 0.001) foram preditores independentes de uma perfusion de dessincronia mecânica.

Conclusões: As alterações da perfusão do miocárdio não tiveram qualquer relação com a presença de fatores de risco cardiovascular. As alterações no padrão de ECG foram preditoras de uma perfusão anormal e, juntamente com a evidência eletrocardiográfica de hipertrofia miocárdica, foram preditoras de uma função ventricular esquerda diminuída, sem relação com a presença de dessincronia mecânica. A baixa prevalência de defeitos de perfusão encontrada, que foi, de igual modo, muito heterogénea no que concerne a idade, justifica a necessidade premente de realizar mais estudos, de forma a definir o melhor protocolo e processo de aquisição de imagens mais adequado na CPM, bem como a população ideal a ser submetida a este exame, no que respeita à avaliação de pacientes com DRT em lista de espera para transplante renal.

Palavras-chave: doença renal terminal • doença arterial coronária • fatores de risco cardiovascular • cintigrafia de perfusão do miocárdio • ECG • fração de ejeção do ventrículo esquerdo • dessincronia ventricular.

INTRODUCTION

Cardiovascular disease is the leading cause of morbidity and mortality in patients with chronic kidney disease (CKD), particularly in those with end stage renal disease (ESRD) ^[1-6], where 45% of the overall mortality is attributed to cardiovascular causes ^[2, 7]. In fact, the incremental risk of cardiovascular disease in those with CKD, compared to the age- and sexmatched general population, ranges from 10- to 20-fold, depending on the stage, being CKD an independent risk factor for coronary artery disease (CAD) ^[1, 8-10]. Therefore, the increased prevalence of vascular disease in CKD patients derives from both traditional and non-traditional (CKD-related) risk factors. The first ones include hypertension (HTN), diabetes (DM) and dyslipidemia. The CKD-related risk factors include anemia, hyperphosphatemia, hyperparathyroidism and generalized inflammation ^[1, 3, 9, 11, 12].

Patients with ESRD, with an indication for renal replacement therapy, represent a particularly challenging population as CAD remains a leading cause of mortality, limiting the long term success of renal transplantation. This procedure improves both survival and quality of life in this subgroup of patients. However, concerning the intense utilization of resources and the limited availability of donors, it is vital to offer this therapy to individuals most likely to achieve long-term benefit ^[1, 4]. Thus, cardiovascular risk stratification is essential in the pre-transplant screening, helping to identify individuals that may require a more aggressive evaluation and treatment. Moreover, it helps to detect existing cardiac conditions amenable to risk modification, and to exclude individuals with such short life expectancy that transplantation would not yield acceptable benefit from the allograft ^[6, 8, 9, 11, 13-21].

Among other techniques, testing for CAD may be performed non-invasively by modalities including single-photon emission computed tomography myocardial perfusion imaging (SPECT-MPI). It has been shown that these tests have prognostic value for mortality but imperfect sensitivity and specificity for detecting angiographically-defined CAD in patients with renal failure ^[1, 4-6, 11, 13-15, 17, 21-24]. However, encouraging results have been already reported ^[25-27], suggesting that this subject requires further evaluation.

Nevertheless, SPECT-MPI is a powerful tool to diagnose CAD, identifying patients at high and low clinical risk, and aid in their treatment. It predicts adverse cardiovascular outcomes in CKD patients with known or suspected CAD, due to the provided data such as left ventricular (LV) function, myocardial perfusion defects and, likewise, the existence of ventricular dyssynchrony ^[7, 8, 16, 20, 22, 28-30].

With this study, we intend to evaluate the prevalence of changes in the SPECT-MPI and its relationship with cardiovascular risk factors, clinical manifestations of ischemia, electrocardiographic pattern and heart rate response to adenosine in patients with ESRD.

MATERIAL AND METHODS

A. Patient population

The study population was selected from a database of all patients with ESRD on dialysis, who were referred to our institution to perform SPECT-MPI for pre-operative risk stratification before renal transplant. From October, 1st of 2011, to April, 30th of 2013, 125 SPECT-MPI were performed in these patients.

In brief, demographic and clinical data was possible to collect from 112 cases, including gender, age, the presence of risk factors for atherosclerosis (diabetes (DM), hypertension (HTN), dyslipidemia and smoking habits), presence of previous angina and ischemic basal ECG as well as reference to an ECG suggestive of myocardial hypertrophy or bundle branch block, rest heart rate and baseline QRS width. Due to the presence of arrhythmia, gated SPECT was not possible to perform in 13 patients.

B. Protocol

Gated SPECT-MPI was obtained at stress followed by rest with Tc-99m tetrafosmin.

For stress images patients were injected with 370 to 555 MBq (10 to 15 mCi) of Tc-99m tetrafosmin during adenosine protocol. Adenosine was infused at a dose of 140 μ g/Kg/min during 4 minutes and the tracer was injected at the end of the second minute. ST deviation during adenosine and heart rate after vasodilation were recorded for analysis.

Rest images were acquired by injecting 740 to 1110 MBq (20 to 30 mCi) of the tracer, 3 hours later if an abnormality (in perfusion and/or ventricular function) was noticed in stress images. The injected dose was calculated according to the weight of the patient.

Images were acquired 30 to 45 minutes after the injection of the tracer. They were performed by a hybrid system SPECT-CT, with a dual-head gama camera (BrightView XCT), using a stop and shoot acquisition, with 64 projections per study and a 180° arc, from right anterior to left anterior oblique. A single low-dose CT (computed tomography) scan (helical, 120 KeV, 1mA with 1.9 pitch) was acquired before stress and rest acquisitions for attenuation correction.

C. Interpretation of images

Images were visualized and classified as abnormal according to the presence of a perfusion defect (Figure 1). Concerning the current guidelines, a 17 segment score system was used to semi-quantify the perfusion defects, allowing to obtain a perfusion score (stress, rest and reversibility score).



Figure 1. A - Stress images presenting a perfusion defect in the inferior and lateral segments of the left ventricle without attenuation correction and an apical defect with attenuation correction. **B** - Rest images of the same patient presenting a perfusion defect in the inferior segment (smaller than in A) without attenuation correction and an almost normal exam with attenuation correction.

The left ventricular ejection fraction (LVEF) was calculated automatically in patients with a regular cardiac rhythm. A LVEF equal or under to 45% was considered abnormal. Using *Emory toolbox*, left ventricular synchrony was also estimated through the values of the standard deviation (SD) on the phase histogram (Figure 2). According to the literature ^[30, 31], a phase SD equal or above 43° is synonymous of significant ventricular dyssynchrony.



Figure 2. Phase histogram of the patient in Figure 1 showing a $SD < 43^{\circ}$.

D. Statiscal analysis

Continuous variables were presented as mean ± 1 standard deviation (M ± 1 SD) and categorical variables were presented as their proportion in the total study population.

Continuous variables were compared using the ANOVA and the nonparametric U-Mann-Whitney test. The Fisher's exact test was used for categorical data.

Considering the presence of an abnormal perfusion, a LVEF $\leq 45\%$ and a SD $\geq 43^{\circ}$ as the dependent variables, univariate logistic regression analysis was used to assess the predictors of perfusion defects (ischemia), impairment in LVEF (left ventricle dysfunction) and mechanical dyssynchrony.

The level of statistical significance adopted was 0.05. All statistical analysis was performed using *StatView 5.0.1*, version for Macintosh and Windows, SAS Institute.

RESULTS

The demographic, clinical and electrocardiographic data collected from the 112 patients in this study are shown in Table 1. The mean age was 51.8 ± 10.8 and the majority of patients were male. Over 60% of the patients had HTN and 25% were presented with an ischemic basal ECG.

Variables	n = 112 (100%)
Male gender	87 (77.7%)
Age (years)	51.8 ± 10.8
Previous angina	12 (10.7%)
DM	39 (34.8%)
HTN	70 (62.5%)
Dyslipidemia	28 (25%)

Table 1. Baseline characteristics

Smoking habits	10 (8.9%)
ST segment /T wave changes	28 (25%)
Baseline QRS width (ms)	107.8 ± 23.6
Bundle branch block	11 (9.8%)
ECG suggestive of myocardial hypertrophy	7 (6.3%)
Rest heart rate (beats/min)	70.3 ± 10.9

DM, Diabetes mellitus. HTN, Hypertension. ECG, Electrocardiogram.

The adenosine stress test and imaging results collected from SPECT-MPI are presented in Table 2. Myocardial perfusion abnormalities, defined as a summed stress score $(SSS) \ge 1$, were presented in 25 patients (22.3%). An LVEF equal or inferior to 45% was registered in 13.4% of the patients and about 16.1% had significant mechanical ventricular dyssynchrony (SD \ge 43°).

	Table 2	. SPE	CT-N	IPI	result	ts
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Variables	n = 112 (100%)
Adenosine heart rate (beats/min)	88.6 ± 14.3
ST depression during adenosine	3 (2.7%)
Abnormal myocardial perfusion	25 (22.3%)
SSS	2.6 ± 5.8
SRS	1.8 ± 4.9
RS	0.8 ± 2.7
LVEDV (mL)	110.2 ± 57.4
LVESV (mL)	52.9 ± 38.1

LVEF (%)	61.3 ± 13.6
$LVEF \leq 45\%$	15 (13.4%)
SD	27.7 ± 14.3
$SD \ge 43^{\circ}$	18 (16.1%)

SSS, Summed stress score. SRS, Summed rest score. RS, Reversibility score. LVEDV, Left ventricular end diastolic volume. LVESV, Left ventricular end systolic volume. LVEF, Left ventricular ejection fraction. SD, Standard deviation.

In Table 3, clinical, electrocardiographic and adenosine stress test characteristics were compared in patients with and without myocardial perfusion defects. The major differences between patients with abnormal and normal myocardial perfusion were related with the rest QRS width (P < 0.005) and the presence of bundle branch block (P < 0.01). There were no significant differences between the incidence of the non-modifiable and modifiable risk factors for cardiovascular disease between both groups.

	Abnormal perfusion	Normal perfusion	P value
	n = 25 (22.3%)	n = 87 (77.7%)	
Male gender	20 (80%)	67 (77%)	ns
Age (years)	52.1 ± 11.8	51.7 ± 10.6	ns
DM	11 (44%)	28 (32.2%)	ns
Dyslipidemia	7 (28%)	21 (24.1%)	ns
HTN	17 (68%)	63 (72.4%)	ns
Smoking habits	2 (8%)	8 (9.2%)	ns
Rest heart rate (beats/min)	75.0 ± 14.0	68.9 ± 9.6	ns (0.06)
ST segment/T wave changes	10 (40%)	18 (20.7%)	ns (0.06)

Table 3.	. Myocardia	l perfusion	defects
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Bundle branch block	6 (24%)	5 (5.7%)	< 0.01
ECG suggestive of	2 (8%)	5 (5.7%)	ns
myocardial hypertrophy			
Baseline QRS width	122.1 ± 29.1	103.6 ± 20.2	< 0.005
Previous angina	3 (12%)	9 (10.3%)	ns
Adenosine heart rate	92.2 ± 15.9	87.6±13.8	ns
(beats/min)			
ST depression during	0 (0%)	3 (3.5%)	ns
adenosine			

DM, Diabetes mellitus. HTN, Hypertension. ECG, Electrocardiogram.

Using logistic regression analysis, the univariate predictors of myocardial perfusion defects were, in this group, the baseline heart rate, the presence of ischemic changes in the baseline ECG, the baseline QRS width and, likewise, the evidence of bundle branch block (Table 4).

A multivariate model was built with the variables found to be predictors of an abnormal perfusion in the univariate analysis (Table 5). This model has the QRS width in addition to the rest heart rate as independent predictors of an abnormal perfusion. It predicts correctly 83.6% of the cases, 97.7% of which were presented without any myocardial perfusion defects and 33.3% with an abnormal myocardial perfusion.

	Odds ratio	95% CI odds ratio	P value
Rest heart rate	1.0	0.9 - 1.0	< 0.05
ST segment /T wave changes	2.6	1.0 - 6.6	< 0.05

Bundle branch block	5.2	1.4 - 18.8	< 0.05
Baseline QRS width	1.0	1.0 - 1.1	< 0.005

Table 5. Multivariate model used to predict myocardial perfusion defects

Likelihood test: $\chi 2 = 16.0$; P value < 0.0001

	Odds ratio	95% CI odds ratio	P value
Rest heart rate	1.1	1.0 - 1.1	< 0.05
ST segment /T wave changes	3.0	1.0 - 9.0	ns
Baseline QRS width	1.0	1.0 - 1.0	< 0.005

In Table 6, clinical, electrocardiographic and SPECT-MPI characteristics were compared in patients with LVEF \leq 45% and LVEF > 45%. The major differences between these groups were related to the electrocardiographic changes (ischemic basal ECG, evidence of bundle branch block, ECG pattern of myocardial hypertrophy and the baseline QRS width) as well as to the SPECT-MPI results (abnormal myocardial perfusion, SSS and SRS).

	LVEF ≤ 45%	LVEF > 45%	<i>P</i> value
	n = 15 (13.4%)	n = 97 (86.7%)	
Male gender	11 (73.3%)	76 (78.4%)	ns
Age (years)	51.1 ± 11.3	51.8 ± 10.8	ns
DM	5 (33.3%)	34 (35.1%)	ns
Dyslipidemia	5 (33.3%)	23 (23.7%)	ns
HTN	9 (60%)	61 (62.9%)	ns
Smoking habits	2 (13.3%)	8 (8.2%)	ns

Table V. Delt ventilenal ejection fraction
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Rest heart rate (beats/min)	76.3 ± 15.2	69.3 ± 9.8	ns
ST segment/T wave	7 (46.7%)	21 (21.6%)	< 0.05
changes			
Bundle branch block	5 (33.3%)	6 (6.2%)	< 0.01
ECG suggestive of	3 (20%)	4 (4.1%)	< 0.05
myocardial hypertrophy			
Baseline QRS width (ms)	123.1 ± 31.8	105.4 ± 21.3	< 0.05
Previous angina	4 (26.7%)	8 (8.2%)	ns (0.06)
Adenosine heart rate	91.5 ± 16.4	81.1 ± 14	ns
(beats/min)			
ST depression during	0 (0%)	3 (3.2%)	ns
adenosine			
SSS	5.5 ± 7.5	2.2 ± 5.4	< 0.05
SRS	4.7 ± 7.6	1.4 ± 4.2	< 0.05
RS	0.8 ± 1.7	0.8 ± 2.8	ns

DM, Diabetes mellitus. HTN, Hypertension. ECG, Electrocardiogram. SSS, Summed stress score. SRS, Summed rest score. RS, Reversibility score.

Using logistic regression analysis, the univariate predictors of LVEF $\leq 45\%$ were, in this group, the electrocardiographic changes, the reference to previous angina and the SRS (Table 7).

The multivariate model (Table 8) showed that the evidence of an ECG suggestive of myocardial hypertrophy, the baseline QRS width and the reference to previous angina were independent predictors of a LVEF \leq 45%. This model, predicted appropriately 91.7% of the cases: 100% of which were presented with a LVEF > 45% and 40% with a LVEF \leq 45%.

	Odds ratio	95% CI odds ratio	P value
ST segment /T wave	3.2	1.0 - 9.7	< 0.05
changes			
Bundle branch block	7.6	2.0 - 29.4	< 0.005
ECG suggestive of	5.8	1.2 - 29.2	< 0.05
myocardial hypertrophy			
Baseline QRS width	1.0	1.0 - 1.1	< 0.05
Previous angina	4.0	1.0 - 15.7	< 0.05
SSS	1.1	1.0 - 1.2	ns (0.06)
SRS	1.1	1.0 - 1.2	< 0.05

Table 7. Univariate predictors of LVEF $\leq 45\%$

ECG, Electrocardiogram. SSS, Summed stress score. SRS, Summed rest score.

Table 8. Multivariate predictors of LVEF $\leq 45\%$

Likelihood test: $\chi 2 = 15.8$; *P* value < 0.0001

	Odds ratio	95% CI odds ratio	<i>P</i> value
ST segment/T wave	3.3	0.9 - 12.3	ns
changes			
ECG suggestive of			0.0 7
myocardial hypertrophy	8.2	1,4 - 50.8	< 0.05
Baseline QRS width	1.0	1.0 - 1.0	< 0.05
Previous angina	5.4	1.1 - 26.5	< 0.05
SRS	1.1	0.9 - 1.2	ns

ECG - Electrocardiogram; SRS - Summed rest score.

In Table 9, we compared clinical, electrocardiographic and SPECT-MPI characteristics in patients with a SD \geq 43° and SD < 43°, defining left ventricle mechanical dyssynchrony. The major differences between both groups were related to the age and the scores obtained with SPECT-MPI (SSS and SRS) as well as a LVEF \leq 45%.

	$SD \ge 43^{\circ}$	SD < 43°	<i>P</i> value
	n = 18 (16.07%)	n = 94 (83.9%)	
Male gender	15 (83.3%)	72 (76.6%)	ns
Age (years)	47.1 ± 9.3	52.6 ± 10.9	< 0.05
DM	8 (44.4%)	31 (33.0%)	ns
Dyslipidemia	7 (38.9%)	21 (22.3%)	ns
HTN	9 (50%)	61 (64.9%)	ns
Smoking habits	3 (16.7%)	7 (7.4%)	ns
Rest heart rate (beats/min)	72.2 ± 13.2	69.9 ± 10.5	ns
ST segment/T wave changes	7 (38.9%)	21 (22.3%)	ns
Bundle branch block	2 (11.1%)	9 (9.6%)	ns
ECG suggestive of	2 (11.1%)	5 (5.3%)	ns
myocardial hypertrophy			
Baseline QRS width (ms)	112.6 ± 24.3	106.8 ± 23.5	ns
Previous angina	3 (16.7%)	9 (9.6%)	ns
Adenosine heart rate	87.3 ± 15.0	88.8 ± 14.3	ns
(beats/min)			
ST depression during	0 (0%)	3 (3.2%)	ns
adenosine			

 Table 9. Left ventricle mechanical dyssynchrony

$LVEF \leq 45\%$	47.6 ± 12.4	64.0 ± 12.2	< 0.0001
SSS	8,6 ± 10.1	1.5 ± 3.6	< 0.005
SRS	6.9 ± 9.6	0.8 ± 2.3	< 0.01
RS	1.7 ± 4.5	0.6 ± 1.8	ns

DM - Diabetes mellitus; HTN - Hypertension; ECG, Electrocardiogram. SSS, Summed stress score. SRS, Summed rest score. RS, Reversibility score.

With the logistic regression analysis, we found that the age, a LVEF \leq 45% and the scores obtained with SPECT-MPI, mainly SSS and SRS, were the univariate predictors of mechanical dyssynchrony (Table 10).

Table 11 shows the multivariate model for this group, which had the age, a LVEF \leq 45% and the SRS as independent variables, being the first one a protective factor of mechanical dyssynchrony (Odds ratio = 0.9, *P* < 0.05). It predicts correctly 89.0% of the cases, 97.8% of which were presented with a SD \geq 43° and 44.4 % with a SD < 43°.

	Odds ratio	95% CI odds ratio	P value
Age	0.9	0.9 - 1.0	< 0.05
$LVEF \leq 45\%$	0.9	0.9 - 1.0	< 0.0001
SSS	1.2	1.1 - 1.3	< 0.0005
SRS	1.2	1.1 - 1.4	< 0.001

 Table 10. Univariate predictors of left ventricle mechanical dyssynchrony

LVEF, left ventricular ejection fraction. SSS, Summed stress score. SRS, Summed rest score.

Table 11. Multivariate predictors of left ventricle mechanical dyssynchrony

Likelihood test: $\chi 2 = 35.3$; *P* value < 0.0001.

	Odds ratio	95% CI odds ratio	<i>P</i> value
Age	0.9	0.9 - 1.0	< 0.05
$LVEF \le 45\%$	0.9	0.9 - 1.3	< 0.005
SRS	1.2	1.0 - 1.4	< 0.05

LVEF, left ventricular ejection fraction. SSS, Summed stress score. SRS, Summed rest score.

DISCUSSION

This is a study that involves a group of consecutive patients with ESRD on dialysis referred to gated SPECT-MPI for risk stratification before renal transplantation. Our aim was to find a relationship between the prevalence of changes in the SPECT-MPI and cardiovascular risk factors, clinical manifestations of ischemia, electrocardiographic pattern, as well as heart rate response to adenosine in this group of patients.

The mean age of this group was 51.8 years, approximately 78% were male and 62.5% of the patients had HTN, being the prevalence of DM also considerable among them (34.8%). In summary, the present study relies on a heterogeneous population in what concerns to age, with the majority of patients under 60 years old (a minimum of 27 and a maximum of 76 years), already with a high prevalence of traditional cardiovascular risk factors, namely HTN, which can be explained as a cause or, more consistently, as a consequence of the severe renal dysfunction ^[32].

In previous studies, there is reference to variable and more often reduced sensitivities (37-90%) and specificities (40-90%) of SPECT-MPI in patients with ESRD ^[4]. There is no

definitive explanation to this fact, but it has been speculated that it could be related to the increased circulating levels of adenosine in some patients with CKD, a reduced coronary flow reserve or even the presence of left ventricular hypertrophy ^[16]. Moreover, we could not discard the possibility that diverse values are obtained with different protocols in the acquisition of the images with the gated SPECT-MPI. Attenuation correction seems to improve the specificity of the test according to Mathur et al. ^[33]. In this study, a low prevalence of perfusion abnormalities had been found (n = 25, 22.3%), which could always raise the question of sensitivity and the doubt related with a negative test ^[1, 4].

Univariate and multivariate logistic regression analysis were performed and we found that in these patients the independent predictors of myocardial perfusion defects were the QRS width (OR = 1.0, P value < 0.005) and the rest heart rate (OR = 1.1, P value < 0.05). Regarding the cardiovascular risk factors analyzed, although the sample of patients with an abnormal perfusion is reduced, the presence of DM is higher in this group (n = 11, 44%)comparatively to the patients with a normal perfusion (n = 28, 32.2%), even though it was not statistically significant. HTN appears with an identical prevalence in both groups with an abnormal and normal perfusion, consistent with the high prevalence in the overall population, being this factor, as mentioned, a possible cause or effect of the CKD ^[32]. An increased baseline heart rate is a well known marker of disease, particularly in situations of metabolic or hemodynamic stress ^[34, 35]. Therefore, it was expected to be more elevated in the patients with perfusion defects, with an almost significant statistical difference (P value < 0.06). Similar results were found comparing the presence of an ischemic ECG in these groups, being more prevalent in the group with an abnormal perfusion (P value < 0.06). The presence of variations in the baseline QRS width, mainly the presence of bundle branch block, was the characteristic that showed a more significant statistical difference between the groups with an abnormal and normal perfusion. In fact, perfusion defects are known to be a common cause of

changes in the cardiac electrical conduction. Nonetheless, the bundle branch block, namely the left bundle branch block, is frequently associated with anteroseptal perfusion defects that are not always an expression of CAD but have a definite prognostic value ^[36-38].

Concerning the LVEF, only 15 patients showed a LVEF $\leq 45\%$ (13.4%). However, in spite of the small sample, it was evident the higher prevalence of ECG changes in this group: ischemic pattern (P value < 0.05), variations in baseline QRS width and bundle branch block (P value < 0.05 and < 0.01, respectively) as well as evidence of myocardial hypertrophy (P value < 0.05). Univariate and multivariate logistic regression analysis were performed and it was found that regarding these variables the independent predictors of a LVEF $\leq 45\%$ were the QRS width (OR = 1.0, P value < 0.05) and an ECG suggestive of myocardial hypertrophy (OR = 8.2, P value < 0.05). The ECG alterations, particularly the increased duration of the QRS interval and the presence of a bundle branch block pattern, could lead to changes in the ventricular synchrony, causing a diminished LVEF ^[39]. On the other hand, an ischemic ECG could be associated to the presence of established ischemia, which is likewise a cause of contractility changes and reduced LVEF. The evidence of left ventricular hypertrophy, most likely related to volume overload in patients with advanced CKD, with an undoubtable relationship with HTN, could thus be a consequence of the disease or a preexisting condition ^[40, 41], and lead to ventricular dyssynchrony. A clinical history of previous angina was more prevalent in the patients with a LVEF $\leq 45\%$ and was an independent predictor of this feature (OR = 5.4, P value < 0.05) as a clinical manifestation of ischemia that could lead to an impaired left ventricle function. Its influence in ventricular function and not in perfusion abnormalities could make us suspect of false negative results of perfusion or even small vessels disease. As we expected, this group of patients revealed increased values on the SPECT-MPI scores (SSS and SRS) with a significant statistical difference in comparison to those with a normal left ventricle function.

The presence of mechanical ventricular dyssynchrony, defined as a SD \geq 43°, seemed to be influenced by an abnormal perfusion, with the SPECT-MPI scores increased in this group of individuals, with a significant statistical difference. This was also observed in several other studies ^[7, 30, 42-45]. The age was also an independent predictor of mechanical dyssynchrony (OR = 0.9, *P* value < 0.05). Surprisingly, it was more prevalent at a younger age. As expected, there was a clear relationship between mechanical dyssynchrony and a LVEF \leq 45% (OR = 0.9; *P* value < 0.0001). Furthermore, it is important to note that in this group of patients the presence of a mechanical ventricular dyssynchrony had no significant relationship with the baseline QRS width, although a wider QRS is seen in these individuals. As stated by previous studies, mechanical dyssynchrony could be identified in patients with a normal QRS width ^[43] and it is more prevalent in the presence of ESRD, even in the absence of electrical dyssynchrony and abnormal LV perfusion ^[42]. This higher prevalence happens in CKD patients already prior to dialysis treatment and is associated with left ventricle hypertrophy, left ventricular dysfunction and load conditions, which underlines the relevance of volume status for mechanical dyssynchrony in this group of patients ^[46-48].

This investigation was a single-center retrospective study that included only patients on the waiting list for kidney transplantation, with no reference to the time interval between the beginning of the CKD or the occurrence of the last session of hemodialysis and the performance of the exam. In addition, gated SPECT-MPI was not repeated unless clinically warranted, limiting our ability to follow the progression of the disease. Likewise, it was not possible to have access to the coronary angiography performed in the patients with positive results on the SPECT-MPI until the end of this study. Moreover, the observations could not be extended to the post-transplant period, since most of these patients are still waiting for surgery.

CONCLUSIONS

In this study it was found that an abnormal gated SPECT-MPI in ESRD patients, with perfusion defects, impaired LVEF and/or evidence of mechanical dyssynchrony were not associated with the presence of the most common risk factors for atherosclerotic disease (gender, age, DM, dyslipidemia, HTN and smoking habits).

A history of angina and an increased rest heart rate were higher in patients with perfusion defects, lower EF and mechanical dyssynchrony, although the rest heart rate was the only predictor of perfusion abnormalities and the history of angina predictor of a LVEF \leq 45%. The changes on the ECG pattern, namely the presence of variations in the baseline QRS width, including the bundle branch block, were associated with an abnormal perfusion. These variations along with the electrocardiographical evidence of myocardial hypertrophy were also predictors of an impaired left ventricle function. Mechanical dyssynchrony was associated to younger patients with a lower LVEF and higher perfusion scores.

To clarify the low prevalence of perfusion abnormalities and also some surprising findings, such as the influence of angina in ventricular function and not in perfusion abnormalities, further studies are necessary. In our point of view, it is essential to define a homogeneous protocol when evaluating patients with ESRD on the waiting list for transplantation.

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