Prognostic value of myocardial perfusion imaging and coronary artery calcium measurements in patients with end-stage renal disease

Abstract
Objective: Coronary artery disease (CAD) is highly prevalent in patients with end-stage renal disease (ESRD), owing to clustering of traditional and uremic-specific risk factors. However, in this population asymptomatic course of CAD is common and it has been reported that myocardial perfusion imaging (MPI) with single-photon emission tomography (SPET) has lower sensitivity. In the current study, we assessed the value of MPI gated-SPET and its combination with coronary artery calcium (CAC) score measurements in risk stratification of ESRD patients. Materials and Methods: MPI gated-SPET was performed with dual-headed SPET camera and CAC score measured by multi-detector computed tomography (MDCT) system. There were tested 77 ESRD individuals. During the follow-up study, cardiac events (CE) defined as cardiac death or nonfatal myocardial infarction (MI) or the necessity for coronary revascularization were recorded. Univariate and stepwise multivariable Cox proportional hazards-models were used to identify the predictors of CE. Results: Eighteen CE were recorded during the follow-up. They were significantly associated with higher summed stress scores on MPI, higher percentage of ischaemic myocardium, higher occurrence of defects in multiple territories and higher CAC score (all with P<0.05). Univariate Cox proportional hazard-models showed that severe perfusion abnormalities as well as CAC score >1000 were significantly associated with cardiac events (P<0.0001, P=0.0056). In stepwise Cox proportional hazards-models considering age, gender, history of diabetes mellitus, post-stress left ventricular stunning, the degree of perfusion abnormality and CAC score, only severe perfusion abnormalities and CAC score ≥1000 were independent predictors of CE. There was no CE in patients with normal perfusion, normal function and zero CAC score. Conclusion: This study suggests that combined evaluation of MPI and CAC can predict the outcome in ESRD individuals, while severe perfusion abnormality on gated-SPET and high CAC score ≥1000 are predictors of future cardiac events.

Introduction

End-stage renal disease (ESRD) is renal function impairment, where the level of glomerular filtration rate (GFR), signs and symptoms of kidney failure make hemodialysis, peritoneal dialysis or kidney transplantation necessary [1]. The main causes of morbidity and mortality in patients with ESRD are based on the clustering of the traditional coronary risk factors and also uremia-related risk factors, cardiovascular disease (CVD) and high prevalence of asymptomatic coronary artery disease (CAD) [2-4]. Many patients with ESRD and myocardial infarction (MI) may not have typical symptoms and/or ECG changes. On the other hand chest pain with unobstructed coronaries was described in ESRD patients. One of the reasons for this discrepancy is dysfunction of autonomic nervous system [5-7]. For all ESRD patients at the initiation of dialysis the importance of cardiac risk screening is emphasized by the outcome of kidney diseases and the quality initiative (KDOQI) guidelines [8].

In patients with renal function impairment, such as in ESRD, the risk of CAD increases with decreasing GFR [2, 5, 9, 10]. A validated CAD risk prediction tool, Framingham risk score, does not include renal function, thus predictive accuracy in patients with ESRD can be underestimated [4]. One of the non-invasive methods suitable for CAD risk stratification is myocardial perfusion imaging (MPI) by single-photon emission tomography (SPET) combined with ECG gating. It assesses perfusion, function and myocardial viability of the left ventricle (LV). However, lower sensitivity of the test has been reported in patients with ESRD [11-15].

Keywords: Myocardial perfusion imaging
- Coronary artery calcium scoring
- Prognosis - Myocardial ischemia
- End stage renal disease

Correspondence address:
Martin Havel, MD,
Department of Nuclear Medicine, Faculty of Medicine and Dentistry, Palacky University Olomouc and University Hospital Olomouc, Czech Republic
havel.martin@gmail.com

Received:
11 August 2015
Accepted revised:
21 October 2015
The measurement of coronary artery calcium (CAC) by ECG-gated multi-detector computed tomography (MDCT) brings incremental value in patients with false-negative gated-SPET study [16]. The CAC score showed an impact on the interpretation of MPI examinations. [17]. In the current study, we assess the value of MPI gated-SPET and in combination with the CAC score in the risk stratification of ESRD patients.

Patients and Methods

Study population
The study group consisted of 77 prospectively examined ESRD individuals, who underwent cardiac gated-SPET imaging. They were: mean age 59.5±11.0 years, 53 men (68.8%, mean age 57.1±10.8) and 24 women (31.2%, mean age 64.9±9.7). Diabetes mellitus (DM) was present in 35 patients, there was a history of previous MI in 6 patients. All underwent gated SPET MPI and CAC score measurements.

Stress and rest testing
Patients were examined according to one day or to two days stress-rest protocol. The selection of the protocol depended mostly on the distance of the patients’ residence from the laboratory. The stress test was exercise on a bicycle ergometer in the sitting position. Exercise was conducted up to 85% of the age-predicted maximal heart rate or until the onset of angina pectoris, dyspnoea, fatigue, dizziness, frequent (more than 10 per min) multifocal or paired ventricular extrasystoles, ST segment depression (more than 0.2mV) or when a blood pressure decreased below the previous stage value by more than 10mmHg.

If the subject did not fulfil the criteria for adequate exercise stressing or was unable to exercise at all, dipyridamole infusion for 4min at a standard dose of 0.56mg per kg of body weight in 14 patients, or 0.4mg of regadenoson injection in 2 patients, combined with low level of exercise, was performed. Patients with left bundle branch block were stressed by dipyridamole alone to avoid tachycardia and to reduce the possibility of septal artefacts [18]. One patient was examined after dobutamine stress. If the stress study was completely normal in terms of perfusion and function of the left ventricle, as was the case in 3 patients, the rest study was waived.

The radiopharmaceuticals were: technetium-99m (Tc) labelled to methoxy-isobutylisonitril (MIBI) or to tetrofosmin. The administered activity of the radiotracer calculated according to the reference man (adult of 70kg) was basically 300MBq for the stress study, and 750MBq for the rest study in a one-day protocol or 300MBq for each rest and stress study in a two-day protocol and adjusted accordingly.

Gated-SPET acquisition and processing
We used a dual-headed SPET gamma camera system (e.cam, Siemens, Germany) equipped with low-energy high-resolution collimators in L-mode configuration (90° angle among two detector heads). Images were gated at 8 frames per cardiac cycle. Additional prone position imaging was used in case of inferior wall defect in order to identify the possibility of attenuation artefact [18]. No other attenuation correction was applied. Acquired studies were processed and automatically evaluated in a 4-DM software application (INVIA, Ann Arbor, Michigan, USA), to calculate the following factors: summed stress score (SSS), summed difference score (SDS), SDS converted to percentage of ischaemic myocardium, stress and rest LV volumes, LV ejection fraction (LVEF), and transient ischaemic dilatation (TID).

The severity of perfusion deficit on SPET was stratified into three groups: a) Normal perfusion: no perfusion defect, b) mild perfusion abnormality: <10% ischaemic myocardium in one coronary territory and c) severe perfusion abnormality: >10% ischaemic myocardium and/or defects in multiple coronary territories. Post stress left ventricular stunning was defined as worsening of LVEF >5% or as transient ischaemic dilatation (TID) ratio >1.17.

CAC scoring
The evaluation of CAC score followed the MPI SPET examination and was estimated by a PET/CT scanner (Biograph 16, Siemens, Germany) using standard software based on Agatson method (with a cut-off >130 Hounsfield units). A CAC score of >1000 was defined as extensive calcification with high risk of future cardiac events [19].

Follow-up
The CE were recorded during a median follow-up period of 26.4 months. As CE were defined: cardiac death, nonfatal MI and/or the necessity of coronary revascularization. Patients were categorised into two groups: having CE and not having CE.

Statistical analysis
Continuous variables were expressed as mean±standard deviation and categorical variables were summarized by count and percentages. The CAC was assessed as a continuous variable and as a dichotomous variable (CAC scores <1000 and CAC scores ≥1000). Perfusion abnormality was assessed as categorical variable (normal, mild abnormal and severe abnormal). Categorical variables were compared using Fisher exact test. Continuous and ordinal variables were compared using Mann-Whitney U test. Univariate Cox proportional hazards-models were utilized to determine whether evaluated variables predicted cardiac event. Stepwise multivariable Cox proportional hazards models were used to identify independent predictors of CE. Hazard ratio (HR) and corresponding 95% confidence interval (CI 95%) were calculated. Kaplan-Meier analysis with survival curves plots were processed for the effect of CAC score and perfusion abnormalities on survival time to cardiovascular event; data were evaluated using a Long-Rank test. The level of significance was set for all tests at P<0.05 (two tailed). Statistical analysis was done using SPSS for windows, version 23.0 (IBM corp., Armonk, NY, USA).
During the follow-up we registered 18 patients with CE: 6 cardiac deaths, 4MI and 8 revascularizations. There were not significant differences in age, gender, history DM or prevalence of previous MI between the CE+ and the CE- group. Based on perfusion SPET examination we found in the CE+ group significant higher SSS (mean value 7.7±7.4 vs. 1.8±3.0, P<0.0001), percentage of ischaemic myocardium (mean value 6.1%±7.3% vs. 1.3%±2.5%, P =0.0004), higher prevalence of defects in multiple territories (44.4% vs. 1.7%, P<0.0001). CAC scores were also significantly higher in the CE+ group (mean value 1607.2±1640.3 vs. 666.6±1139.9, P=0.0045). Functional parameters as stress LVEF, EDV, ESV as well as TID ratio did not show significant differences between the two groups. The baseline characteristics of individuals with and without CE are summarized in Table 1.

Concerning the severity of perfusion deficit, in the CE+ group there was normal perfusion pattern reported in 4/18 of the patients, mild perfusion abnormality in 5/18 and severe perfusion abnormality in 9/18 of examined individuals. In the CE- group these proportions were significantly different: 41/59, 16/59 and 2/59, P<0.0001. Severe perfusion abnormality was more frequent in the CE+ group (Graph 1).

Graph 1: Bar graph expressing different proportions of SPECT perfusion abnormalities (in %) in patients with and without cardiac events. Normal-normal perfusion, Mild-<10% of ischaemic myocardium in one coronary territory, Severe - >10% ischaemic myocardium and/or defects in multiple coronary territories. Proportions between the two groups are significantly different (P<0.0001).

The CAC score ≥1000 was more prevalent in patients with CE 9/18, than in those without CE 12/59, P=0.0311, Table 1 and Graph 2). There were 4 of 45 patients with normal perfusion who encountered CE three of them had CAC score values ≥1000. Zero calcium score was identified in 8 subjects, none of them encountered CE.

In Kaplan-Meier analysis, severe abnormal perfusion and an elevated CAC score ≥1000 were both associated with the occurrence of CE during the follow-up (P<0.0001 and P=0.0026, Graph 3 and Graph 4). In the cohort of patients with normal perfusion SPET, there was also noticeable trend for association of cardiac event with CAC score ≥1000 (P=0.0315, Graph 5), however the number of considered subjects was low.

Univariate Cox proportional hazard models found severe perfusion abnormality, with HR 15.06 (CI 95% 4.58-49.48), as well as CAC score ≥1000, with HR 3.94 (CI 95% 1.49-10.38) significantly associated with cardiac events (P<0.0001, P=0.0056).

Graph 2: Bar graph expressing different distribution of CAC score <1000 and CAC score ≥1000 (in %) in patients with and without cardiac events. Proportions between the two groups are significantly different (P=0.0311).

Graph 3: Kaplan-Meier curves: Patients with normal perfusion (45, 4 with CE), mild perfusion abnormality (21, 5 with CE) and severe perfusion abnormality (11, 9 with CE). Subjects with severe perfusion abnormality have significantly poorer outcome (P < 0.0001).

Age, gender, history of DM, post-stress LV stunning and the degree of perfusion abnormality were considered in stepwise Cox proportional hazards models. In this setting, only severe perfusion abnormality, with HR 13.94 (CI 95% 4.25-45.78, P<0.0001), was independent predictor of CE. After adding the CAC score as a stratified variable into the model, severe perfusion abnormality with HR 30.39 (CI 95% 7.86-117.49, P<0.0001) and CAC score ≥1000 with HR 9.29 (CI 95% 3.00-28.73, P=0.0001) were both independent predictors of CE.
Table 1. Baseline clinical characteristics of patients with and without cardiac events. Values given as M±SD or counts/global and percentage.

<table>
<thead>
<tr>
<th></th>
<th>Global n = 77</th>
<th>Cardiac events n = 18</th>
<th>No cardiac event n = 59</th>
<th>P value</th>
<th>OR</th>
<th>OR CI (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>59.5 ± 11.0</td>
<td>62.1 ± 13.4</td>
<td>58.7 ± 10.1</td>
<td>0.3995</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Male sex</td>
<td>53 (68.8%)</td>
<td>14 (77.8%)</td>
<td>39 (66.1%)</td>
<td>0.4003</td>
<td>1.79</td>
<td>0.52-6.17</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>35 (45.5%)</td>
<td>9 (50.0%)</td>
<td>26 (44.1%)</td>
<td>0.7882</td>
<td>1.27</td>
<td>0.44-3.65</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>6 (7.8%)</td>
<td>3 (16.7%)</td>
<td>3 (5.1%)</td>
<td>0.1362</td>
<td>3.73</td>
<td>0.68-20.41</td>
</tr>
<tr>
<td>Summed stress score</td>
<td>3.2 ± 5.0</td>
<td>7.7 ± 7.4</td>
<td>1.8 ± 3.0</td>
<td>&lt;0.0001*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Percentage of ischaemic myocardium</td>
<td>2.4 ± 4.6</td>
<td>6.1 ± 7.3</td>
<td>1.3 ± 2.5</td>
<td>0.0004*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Perfusion defect in multiple territories</td>
<td>9 (11.7%)</td>
<td>8 (44.4%)</td>
<td>1 (1.7%)</td>
<td>&lt;0.0001*</td>
<td>46.40</td>
<td>5.22-412.33</td>
</tr>
<tr>
<td>Stress LVEF (%)</td>
<td>57.0 ± 12.3</td>
<td>54.8 ± 12.0</td>
<td>57.7 ± 12.4</td>
<td>0.4062</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Stress EDV (mL)</td>
<td>145.9 ± 65.7</td>
<td>151.9 ± 69.2</td>
<td>144.0 ± 65.1</td>
<td>0.6868</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Stress ESV (mL)</td>
<td>68.4 ± 47.3</td>
<td>74.1 ± 49.8</td>
<td>66.7 ± 46.9</td>
<td>0.5964</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rest LVEF (%)</td>
<td>56.1 ± 12.0</td>
<td>54.8 ± 12.3</td>
<td>56.4 ± 12.0</td>
<td>0.5123</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Post-stress LV stunning</td>
<td>18 / 74 (24.3%)</td>
<td>4 (22.2%)</td>
<td>14 / 56 (25.0%)</td>
<td>1.0000</td>
<td>0.86</td>
<td>0.24-3.04</td>
</tr>
<tr>
<td>TID ratio</td>
<td>0.97 ±0.15</td>
<td>1.00 ± 0.13</td>
<td>0.97 ± 0.15</td>
<td>0.5285</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CAC score</td>
<td>886.4 ± 1324.4</td>
<td>1607.2 ± 1640.3</td>
<td>666.6 ± 1139.9</td>
<td>0.0045*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CAC score &gt;1000</td>
<td>21 (27.3%)</td>
<td>9 (50.0%)</td>
<td>12 (20.3%)</td>
<td>0.0311*</td>
<td>3.92</td>
<td>1.28-12.01</td>
</tr>
</tbody>
</table>

LVEF: left ventricular ejection fraction; EDV: end-diastolic volume; ESV: end-systolic volume; TID: transient ischaemic dilatation; CAC score: coronary artery calcium score; OR: odds ratio; OR CI (95%): odds ratio 95% confidence interval, *: significant P.
Graph 4: Kaplan-Meier survival curves. Patients with CAC score $\geq 1000$ (21, 9 with CE) and CAC score $< 1000$ (56, 9 with CE). Subjects with CAC scores $\geq 1000$ have significantly poorer outcome ($P=0.0026$).

Graph 5: Kaplan-Meier survival curves in subgroup of patients with normal perfusion SPECT. CAC score $\geq 1000$ (14 patients, 3 with CE) and CAC score $< 1000$ (31 patients, 1 with CE). Individuals with CAC scores $\geq 1000$ have significantly poorer outcome ($P=0.0315$).

**Table 2:** Unadjusted HR with 95% CI. Significant association with cardiac event was found for severe perfusion abnormality and CAC score $\geq 1000$.

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$P$ value</td>
<td>HR</td>
<td>HR CI</td>
</tr>
<tr>
<td>Age</td>
<td>0.1472</td>
<td>1.03</td>
<td>0.99-1.08</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.2920</td>
<td>1.82</td>
<td>0.60-5.53</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.8476</td>
<td>1.10</td>
<td>0.43-2.76</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>0.1816</td>
<td>2.34</td>
<td>0.67-8.15</td>
</tr>
<tr>
<td>Post-stress LV stunning</td>
<td>0.8975</td>
<td>0.93</td>
<td>0.31-2.83</td>
</tr>
<tr>
<td>Mild perfusion abnormality</td>
<td>0.1281</td>
<td>2.78</td>
<td>0.75-10.35</td>
</tr>
<tr>
<td>Severe perfusion abnormality</td>
<td>$&lt;0.0001^*$</td>
<td>15.06</td>
<td>4.58-49.48</td>
</tr>
<tr>
<td>CAC score $\geq 1000$</td>
<td>$0.0056^*$</td>
<td>3.94</td>
<td>1.49-10.38</td>
</tr>
</tbody>
</table>

$^*$ - significant $P$

**Discussion**

Patients with ESRD are a high-risk group for CAD, but they often do not have a typical presentation of myocardial ischemia.

Atherosclerosis (AS) is enhanced in ESRD patients [4]. Etiology of AS on the background of impaired renal function is more complex. Instead of traditional risk factors for AS as older age, male gender, hypertension, DM, dyslipidaemia, cigarette-smoking, physical inactivity and a family history of premature cardiovascular disease, there are also specific fac-
tors as hyperhomocysteinaemia, increased oxidative stress, endothelial cell dysfunction, inflammation, activation of the renin–angiotensin–aldosterone system and sympathetic nervous system, anaemia and abnormal calcium and phosphate metabolism [20-21]. Screening for CAD in patients with ESRD before renal transplantation does not assess only perioperative cardiovascular risk, but it can also stratify such a risk in the early years after transplantation [11].

Previous studies described high prevalence of perfusion defects in ESRD patients, of which occurrence is a predictor of cardiac outcomes [4, 22-25]. However, lower sensitivity of MPI SPET in these patients has been reported [11-15]. In our study, severe myocardial perfusion abnormality was significantly associated with a greater risk of CE. Semiquantitative SSS were significantly higher in individuals with recorded CE. On the other hand, there were no significant differences when comparing functional parameters as stress LVEF values and LV volumes. We also did not find post-stress stunning of LV as a significant marker for future CE in study population. These functional evaluation outcomes correlate well with reported lower sensitivity of dobutamine stress echocardiography (DSE) in patients with ESRD, which can be explained by the remodelling of the LV and the inability of these patients to achieve the maximum heart-rate responses during the stress test [11]. In contrast, Bergeron et al. (2007) found the percentage of ischemic segments during DSE as an independent predictor of mortality in individuals with chronic kidney disease (CKD), similarly Rakhit et al. (2006) described the high-risk finding from the DSE as an outcome predictor in CKD patients [26, 27].

DM is one of the traditional CAD risk-factors, more prevalent in patients with ESRD, who are particularly prone to asymptomatic ischemic heart disease due to visceral neuropathy [2, 4, 20]. In our followed-up population, DM was present in 45.5% of patients. Surprisingly, we did not find significant correlation between this potential AS risk factor and CE during the study. Coronary artery calcification is absent in healthy vessel wall, conversely calcification finding denotes presence of AS. Vascular calcification is enhanced in the condition of ESRD, while there are two types of arterial calcification. First type occurs in the media of the vessel wall, where it is not associated with lipid-laden macrophages and intimal hyperplasia, and the second type in the intima, where it is regularly associated with AS [28, 29].

CAC quantification was first described by Agatston et al. (1990) [30] by electron beam CT (EBCT). Consequently, MDCT showed results well correlated with EBCT [31, 32]. Previous studies from other researchers stated CAC in the population with ESRD as a predictor of future cardiac events [33-37]. As in our study population, CE were significantly associated with higher CAC scores. The distribution of the values varied among the individuals studied (minimum 0, maximum 7298, mean 886.4±1324.4). We stratified the patients into two subgroups with discriminating CAC score at the level of 1000, for predicted higher clinical risk in values over this cut-point [19, 38]. Such CAC scores greater than 1000 were more prevalent in patients with recorded CE and were identified, as a severe perfusion abnormality, as an independent predictor of future CE with substantially high risk ratios. Moreover, CAC scores >1000 were found in 3 of 4 patients with normal perfusion and encountered CE, this can make pronounced CAC an additional indicator for poor outcome. We consider that there were no CE in patients with normal myocardial perfusion, normal function and zero CAC score. (Figure 1 and 2).

Figure 1: A 77-years old diabetic female with end-stage renal disease underwent stress gated SPECT with a normal perfusion (A) and left ventricular function (B). We observed diffused calcifications in coronary arteries and calcium score was a highly elevated at 3784. Despite of severe three-vessel disease on invasive angiography, she was treated by medicaments only. She died due to the myocardial infarction 16 months later.

Figure 2: A 57-years old diabetic male with end-stage renal disease underwent stress gated SPECT imaging before kidney transplant. There was normal perfusion (A), normal left ventricular function at stress and rest (B), and no calcification in the coronary arteries with a zero calcium ©

Limitations of our study were the relatively low number of examined subjects and the rather short length of the follow-up period. Consequent MDCT examination brings additional radiation burden to the patient. However some researchers described only very low radiation load when utilizing modern dual-source CT system for CAC with an effective dose reduced to 0.3mSv [39].

An interesting detecting and quantifying AS inflammation in the context of cardiovascular risk, by 18-fluorodeoxyglucose (18F-FDG) positron emission tomography was described recently, whereas 18F-FDG uptake was a marker of potential plaque instability [40]. The possibility to combine information about the inflammation activity and plaque instability with CAC state obtained from single examination is challenging for future studies. Concerning the degree of calcification, it is somewhat controversial if calcification should represent a process which can result to the stabilization of an atherosclerotic plaque. This factor can lead to un-
certainty if CAC is related to the pathogenesis of CAD in a favourable or unfavourable way [41]. Our recent results, (although in a limited number of patients) however, suggest the latter option.

In conclusion, our study suggested that severe perfusion abnormalities on gated-SPECT and high CAC score > 1000 are predictors of future cardiac event in ESRD patients. Identification of pronounced CAC can bring an additional value for future CE prediction in subjects with false-negative MPI SPECT studies. Conversely, normal perfusion and zero CAC score predict favourable outcome.

Acknowledgment
This study was supported by European Regional Development Fund - Project FNUSA-ICRC (No. CZ.1.05/1.1.00 /02.0123). The authors would like to thank Mrs. Katerina Langova for consultation of statistical evaluation.

The authors declare that they have no conflicts of interest

Bibliography


