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ORIGINAL ARTICLE

Prognostic utility of negative stress/rest myocardial SPECT studies among patients with different clinical categories of chronic kidney disease: Data from an Egyptian cohort

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Abstract Prognostic value of negative myocardial SPECT study is well established. However, patients with chronic kidney disease (CKD) are a special group showing increased risk of cardiac events. We thought to investigate the prognostic value of negative SPECT study among patients on regular hemodialysis compared to other clinical categories of CKD.

Methods: 186 consecutive patients with CKD and negative SPECT study were enrolled. 93 (50%) were on hemodialysis with an eGFR < 30 mL/min/1.73 m^2 (Group I); 25 (13.4%) had uncomplicated renal transplantation with eGFR between 45 and 90 mL/min/1.73 m^2 (Group II) and 68 (36.6%) with CKD on conservative management and no prior history of hemodialysis (eGFR between 30 and 60 mL/min/1.73 m^2), Group (III). End points (CD, STEMI/NSTEMI, need for revascularization and hospitalized HF) were traced at 6 months, one year and 2 years.

Results: Total events in all groups were 5 (2.70%) at 6 months, and 18 (9.70%) and 36 (19.30%) at one year and 2 years respectively. At one year 16 (17.20%) cardiac events happened in Group I compared to one (4.0%) and one (1.50%) event(s) in Groups II and III respectively (p values 0.001). At 2 years, 29 (31.20%) cardiac events happened in Group I while 2 (8.0%) and 5 (7.30%) happened in Groups II and III respectively (p values 0.01, 0.001 respectively). eGFR and duration of hemodialysis were the independent predictors of cardiac events.

Abbreviations: BMI, Body mass index; CD, cardiac death; CKD, chronic kidney disease; EF%, ejection fraction; eGFR, estimated glomerular filtration rate; HF, heart failure; LHR, lung heart ratio; LV, left ventricle; LVED volume, LV end-diastolic volume; LVES volume, LV end-systolic volume; LVH, left ventricular hypertrophy; METs, metabolic equivalents; MI, myocardial infarction; MPI, myocardial perfusion imaging; NPV, negative predictive value; NSTEMI, non-ST elevation myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass surgery; SD, standard deviation; SPECT, single photon emission computed tomography; SSS, summed stress score; SRS, summed rest score; SDS, summed difference score; STEMI, ST elevation myocardial infarction

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Conclusion: Despite negative MPI study, patients on hemodialysis showed higher event (including CD, STEMI/NSTEMI and revascularization) rate at one and 2 years of follow-up compared to other clinical categories of CKD.

1. Introduction

Negative predictive value (NPV) of SPECT scans for detection of myocardial infarction (MI) and cardiac death (CD) was shown to be in the neighborhood of 98.8% (95% confidence interval [CI] 98.5–99.0) during 36 months of follow-up.[1] Patients with chronic kidney disease (CKD) are at increased risk of early and progressive coronary artery disease (CAD).[2] Data coming from Egyptian centers discussing value of SPECT in patients with CKD are lacking. Hence, we thought to evaluate the prognostic value of negative SPECT studies among Egyptian patients on regular hemodialysis compared to other clinical categories of CKD.

2. Methods

2.1. Study cohort

The study cohort consisted of 193 consecutive patients referred for ^{99m}Tc sestamibi gated SPECT study at Al-Azhar school of medicine (Cairo, Egypt), and Alfa scan center (Heliopolis, Cairo, Egypt) nuclear cardiac laboratories between September 2011 and May 2013. Seven patients were excluded due to non-cardiac deaths during the follow-up period. All enrolled patients had a documented CKD. The study population was divided into 3 groups according to the main treatment received for CKD. *Group* (I), 93 patients (50%) were on regular hemodialysis with an eGFR < 30 mL/min/1.73 m^2. *Group* (II), 25 patients (13.4%) had uncomplicated renal transplantation surgery after variable period of hemodialysis with eGFR values between 45 and 90 mL/min/1.73 m^2. *Group* (III), 68 patients (36.6%) had CKD (eGFR between 30 and 60 mL/min/1.73 m^2) on conservative medical management of CKD and no prior history of hemodialysis. Mean period of hemodialysis among Group I was 3 ± 2.2 years while mean period of hemodialysis among Group II before renal transplantation surgery was 2.5 ± 1.9 years.

All patients enrolled on this study had a negative myocardial SPECT study. All patients with quantitatively and qualitatively normal myocardial perfusion on SPECT, who showed any other high risk non-perfusion abnormalities (e.g. namely stress induced LV cavity dilatation and stress induced myocardial stunning), were excluded for sake of reproducibility. All patients with advanced comorbidities (e.g. cancer, advanced liver failure) were also excluded. Patients post-renal transplantation with rejection (acute, subacute or chronic) who are currently on regular dialysis were excluded for sake of reproducibility. Patients with echocardiographic data of significant valvular heart disease, pericardial disease or LV systolic dysfunction (EF% $< 50\%$) were also excluded.

2.2. Stress protocol

A total of 109 (58.6%) patients underwent treadmill exercise stress according to the standard *Bruce* protocol. 77 (41.4%) had pharmacologic stress using *Dipyridamole* according to the standard infusion protocol.[7,8] Stress testing was symptom-limited. Premature termination of the stress test was done according to the recommendations in the updated guidelines of exercise testing.[7,8]

2.3. Myocardial perfusion imaging

All subjects underwent a gated-SPECT MPI according to a two-day protocol. Supine images were acquired with a dual-head (Philips JetStream or Siemens WorkSpace cameras) with low-energy, high-resolution collimators. All radionuclide images and associated data were processed according to the standard protocols. ^{99m}Tc sestamibi was used in all patients (the routine tracer used in our laboratories). Myocardial perfusion was calculated as a relative percent of tracer uptake in the standard model "17 segment model".[8]

Experienced nuclear cardiology specialists used these data on a *semi-quantitative* approach to interpret each MPI study. Readers assigned a score (0–4) to each segment: (0) for normal uptake; (1, 2 and 3) for mild, moderate and severe reduction of uptake respectively; and (4) for absent uptake. Sum stress score (SSS), sum rest score (SRS) and sum difference score (SDS) were reported. Other markers of high risk perfusion scans were reported separately (e.g. increased LHR, Transient LV cavity dilatation, abnormal regional and global wall motion abnormalities). Negative SPECT study was defined as SSS < 4 and SDS $= 0$.

2.4. Follow-up data

6 months, one year and 2 years follow-up data were collected through telephone calls and hospital records. End points were cardiac death, STEMI/NSTEMI, the need for revascularization procedure and documented HF.

2.5. Statistical analysis

Continuous variables were expressed as mean and SD, and categorical variables were expressed as percentages. Student's *t*-tests were used to compare the groups in view of different clinical and MPI data. The primary end point was the occurrence of cardiac events, defined as cardiac death, nonfatal MI, need for revascularization procedure and documented HF. Cox regression hazard analysis was used to assess the impact of different demographic and clinical data. p value of less than 0.05 was considered significant. Statistical analysis

was performed with free and commercially available Software; JMP4.0 (SAS Institute Inc.); SPSS 16.0 (SPSS Inc).

3. Results

Demographic characteristics of the study cohort are presented in Table 1.

All myocardial SPECT studies were reported as negative for evidence of myocardial ischemia (mean SSS, SRS and SDS were 2 ± 1, 1 ± 1 and 0 for the three groups). As shown in Table 1 differences between different groups as regards LVES and LVED volumes and EF% were very insignificant. Primary end points (cardiac death and STEMI/NSTEMI, need for revascularization and documented HF) were traced at 6 months, one year and two years of follow-up (see Tables 2–4).

At 6 months follow-up; 5 (2.70%) total cardiac events happened: one (0.50%) STEMI/NSTEMI, 4 (2.40%) HF necessitating hospitalization. No cardiac deaths happened at 6 months of follow-up.

Group I showed one (1.10%) STEMI/NSTEMI and 2 (2.15%) HF necessitating hospitalization. *Groups* II and III showed one HF event (4%) and (1.47%) respectively,

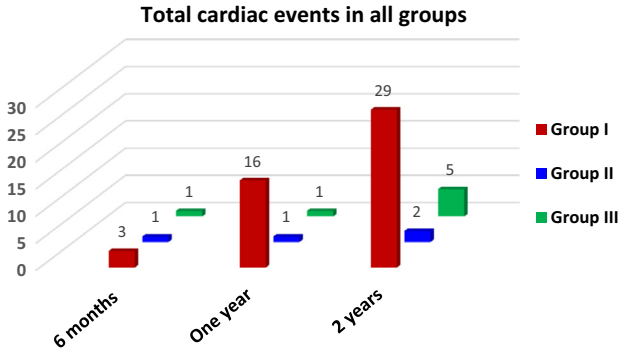

Figure 1 Cardiac events during the follow-up period among study groups.

Table 1 Demographic and clinical characteristics of the study cohort.

Total number of study population	186 patients
Mean age	56 ± 11 years
Male sex	113 (61.0%)
DM	136 (73.0%)
HTN	158 (85.0%)
Dyslipidemia	109 (59.0%)
BMI (kg/m^2) 20–25	119 (64.0%)
BMI (kg/m^2) 25–35	51 (27.0%)
BMI (kg/m^2) > 35	16 (9.0%)
Abnormal baseline ECG	165 (89.0%)
Mean exercise duration (mins)	6.5 ± 2.9
Mean workload (METs)	7.9 ± 1.2
Cause of termination	
• Leg fatigue	47 (25.0%)
• Significant SOB	46 (25.0%)
• Significant chest pain	16 (9.0%)
• Injection of pharmacologic agent	77 (41.0%)
LVH (IVS > 1.5 mm)	56 (30.0%)
LVH (IVS 1.3–1.5 mm)	101 (54.0%)
LVH (IVS < 1.3 mm)	29 (16.0%)

(p value = 0.57). No STEMI/NSTEMI events occurred among Groups II and III at 6 months of follow-up. A negative myocardial SPECT study showed an excellent predictive value for cardiac events among all patients with CKD at 6 months of follow-up.

At one year of follow-up; 18 (9.70%) total cardiac events happened (5 STEMI/NSTEMI, 12 HF necessitating hospitalization and one revascularization event). Group I showed 2 (5.40%) STEMI/NSTEMI, 10 (10.70%) HF necessitating hospitalization and one (1.10%) revascularization event. Groups II and III showed one HF event (4.0%) and (1.50%) respectively.

Patients on regular hemodialysis showed a higher rate of STEMI/NSTEMI compared to the other 2 groups at one year of follow-up. Differences were of borderline statistical significance (p value = 0.06). HF requiring hospitalization was statistically higher among patients on regular hemodialysis compared to the other 2 groups (p value <0.01 and 0.0001 respectively). No cardiac deaths occurred among the study population at one year of follow-up.

Figure 1 shows the total cardiac events among study groups at 6 months, one year and two years of follow up.

At two years of follow-up; 36 (19.3%) total cardiac events happened (2 cardiac deaths, 11 STEMI/NSTEMI, 18 HF necessitating hospitalization, 5 revascularization events). Group I showed 2 (2.15%) cardiac deaths, 9 (9.7%) STEMI/NSTEMI, 14 (15.0%) HF necessitating hospitalization and 4 (4.3%) revascularization events. Group II showed one (4.0%) STEMI/NSTEMI and one (4.0%) HF event. Group III showed one (1.50%) STEMI/NSTEMI, 3 (4.50%) HF and one (1.50%) revascularization events. Patients on regular hemodialysis had a higher statistically significant cardiac event rates compared to the other 2 groups at 2 years of follow-up (p values <0.01 and <0.0001 respectively).

Univariate cox regression analysis showed that eGFR and duration of hemodialysis are the only predictors of cardiac events among the studied cohort. This study cohort is a relatively low risk cohort owing to the fact that all patients included in this study had negative MPI results, normal LV dimensions and LVEF%.

4. Discussion

MPI study is a well-established prognostic tool for effective cardiovascular risk stratification among the general population. Renal dysfunction is also an important independent predictor of cardiac death among patients with significant ischemia burden (moderate to large perfusion defects on MPI studies). Annualized hard cardiac event rate among patients with normal MPI studies is in the range of 0.2–0.8%. However, most MPI prognostic studies and large clinical trials have not included kidney function in their analyses.[3–6] Hence, we thought to investigate the cardiac event rate among an Egyptian cohort with CKD in different stages of the disease according to eGFR.

Our results point to a statistically significant difference in cardiac events including non-fatal MI and need for revascularization procedures at one and 2 years of follow-up after a negative MPI study among hemodialysis patients compared to other clinical categories of CKD. It also confirmed that eGFR value and duration of CKD were the independent predictors of

Table 2 Demographic and clinical characteristics of the study groups.

	Group I = hemodialysis	Group II = post renal transplant	Group III = CRI	*p* value
Number	93 (50%)	25 (13.4%)	68 (36.6%)	
Mean age (years)	55 ± 9	54 ± 7	55 ± 6	
Male sex	59 (63.0%)	15 (60.0%)	39 (57.0%)	
DM	67 (72.0%)	18 (72.0%)	51 (75.0%)	$p = 0.59$
HTN	79 (85.0%)	21 (84.0%)	58 (85.0%)	$p = 0.66$
Dyslipidemia	55 (60.0%)	14 (52.0%)	40 (58.0%)	$p = 0.57$
Period of hemodialysis (years)	3 ± 2.2	2.5 ± 1.9	–	
BMI (kg/m^2) 20–25	59 (64.0%)	16 (64.0%)	44 (65.0%)	$p = 0.81$
BMI (kg/m^2) 25–35	27 (29.0%)	7 (28.0%)	17 (25.0%)	$p = 0.67$
BMI (kg/m^2) > 35	7 (7.5%)	2 (8.0%)	7 (10.0%)	$p = 0.88$
Abn. baseline ECG	81 (87.0%)	22 (88.0%)	62 (91.0%)	$p = 0.94$
Mean Ex. Time (mins)	6.5 ± 1.2	7.1 ± 1	6.9 ± 1.3	$p = 0.63$
Mean workload (METs)	8 ± 1	9 ± 1	9 ± 1	$p = 0.54$
Cause of termination				
• Leg fatigue	31 (33.0%)	9 (36.0%)	7 (10.0%)	
• Significant SOB	27 (29.0%)	6 (24.0%)	13 (19.0%)	
• Chest pain	8 (8.60%)	2 (8.0%)	6 (8.80%)	
• Injection of pharmacologic agent	27 (29.0%)	8 (32.0%)	42 (61.0%)	

Table 3 Cardiac events during the follow-up period in different groups.

	Group I	Group II	Group III	
6 months follow-up data				
• Cardiac death	0	0	0	
• STEMI/NSTEMI	1 (1.0%)	0	0	*p* value = 0.83
• HF	2(2.0%)	1 (4.0%)	1 (1.50%)	*p* value = 0.59
• PCI/CABG	0	0	0	
• PCI/CABG	0	0	0	
1 year follow-up data				
• Cardiac death	0	0	0	
• STEMI/NSTEMI	5 (5.40%)	0	0	
• HF	10 (10.70%)	1 (4.0%)	1 (1.50%)	*p* value = 0.017
• PCI/CABG	1 (1.0%)	0	0	
2 years follow-up				
• Death	2 (2.20%)	0	0	*p* value = 0.002
• STEMI/NSTEMI	9 (9.70%)	1 (4.0%)	1 (1.50%)	*p* value = 0.05
• HF	14 (15.0%)	1 (4.0%)	3 (4.50%)	*p* value = 0.001
• PCI/CABG	4 (4.30%)	0	1 (1.50%)	*p* value = 0.015

Table 4 Univariate cox regression analysis of different demographic and clinical data affecting outcomes.

Variable	Hazard ratio	CI (95%)	*p* value
Mean age	1.29	0.33–2.21	0.69
Male sex	0.77	0.99–1.77	0.77
DM	3.99	0.9–11.2	0.45
BMI (kg/m^2) > 30	2.8	1.54–7.55	0.66
HTN	3.47	1.05–9.98	0.89
eGFR (mL/min/1.73 m^2) < 30	0.91	0.9–0.99	0.0004
Mean duration of HD (years) > 3	0.88	0.78–0.92	0.001

these findings. Moreover, at 2 years of follow-up after a negative MPI study, hard cardiac event rate including cardiac death appeared higher among patients on regular hemodialysis than patients with chronic renal impairment on conservative protocol or recipients of successful renal transplant. This correlates with multiple reports emphasizing the deleterious effect of lower eGFR on incidence and severity of myocardial ischemia and subsequently on cardiac event rate.

Al-Mallah et al. studied a big cohort of patients with different stages of CKD referred for MPI study, and correlated MPI results to level of eGFR. Those with eGFR < 30 mL/min/1.73 m^2 were 256 patients. They demonstrated a close interaction between renal function and the magnitude of perfusion deficit as assessed by stress MPI such that mortality rates almost double among patients with moderate or severe renal impairment (GFR < 60 mL/min/1.73 m^2) in the presence of abnormal stress nuclear scans.[9,10]

Hakeem et al. reported that patients with normal MPI but with CKD had a significantly higher CD rate (2.7% per year) than those with normal MPI and no CKD (0.8% per year). The survival probabilities for patients with CKD alone (normal MPI) and abnormal MPI alone (no CKD) were similar. This means that event free survival after a negative MPI in

the absence of CKD seemed to be different if compared to those with negative MPI in the presence of CKD.[11]

Our results also correlate with the results of Furuhashi et al. They studied 108 Japanese patients with CKD defined as eGFR < 60 mL/min/1.73 m^2 with normal MPI studies and no history of hemodialysis or CAD. They concluded that normal stress MPI cannot guarantee an event free survival for patients with CKD. They followed up this cohort over a mean period of 24 months and concluded that the cardiac event rate was 7%. The following were determined as significant predictors of cardiac events: age, hemoglobin levels, eGFR, SSS, and SDS.[12]

However, our results point to a significantly higher incidence of total cardiac events (2.68%, 8.06% and 20.9%) at 6 months, one year and two years of follow-up respectively. CD and STEMI/NSTEMI were also significantly higher at 2 years of follow-up after a negative MPI study (2.15% and 9.7% respectively). The poorer kidney function might explain the relatively higher cardiac events in our cohort compared to Japanese cohort (50% of our cohort had eGFR < mL/min/1.73 m^2).

Again, Furuhashi et al. suggested that after a negative MPI study, follow-up MPI should be indicated within 1–2 years. However, our results point to the need for much closer MPI follow-up studies particularly among those patients on regular hemodialysis. Also, more aggressive medical control should be planed and strictly observed.[12]

Multiple reports evaluating prevalence of CAD in dialysis patients using myocardial perfusion imaging coming from different ethnic groups found significant variations. Majeed et al. in a Pakistanian cohort of 100 consecutive patients with ESRD in the waiting list for renal transplantation showed that the prevalence of positive MPI results among the study population was 47%.[13] Kim et al. in a Korean cohort of 227 patients recently starting renal dialysis showed that the prevalence of positive MPI was 22.5%.[14] Stack et al. studied 4025 patients with ESRD in United States and showed that the prevalence of positive MPI was 38%. The presence of moderate to large perfusion defects among patients with ESRD had an incremental prognostic effect than either alone.[15] All reports confirmed the finding that positive MPI result in the setting of ESRD is associated with higher cardiac morbidity and mortality.

Multiple mechanisms have been suggested to explain the increased mortality rates in patients with CKD. These mechanisms include anemia, increased oxidative stresses, derangements in calcium-phosphate homeostasis, inflammation, ventricular loading conditions and coagulation tendency. Indeed, the rapid progression of atherosclerotic vascular disease among patients with CKD is well-established in literatures. Beyond this, the increased cardiac event rate among hemodialysis patients was primarily explained by the enhanced myocardial and arterial remodeling, predominantly secondary to pressure and volume overload. Pressure overload results from the frequent association of uncontrolled HTN, aortic stenosis and anemia, resulting in concentric LVH. Volume overload is the result of arteriovenous shunting, salt and water overload, anemia and hypoalbuminemia resulting in left ventricular dilation. The process of concentric and subsequently eccentric LVH ultimately ends in congestive (mostly, refractory) heart failure and arrhythmogenic complications. Endothelial dysfunction, microcirculatory abnormalities and abnormal coronary reserve are important pathophysiologic mechanisms.[15–24]

In an outstanding work done by Fukushima et al., they studied a group of CKD patients for evidence of inducible ischemia and quantification of global and regional absolute myocardial blood flow (MBF) by PET imaging. They reported that even among those with normal clinical myocardial perfusion by PET scan, patients with CKD had reduced global myocardial flow reserve, which implied an underlying microvascular dysfunction in this population that could explain the poorer prognosis.[25]

5. Conclusion

Patients on regular hemodialysis had a higher statistically significant cardiac event rate compared to the other clinical categories of CKD at one year and 2 years of follow-up. Subsequently, a more rigorous approach of follow-up should be applied among hemodialysis patients. The lower is the eGFR and longer is the hemodialysis duration the higher is the cardiac event rate.

6. Recommendation

A large volume study from different Egyptian centers should be conducted to estimate the follow-up duration applicable for each clinical category of CKD based on eGFR values.

Conflict of interest

None declared.

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