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Research Paper

Epidemiologic Evaluation of the Blunted Heart Rate Response in Chronic Kidney Disease and Its Associated Factors

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ABSTRACT

Background and Aim: Previous studies on heart response rate (HRR) were conducted in diabetic patients. This study aims to evaluate HRR in end-stage renal disease (ESRD) patients and its correlation with myocardial perfusion imaging (MPI) findings and patients' prognosis.

Materials and Methods: The present study was conducted on patients with chronic kidney disease (CKD) who visited Shahid Hasheminejad Hospital between October 1, 2011, and September 30, 2019. Before the stress test, the patient was asked to rest in a supine position for 3 minutes while an electrocardiogram, blood pressure, and heart rate were recorded. Dipyridamole was then administered as an infusion with a dose of approximately 0.56 mg/kg of the patient's monitoring of the electrocardiogram. The patient's heart rate was recorded at 2-minute intervals after the start of the dipyridamole injection. Three minutes after the completion of the dipyridamole injection, radiopharmaceutical was injected. Finally, the findings of the myocardial perfusion scan were analyzed.

Results: The summed stress score (SSS), and summed rest score (SRS) had a significant relationship with the female gender and ejection fraction (EF) with the male gender ($P<0.05$). These results were not significantly related to patients' age and disease history ($P>0.05$). No significant difference was observed in the incidence of blunted HRR in patients with cardiac events by age, gender, and renal disease condition ($P>0.05$).

Conclusion: The frequency of blunted HRR in patients with CKD based on various variables was determined for the first time in the country in the present study, which can be an introduction for future research.

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Introduction

Chronic kidney disease (CKD) is a significant healthcare burden and hurts public health due to its increasing prevalence and high costs. CKD refers to the chronic and irreversible deterioration of renal function, characterized by a glomerular filtration rate of less than 60 mL/min/1.73 m^2 for over three months, irrespective of the underlying cause. It is categorized into five stages, ranging from asymptomatic stage one to end-stage renal disease (ESRD) in stage five. If left untreated, ESRD often leads to fatal outcomes [1]. Unfortunately, no prominent sign or symptom is found in CKD patients until reaching ESRD [2]. The most common cause of mortality in patients with ESRD is cardiovascular disease (CAD). The prevalence of CAD-related mortal events in ESRD patients receiving dialysis or undergoing transplantation is 20-40 times higher than the population [3, 4]. Thus, cardiac evaluation is vital for these patients, and all transplantation candidates should undergo it. Unfortunately, the use of angiography is limited in these patients, not only due to its invasiveness but also due to the prevalent nephrotoxic adverse effects of the contrast agents in this population [5]. Thus, in these patients, less invasive assessment via, for example, computed tomography angiography is not even widely applicable [6-8]. Myocardial perfusion imaging (MPI) has been in the spotlight since 1970, providing high sensitivity and specificity with a minimally invasive procedure [9-11]. In ESRD patients, De Lima et al. reported MPI sensitivity, specificity, positive predictive value, and negative predictive value of 35%, 76%, 49%, and 68%, respectively [12]. Although the reported diagnostic performance is not ideal, MPI is still the cornerstone in the cardiovascular evaluation of these patients [13]. Especially since ESRD patients cannot usually undergo or properly finish exercise-based tests, MPI with pharmacologic stress is of significant value [14]. In England, 66% of patients undergo MPI pharmacologic stress; of them, 23% and 43% receive adenosine and dipyridamole, respectively [15]. In the US, adenosine is the most commonly used drug for this purpose [16, 17]. Both these drugs are classified as vasodilators, which relax the smooth muscles and increase blood flow in the coronary arteries. However, since the diseased vessel cannot be dilated as much as the normal vessels, perfusion is relatively decreased, which can be visualized using MPI [18]. Several parameters can be evaluated using MPI, including the heart response rate (HRR). Blunted HRR in the dipyridamole stress test, which is correlated with MPI findings, is defined as a rest heart rate (HR)/peak HR ratio equal to or <1/20, or defined as Equation 1:

1. (peak HR–rest HR)/rest HR

Ratio equal to or <28%. However, previous studies on HRR were mostly conducted in diabetic patients. This study was conducted to evaluate HRR in ESRD patients and its correlation with MPI findings and patients' prognosis.

Materials and Methods

This cross-sectional study included ESRD patients who underwent MPI from September 2011 to September 2019 in our referral clinic. Patients were undergoing dialysis or had received renal transplantation. The exclusion criteria included patients diagnosed with second or third-degree cardiac block, diabetes, asthma, chronic obstructive pulmonary disease, or sick sinus syndrome, and patients with a documented ejection fraction (EF) of less than 25% or CAD in their history. All included patients signed informed consent.

A detailed clinical history was obtained from each patient. Their blood pressure and HR were documented at the rest phase. Dipyridamole (approximately 0.56 mg/kg) in 20 mL 0.9% saline solution was intravenously injected slowly for four minutes and under electrocardiogram (ECG) monitoring. After initiating the Dipyridamole injection, the patient's HR was documented every two minutes for 30 minutes. Three minutes after the termination of the dipyridamole injection, radiotracer (^{99m}Tc-MIBI) was injected. In case of any side effect after dipyridamole injection, aminophylline (approximately 100 mg) was injected at least one minute after 99mTc-MIBI intravenously.

Image acquisition

Interpretation

Both ECG findings and MPI images were considered in the patients' assessment.

A positive ECG was defined as: 1) Incidence of cardiac arrhythmia; 2) New presentation of ischemic T-wave; 3) ST segment changes: Horizontal ST depression; downward ST depression; ST elevation; MPI results were defined as: 1) Normal: No reversible stress-induced visualized defect in the myocardium; 2) Ischemia: Decreased perfusion in the stress phase, which showed improvement in the rest phase; 3) Fixed defect: Severely decreased or absence of perfusion in the stress phase with a more or less similar appearance on the rest phase images; 4) Fixed defect+ischemia: Finding both 2 and 3 criteria in a scan.

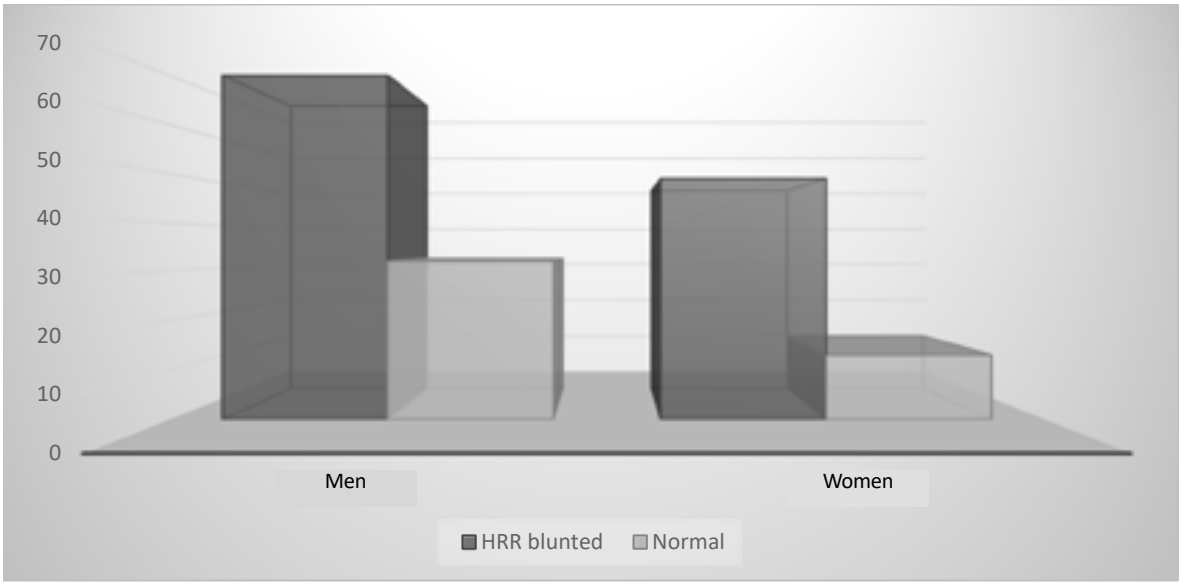

Figure 1. Frequency of patients with and without blunted HRR in both male and female groups

Peak stress HR was defined as the highest HR documented 4-8 minutes after the initiation of the dipyridamole injection. HRR was defined as Equation 2:

2. $\frac{peak\ stress\ HR}{rest\ HR}. \leq 1.2$

For the left myocardium's perfusion evaluation, each myocardial segment was scored using a previously denoted 5-scale scoring [19]. For each scan, the summed stress score (SSS) and the summed rest score (SRS) were calculated by adding the numbers derived from each segment in the stress and rest phases, respectively. Abnormal perfusion was defined as SSS>3 [20]. SSS>3, >8 and >13 were defined as mild, moderate, and severe, respectively [19]. The summed difference score (SDS) was calculated as (SSS-SRS), and a reversible defect was defined as SDS>1 [19]. EF was calculated using QGS software, version 3.36.2 [19]. EF<45% was considered abnormal global function impairment. SSS ≤3, SDS≤1, and EF ³45% were defined as being at risk [19]. All interpretations were made by two nuclear medicine specialists in consensus.

The data from the present study were used for qualitative analysis, utilizing the chi-square test to compare both within and between groups. Data were analyzed using SPSS software, version 22. The significance level for this study was set at 0.05.

Results

A total of 169 patients, including 107 men (63%) and 62 women (37%) were considered eligible to enter the study. From them, 70 men (59%) and 49 women (41%) showed blunted HRR (Figure 1).

Among the studied factors, gender was not associated with the blunted HRR (P=0.06). In the male gender-specific analyses, a significant relationship was observed between EF and blunted HRR (P=0.02). No significant relationship was found between blunted HRR and SSS (P=0.88), SDS (P=0.53) and SRS (P=0.28). In female patients, a relationship was observed between SSS and blunted HRR (P=0.02). However, SDS (P=0.51), SRS (P=0.23), and EF (P=0.43) were not associated. Table 1 presents the details.

We categorized patients based on their age into less and more than 50 years old. In our included population, 67 patients (40%) and 102 patients (60%) aged less and more than 50, respectively. In the young population (<50 y), 41 patients (61%) were diagnosed with blunted HRR, while in the old population (>50 y), 78 patients (76%) showed blunted HRR (P=0.03). No significant relationship was observed between blunted HRR and SSS, SRS, SDS and EF in both populations (P>0.05). Table 2 presents the details.

Table 1. Comparison of the incidence of blunted HRR according to the status of different heart scan criteria by gender

Variables	Gender	Cardiac Response	No. (%)		P
			HRR Blunt	Normal	
Summed stress score	Men	Normal	52(66)	27(34)	0.88
		Abnormal	18(64)	10(36)	
	Women	Normal	35(73)	13(27)	0.02
		Abnormal	14(100)	0	
Summed difference score	Men	Normal	49(64)	28(36)	0.53
		Abnormal	21(70)	9(30)	
	Women	Normal	33(77)	10(23)	0.02
		Abnormal	16(84)	3(16)	
Summed rest score	Men	Normal	62(67)	30(33)	0.28
		Abnormal	8(53)	7(47)	
	Women	Normal	44(77)	13(23)	0.23
		Abnormal	5(100)	0	
EF	Men	<45	10(100)	0	0.02
		>45	55(64)	31(36)	
	Women	<45	4(67)	2(34)	0.43
		>45	37(80)	9(20)	

EF: Ejection fraction

*Chi-square.

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In the next step, we classified ESRD patients based on their disease duration, <3< years. Among the studied patients, 72 patients (40%) were diagnosed with ESRD within 3 years, while 97 patients (60%) were diagnosed for more than 3 years. No significant difference was found between these two groups in terms of blunted HRR incidence (P=0.56). Also, no significant relationship was observed among other studied parameters (P>0.05). Table 3 presents the details.

In the male population, no significant correlation was observed between blunted HRR and ischemia (P=0.87) or infarction (P=0.34). In the female population, similar results (P of 0.09 and 0.45, respectively) were observed. In the old/young and long-term/short-term ESRD subgroups, no significant relationship was observed (P>0.05). Table 4 presents the details.

Discussion

Most ESRD mortal events are related to CAD. The prevalence of cardiac-related deaths in this population is significantly higher than in the normal population, reported to be up to 40 times higher [3]. Our study reported the epidemiology of blunted HRR and its associated factors in MPI for the first time in Iran. Due to the confounding effect of diabetes, we excluded these patients from our study. However, some with pre-diabetic status remained eligible. We found no significant correlation between blunted HRR and gender. Also, the duration of ESRD status was not correlated with blunted HRR. However, when age groups (>50 y vs <50 y) were compared, blunted HRR was significantly associated with an age over 50 years. Al Jaroudi et al. [20] studied the prognostic value of HRR in MPI with vasodilator stress in ESRD patients after renal transplantation [21]. They reported that blunted HRR is significantly correlated with

Table 2. Comparison of the incidence of blunted HRR according to the status of different heart scan criteria by old age and >50 years

Cardiac Response	Age (y)		No. (%)		P
			HRR Blunted	Normal	
Summed stress score	<50	Normal	32(60)	21(40)	0.79
		Abnormal	9(64)	5(36)	
	>50	Normal	55(74)	19(26)	0.40
		Abnormal	23(82)	5(18)	
Summed difference score	<50	Normal	30(59)	21(41)	0.47
		Abnormal	11(68)	5(32)	
	>50	Normal	52(75)	17(25)	0.70
		Abnormal	26(79)	7(21)	
Summed rest score	<50	Normal	38(62)	23(38)	0.55
		Abnormal	3(50)	3(50)	
	>50	Normal	68(77)	20(23)	0.63
		Abnormal	10(71)	4(29)	
EF	<50	<45	28(56)	22(44)	0.09
		>45	7(87)	1(13)	
	>50	<45	28(56)	22(44)	0.53
		>45	7(87)	1(13)	

EF: Ejection fraction.

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increased major cardiovascular events in the first month after transplantation. This was contrary to our results. Regarding our other result in the male population, Lima et al. also reported a correlation between blunted HRR and decreased EF post-dipyridamole injection [21]. Like us, they also reported that major cardiovascular events and the duration of the renal disease were not correlated with blunted HRR. In another study, De Lorenzo et al. classified 303 patients with CKD into two groups with and without blunted HRR [21]. They found no significant difference in the mortality rate and MPI results (SSS, SRS, and SDS) between the two groups. Lastly, Gorur et al. reported that blunted HRR in the Dipyridamole stress test was correlated with cardiac autonomic neuropathy and ventricular dysfunction, which can be a good justification [22]. This study had some limitations, the most prominent one was its retrospective nature. Thus, further studies with cohort design and long-term follow-up may validate the results. Also, we could not perform survival analyses, which is a crucial issue in CAD. Lastly, the COVID-19 epidemic affected our study adversely and limited our study population.

Conclusion

The results of our study indicate no significant relationship between blunted HRR and major cardiovascular events, disease duration, gender, or MPI parameters in patients with ESRD. However, we found no correlation between blunted HRR and low EF (<45%) and older age (over 50 years). Additionally, in female patients, a significant difference was observed between blunted HRR and SSS. Our study provides the first epidemiological evaluation of blunted HRR in ESRD patients, which can potentially enhance local decision-making guidelines.

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Table 3. Comparison of the incidence of blunted HRR according to the status of different heart scan criteria in patients with <3< of kidney disease

Cardiac Response	Disease Background/History (y)		No. (%)		P
			HRR Blunted	Normal	
Summed stress score	<3	Normal	32(60)	21(40)	0.54
		Abnormal	9(64)	5(36)	
	>3	Normal	52(70)	22(30)	0.45
		Abnormal	18(78)	5(22)	
Summed difference score	<3	Normal	32(63)	19(37)	0.13
		Abnormal	17(81)	4(19)	
	>3	Normal	50(72)	19(28)	0.91
		Abnormal	20(71)	8(29)	
Summed rest score	<3	Normal	43(69)	19(31)	0.55
		Abnormal	6(60)	4(40)	
	>3	Normal	63(72)	24(28)	0.87
		Abnormal	7(70)	3(30)	
EF	<3	<45	37(65)	20(35)	0.10
		>45	5(100)	0	
	>3	<45	55(73)	20(27)	0.54
		>45	9(82)	2(18)	

EF: Ejection fraction.

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Table 4. Comparison of the incidence of blunted HRR in patients with cardiac events by age, gender and renal disease status of the patients

Cardiac Response Variables			No. (%)		P
			HRR Blunted	Normal	
Men	Ischemia	Yes	18(67)	9(33)	0.87
		No	52(65)	28(35)	
	Infarction	Yes	1(33)	2(67)	0.34
		No	69(66)	35(34)	
Women	Ischemia	Yes	15(94)	1(6)	0.09
		No	34(74)	12(26)	
	Infarction	Yes	2(100)	0	0.45
		No	47(78)	13(22)	

Cardiac Response Variables				No. (%)		P
				HRR Blunted	Normal	
Age (y)	<50	Ischemia	Yes	10(71)	4(29)	0.37
			No	31(58)	22(42)	
		Infarction	Yes	2(67)	1(33)	0.84
			No	39(61)	25(39)	
	>50	Ischemia	Yes	23(79)	6(21)	0.67
			No	55(75)	18(25)	
		Infarction	Yes	1(50)	1(50)	0.16
			No	77(77)	23(23)	
History of kidney disease (y)	<3	Ischemia	Yes	15(80)	4(20)	0.27
			No	34(64)	19(36)	
		Infarction	Yes	1(50)	1(50)	0.57
			No	48(69)	22(31)	
	>3	Ischemia	Yes	18(75)	6(25)	0.72
			No	52(71)	21(29)	
		Infarction	Yes	2(67)	1(33)	0.18
			No	68(72)	26(28)	

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Ethical Considerations

Compliance with ethical guidelines

This study has been approved by the Ethics Committee of the Iran University of Medical Sciences (Code: IR.IUMS.FMD.REC.1400.006).

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Authors' contributions

All authors participated equally in the design, execution, and writing of all parts of this research.

Conflict of interest

The authors declared no conflict of interest.

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