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# Risk stratification using gated stress myocardial perfusion imaging: comparison between patients with and without sexual dysfunction

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## ABSTRACT

Sexuality is an indispensable part of life. When a problem is encountered related to this topic, the quality of life is negatively affected. Therefore, every problem related to sexuality is extremely private and important to an individual. This study aims to investigate the use of myocardial perfusion scintigraphy (MPS) for advanced assessment of patients with known or suspected coronary artery disease, cardiovascular disease, and in the intermediate risk group for SD. The study included 250 patients (150 male, 100 female, mean age  $54 \pm 12.10$ ) sent by the Cardiology Clinic to the Nuclear Medicine Clinic for MPS due to suspected cardiovascular disease (CVD). The questionnaire study was applied by two methods as face-to-face interviews or online. Data on sociodemographic characteristics and cardiovascular diseases together with risk factors for sexual activity were collected using a general information form. Patients were divided into three categories of risk depending on major risk factors for cardiovascular diseases: low, intermediate, and high risk. On comparing the risk scores between the groups, it was seen that there was a statistically clear reduction in the intermediate risk group of patients with SD according to MPS scoring. MPS is a cost-effective, reliable, and accurate non-invasive diagnostic method necessary for routine use to assess cardiovascular disease and in the intermediate risk group for SD.

## INTRODUCTION

In people with cardiovascular disease (CVD), there is a very high prevalence of sexual dysfunction (SD) in both genders that may affect the quality of life of individuals to a significant degree.<sup>1</sup>

As a result, it is necessary to assess the sexual functioning of patients with CVD and, if there is a problem, to provide appropriate intervention.

A consensus report was published evaluating SD and cardiac risk factors together.<sup>1, 2</sup> This report divided patients into three categories of risk group depending on whether risk factors were low, intermediate, or high, and developed appropriate treatment algorithms for patients. Before sexual activity, especially in the intermediate risk group, it was recommended that patients should have advanced assessment and

be monitored according to the recommended algorithms for low-risk or high-risk group patients.

Currently, the most frequently used non-invasive test with high accuracy for myocardial perfusion assessment is myocardial perfusion scintigraphy (MPS). MPS is a non-invasive cardiac nuclear medicine diagnostic method used to research the severity of disease, and to determine risk and prognosis for patients with known or suspected coronary artery disease (CAD).<sup>3</sup> Additionally, it can be used to research the efficacy of lifestyle changes and medical treatment of patients after myocardial infarction (MI) and coronary revascularization.<sup>4</sup> According to guidelines prepared for the Clinical Use of Cardiac Radionuclide Imaging by the American College of Cardiology (ACC)/ American Heart Association (AHA)/American Society for Nuclear Cardiology (ASNC), cardiac nuclear testing is a cost-effective test for use after cardiac events and to assess patients in the intermediate risk group.<sup>5</sup>

This study aims to investigate the use of MPS for advanced assessment of patients with known or suspected coronary artery disease, cardiovascular disease, and in the intermediate risk group for SD.

## MATERIALS AND METHODS

### Study population

The study included 250 patients (150 male, 100 female, mean age  $54 \pm 12.10$  years) sent by the Cardiology Clinic to the Nuclear Medicine Clinic for MPS due to suspected CVD between May and November 2014.

All patients included in the study were questioned for sociodemographic data, systemic diseases, and medication use.

### Inclusion criteria

- ▶ Above the age of 20 years and below the age of 65 years
- ▶ Married or with a regular sexual partner
- ▶ No perception disorders
- ▶ No previous hysterectomy (for female cases)
- ▶ Acceptance of participation in the study

### Exclusion criteria

- ▶ Pregnancy or suspected pregnancy, to protect from radiation exposure
- ▶ Patients below the age of 20 years or above the age of 65 years



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- ▶ Males with previous prostate or penile surgical operations
- ▶ Excluded in New York Heart Association (NYHA) Class 4
- ▶ Those taking hormone replacement therapy, female patients with previous hysterectomy.

The study was completed after obtaining permission from the local ethics committee (permission no. 050.99–153).

Patients were divided into three categories of risk: low, intermediate, and high risk, depending on major risk factors for cardiovascular diseases.<sup>1</sup>

### Completion and evaluation of SD questionnaire forms

The questionnaire was completed using two methods: face-to-face interviews or online. Data about sociodemographic characteristics and cardiovascular diseases together with risk factors for sexual activity were collected using a general information form. To inquire about sexual function, women completed the Female Sexual Functioning Index (FSFI) while men completed the International Index of Erectile Function (IIEF).<sup>6,7</sup>

The FSFI form was assessed with the aid of a gynecology expert. It is a survey form for those who have had sexual relations within the previous month with points from 2 to 36. A total score below 26.55 indicates a sexual function disorder.<sup>6</sup>

The IIEF form was assessed with a urology expert. It is a survey form applicable to those who have had sexual relations within the previous month and is scored negatively. With maximum points of 30, it assesses erectile dysfunction as severe (6–10 points), intermediate (11–16 points), slight (17–25 points), and no dysfunction (26–30 points).<sup>7</sup>

### GATED MPS

#### Imaging protocol

Patients with sufficient effort capacity had physiological effort measured according to the Bruce or Modified Bruce protocol using a treadmill device. When maximal heart rate reached 85–100%, 8 mCi 99 mTc-sestamibi was injected. In patients with insufficient effort capacity, a pharmacological (adenosine) stress test was performed. An adenosine infusion of 140 µg/kg/min dose was administered for 3–4 min with a maximum dose of 60 mg. About 2.5–3 min after adenosine infusion began, radiopharmaceutical infusion was administered. Forty-five minutes after injections and in a single-day protocol, stress ECG-gated SPECT style MPS imaging was completed. Patients with observed perfusion loss on stress imaging had rest imaging with 25 mCi 99 mTc-sestamibi taken on the same day. Images were taken with a ‘GE-infinia’ gamma camera system with low energy high resolution (LEHR) collimator.

### Visual interpretation

The transaxial, sagittal, and coronal slice images of MPS for stress and rest were evaluated for the presence of hypoperfusion and perfusion defects. The patients were divided into two groups according to the perfusion status: (1) normal, without defects or changes in perfusion in stress and rest images and (2) ischemia (reversible), better perfusion in rest images when compared with the stress images.

### Quantitative interpretation of perfusion

Using QPS software (Cedars-Sinai Medical Center, Los Angeles, California, USA), 17-segment automatic quantification of summed stress score (SSS), summed rest score (SRS), and summed difference score (SDS) was performed. The SSS, SRS, and SDS were automatically calculated using the QPS software. A normal sestamibi database (normal limits; Cedars-Sinai Medical Center) was used by the QPS software for perfusion score analysis. SSS is classified as follows: <4=normal; 4–8=mildly abnormal; 9–13=moderately abnormal; and >13= severely abnormal. SDS were represented as follows: <2=absence of ischemia; 2–4=mild ischemia; 5–8= moderate ischemia; and >8=severe ischemia. A SDS was derived as the difference between stress and rest scores. SSS<4 was considered normal, SSS=4–13, mildly/moderately abnormal, and >13, severely abnormal.<sup>8</sup>

After MPS imaging, risk classification was completed in accordance with [table 1](#). Patients were divided into three groups as low, intermediate, and high risk.

### Statistical evaluation

The data from the research were uploaded to the electronic environment of the SPSS V19.0 statistical program and checks and analyses were completed. The  $\chi^2$  analysis was used for statistical evaluation and  $p<0.05$  was accepted as significant.

### RESULTS

The study included a total of 250 patients with MPS. Of these, 150 were men (60%) and 100 were women (40%). The mean age of participants was  $54.73 \pm 20.35$  years and the age range was 36–65 years.

The sociodemographic characteristics of the patient group with SD and the control group are shown in [table 2](#). The presence of SD was not found to be related to educational level, economic situation, or occupation ( $p>0.05$ ).

Of all participants, 48% had SD. Of patients with SD, 74.1% were male and 25.9% were female ( $p \leq 0.001$ ).

In the age group of 55–65 years, there was a higher rate of SD compared to other age groups (52.2%).

When the occurrence of SD was assessed together with cardiovascular risk factors, there was a statistically significant relationship found between cardiovascular risk factors (diabetes mellitus, hypertension alcohol use, hyperlipidemia, smoking, and obesity) of patients with SD and without SD and the presence of menopause in women ([table 3](#);  $p<0.05$ ).

Additionally there was a statistically significant relationship found between incidence of SD and patients with MI and coronary artery bypass graft (CABG) ([table 3](#);  $p<0.001$ ).

When medication use that may cause SD was examined in participants, there was a statistically significant relationship found with cardiovascular system (CVS) medications ([table 3](#);  $p<0.001$ ).

The results of MPS imaging are presented in [table 4](#).

Of the total of 250 patients included in the study, 126 (50.4%) were normal while 124 (49.6%) had ischemia identified. Of the patients with SD (120), 18 (15%) were normal while 102 (85%) had ischemia ( $p<0.001$ ).

**Table 1** Risk stratification based on non-invasive testing (according to<sup>9</sup>)

Risk	Parameters
<b>High risk</b> >3% annual mortality rate	<ol style="list-style-type: none"> <li>1. Severe resting left ventricular dysfunction (LV EF &lt; 35%)</li> <li>2. High-risk treadmill score (score ≤ -11)</li> <li>3. Severe exercise LV dysfunction (exercise LV EF &lt; 35%)</li> <li>4. Stress-induced large perfusion defect (particularly if anterior)</li> <li>5. Stress-induced multiple perfusion defects of moderate size</li> <li>6. Large, fixed perfusion defect with LV dilation or increased lung uptake (thallium-201)</li> <li>7. Echocardiographic wall motion abnormality (involving &gt;2 segments) developing at a low dose of dobutamine (≤10 mg/kg/min) or at a low heart rate (&lt;120 bpm)</li> <li>8. Stress echocardiographic evidence of extensive ischemia</li> </ol>
<b>Intermediate risk</b> 1–3% annual mortality rate	<ol style="list-style-type: none"> <li>1. Mild/moderate resting LV dysfunction (LV EF=35–49%)</li> <li>2. Intermediate-risk treadmill score (-11 &lt; score &lt; 5)</li> <li>3. Stress-induced moderate perfusion defect without LV dilation or increased lung intake (thallium-201)</li> <li>4. Limited stress echocardiographic ischemia with a wall motion abnormality only at higher doses of dobutamine involving ≤2 segments</li> </ol>
<b>Low risk</b> <1% annual mortality rate	<ol style="list-style-type: none"> <li>1. Low-risk treadmill score (score ≥5)</li> <li>2. Normal or small myocardial perfusion defect at rest or with stress</li> <li>3. Normal stress echocardiographic wall motion or no change in limited resting wall motion abnormalities during stress</li> </ol>

EF, ejection fraction; LV, left ventricular.

CVS risk scoring found that 9 (7.5%) patients with SD were low risk, 81 (67.5%) were intermediate risk, and 30 (25%) were high risk.

In terms of MPS risk scoring, 51 (42.5%) patients with SD were low risk, 10 (8.3%) were intermediate risk, and 59 (49.2%) were high risk (table 5,  $p < 0.001$ ).

On comparing the risk scores between the groups, it was seen that there was a statistically clear reduction in the

intermediate risk group of patients with SD according to MPS scoring (figures 1 and 2).

## DISCUSSION

Sexual activity is an important topic for patients with coronary artery disease and for clinicians treating these patients. As a result, it is necessary to evaluate the sexual functioning situation of patients with cardiovascular disease and, if there is a problem, provide appropriate intervention.

Before patients in the intermediate risk group according to cardiovascular risk factors return to sexual activity, advanced investigation should be completed to understand whether they fall in the low-risk or high-risk group and deciding is of great importance.

In our study, we showed that MPS plays a very effective role in advanced assessment of patients in the intermediate risk group.

In recent years, the increased incidence of SD has brought with it medical, economic, and psychosocial problems.<sup>10</sup> SD affecting the quality of life of individuals occurs with high prevalence in people with cardiovascular disease of both genders. It is related to sociodemographic characteristics such as educational level and age.<sup>11 12</sup>

Additionally different to other studies we found no statistically significant difference between SD and sociodemographic characteristics.

The results of this study found that the socioeconomic levels of cases were generally at moderate and low levels and that the quality of life of men was more affected than that of women among cases with SD. Since there are insufficient studies on the topic, it is not possible to compare with previous studies. However, our study findings show that SD affects every dimension of quality of life of cases. This reveals the necessity to investigate quality of life together with SD. Also, we found a higher prevalence of SD in the advanced age group, compared to other age groups, in accordance with the literature.

In the literature, it is reported that risk factors like obesity, hypertension, diabetes and menopause, and some

**Table 2** The distribution of sociodemographic characteristics of the existence of sexual dysfunction (SD) in patients (n=250)

Sociodemographic characteristics	SD (n=120, 48%)	No SD (n=130, 52%)	p Value*
Sex, n (%)			
Female	31 (25.8)	69 (53)	<0.001
Male	89 (74.2)	61 (47)	
Age groups, n (%)			
20–35	0	1	0.020
36–45	9 (28.1)	23 (71)	
46–55	40 (49.4)	41 (50.6)	
56–65	71 (52.2)	65 (47.8)	
Educational status, n (%)			
No	2 (100)	0 (0.0)	0.126
Primary school	17 (65.4)	9 (34.6)	
Secondary school	45 (50)	50 (50)	
High school	50 (42)	69 (58)	
University	6 (46.2)	7 (53.8)	
Profession, n (%)			
Official	13 (41.9)	18 (58.1)	0.040
Retired	33 (60)	22 (40)	
Free	57 (50.4)	56 (49.6)	
Housewife	17 (33.3)	34 (66.7)	
Economic status, n (%)			
Good	22 (40.7)	32 (59.3)	0.480
Middle	80 (49.7)	81 (50.3)	
Poor	18 (51.4)	17 (48.6)	

\* $\chi^2$  Test.

**Table 3** Patient characteristics by sexual function classification

Characteristics	Total, n/250 (%)	Sexual dysfunction	No sexual dysfunction	p Value
Diabetes mellitus, n (%)	86 (34.4)	49 (57)	37 (43)	0.046
Hypertension, n (%)	184 (73.6)	98 (53.3)	86 (46.7)	0.005
Hyperlipidemia, (%)	114 (45.6)	60 (52.4)	54 (47.4)	0.180
Current smoker, % (n)	47 (18.8%)	24 (51.1%)	23 (48.9%)	0.641
Obesity, n (%)	87 (34.8)	46 (52.9)	41 (47.1)	0.260
Previous MI, % (n)	138 (55.0)	102 (73.9%)	36 (26.1%)	<0.001
Previous CABG, % (n)	150 (60%)	99 (66%)	51 (34%)	<0.001
Menopause (female), % n	67 (26.8%)	25 (37.3%)	42 (62.7%)	0.041
Alcohol, % (n)	19 (7.6%)	14 (73.7%)	5 (26.3%)	0.020
<b>Medication</b>				
No use, % (n)	174 (69.6%)	67 (38.5%)	107 (61.5%)	<0.001
CVS drugs, % (n)*	74 (29.6%)	51 (68.9%)	23 (31.1%)	
Other medications,% (n)†	2	2 (0.8%)	0	
Psychiatric drugs,% (n)‡	0	–	–	
Hormone drugs, % (n)§	0	–	–	

p Value Fisher's exact test.

\*β-Blockers, thiazide diuretics, calcium antagonists, digoxin, lipid-lowering drugs, ACE inhibitors.

†Cimetidine, ranitidine, metoclopramide, carbamazepine, phenytoin, heroin, cocaine, amphetamines, marijuana.

‡Major tranquilizers, anxiolytics, tricyclic antidepressants, monoamine oxidase inhibitors (MAO) inhibitors, lithium, opioid agonists, barbiturates, selective serotonin re-uptake inhibitor.

§Antiandrogens, estrogens, Luteinizing hormone-releasing (LHRH) analogs, testosterone, progestins, anabolic steroids.

CABG, coronary artery bypass graft; CVS, cardiovascular system; DM, diabetes mellitus; MI, myocardial infarction.

medications may cause SD and that SD is increased in cases who have had MI.<sup>11 13–16</sup>

Additionally, many studies have found that among factors causing SD with cardiovascular disease, factors such as reduced libido linked to the psychological effects of symptomatic heart disease, avoidance of sexual activity due to fear in spite of normal libido, depression, changes in sexual activity linked to age, alcohol use, and smoking may be listed.<sup>11–13 17</sup> These clinical situations have been well described in many studies and it has been shown that heart diseases affect sexual life to a significant degree.<sup>18 19</sup>

**Table 4** Myocardial perfusion imaging findings in patients referred for stress-gated myocardial perfusion scintigraphy by sexual function classification

Measures	SD, n (%)	No SD, n (%)	p Value*
SSS <4 (normal)	18 (14.3)	108 (85.7)	<0.001
SSS 4–8 (mildly abnormal)	35 (74.5)	12 (25.5)	
SSS 9–13 (moderately abnormal)	32 (86.5)	5 (13.5)	
SSS>13 (severely abnormal)	35 (87.5)	5 (12.5)	
SDS 0–1 (normal)	34 (23.1)	113 (76.9)	<0.001
SDS 2–4 (mild ischemia)	40 (81.6)	9 (18.4)	
SDS 5–7 (moderate ischemia)	23 (79.3)	6 (20.7)	
SDS ≥8 (severe ischemia)	23 (92)	2 (8)	
SLVEF <35 (severely abnormal)	9 (81.8)	2 (18.2)	<0.001
SLVEF 35–49 (mild-moderately abnormal)	15 (78.9)	4 (21.1)	
SLVEF ≥50 (normal)	96 (43.6)	124 (56.4)	

\* $\chi^2$  Test.

SD, sexual dysfunction; SDS, summed difference score; SLVEF, stress left ventricular ejection fraction; SSS, summed stress score.

In our study, when differences according to risk factors for SD were investigated, there was no statistically significant relationship found for all cases with SD compared to those without it. We consider that our results may have been affected by the heterogeneous nature and small number of cases in our study.

We found a statistically significant relationship between patients with MI and CABG and incidence of SD in the literature, similar to our study.

Many studies have described the situation of sexual function disorders linked to cardiovascular diseases and CVS medication clearly and reported that some medications may cause SD.<sup>14</sup>

Impotence, reduced libido, orgasm problems, gynecostomy, and menstruation disorders are frequently observed to be linked to the medications used. Antihypertensives and diuretics are medications that most frequently cause SD. Similarly, in our study, we found an increase in SD incidence among participants who used CVS medication to a statistically significant degree.

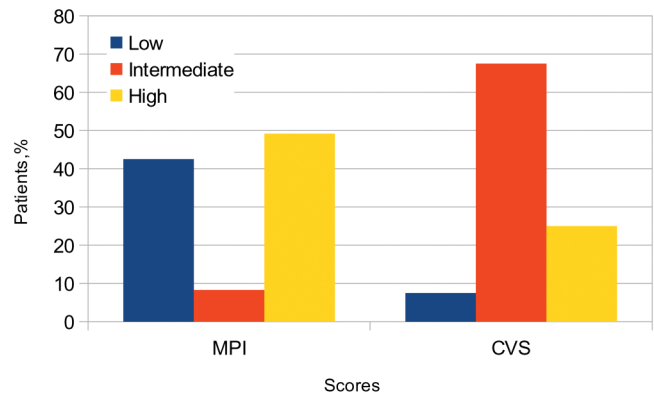
The Princeton guide is used to determine risk of sexual activity in people with cardiovascular disease.<sup>1</sup>

**Table 5** Prognostic score category

Risk score	Category	SD, n (%)	No SD, n (%)	p Value
MPI	Low	51 (42.5)	125 (96.1)	
	Intermediate	10 (8.3)	2 (1.5)	<0.001
	High	59 (49.2)	3 (2.4)	
CVS	Low	9 (7.5)	120 (92.3)	
	Intermediate	81 (67.5)	7 (5.3)	<0.001
	High	30 (25)	3 (2.3)	

CVS, cardiovascular system; MPI, myocardial perfusion imaging; SD, sexual dysfunction.

**Figure 1** Prognostic risk score category of patients with sexual dysfunction (SD). On comparing the risk scores between the groups, it was seen that there was a statistically clear reduction in the intermediate risk group of patients with SD according to myocardial perfusion scintigraphy (MPS) scoring ( $p < 0.001$  for all three groups).



In 2005, it was recommended that patients in the intermediate risk group be given advanced assessment and classified as low or high risk for sexual activity and this was published in the report of the second Princeton consensus conference.<sup>2</sup> Accordingly, while low risk patients do not require advanced examinations, intermediate risk group patients should be given exercise tests or other tests to separate them into low or high risk groups.

One of the common aims of diagnostic tests used in clinical cardiology is to identify risky patients in the early period. Effort ECG and MPS are non-invasive methods widely used for diagnosis and monitoring of CVD. However both methods have false positive and false negative results for CVD diagnosis. When both test results are evaluated together, it is possible to estimate possible coronary artery stenosis very accurately.<sup>20</sup>

In this sense, MPS is a test that provides important prognostic information.<sup>4</sup> After MPS, the size of the region with perfusion disorder is the most important prognostic marker (table 4).

Among the indications for MPS are diagnosis of those with an intermediate possibility of coronary artery disease, those with non-diagnostic ECG (left branch block, left ventricle hypertrophy, digitalized patients) and, as a result for whom it is not possible to obtain information from effort ECG, to evaluate risk in those with a high possibility of coronary artery disease and to indicate the degree of the pathology.<sup>21 22</sup>

To date, studies have shown that as the distribution and severity of pathologies shown on MPS increase, the patient's risk of cardiac events and cardiac mortality increases. Just as MPS can visually evaluate the perfusion disorder in the myocardial region, some semi-quantitative

parameters (amount of MI, amount of damaged myocardia, total stress score showing severity and degree of ischemia, % spread of abnormal myocardial tissue) can also be calculated. According to these assessments, the MPS findings may be grouped as mild, intermediate, or severe.

A study by Sharir *et al*<sup>23</sup> found that from the point of view of mortality the ejection fraction calculated after stress with gated myocardial perfusion imaging was the most important marker for MI development in the total difference score.

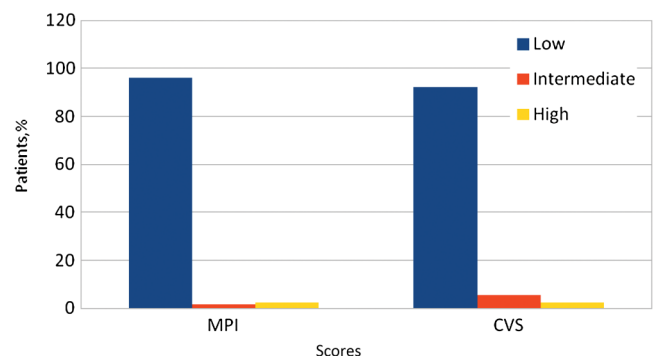
Hachamovitch *et al*<sup>24</sup> reported that stress MPS was a clinically effective and cost-effective tool to classify known or suspected CVD in terms of risk and to choose an appropriate treatment method. However, Beller and Watson<sup>25</sup> stated that the effort test was sufficient to assess the risk to patients in the low risk group, though it may be more appropriate to use direct cardiac catheterization instead of MPS to evaluate patients in the high risk group. In our study, we emphasize that MPS may be a more beneficial method for advanced evaluation of patients mainly in the intermediate risk group.

## Conclusion

Sexuality is an indispensable part of life. When a problem is encountered in this area, the quality of life is negatively affected. Every problem related to sexuality is extremely private and important to an individual. Cultural differences may make it more difficult to get help and consult with appropriate sources. Of course, everyone has the right to receive the most appropriate medical aid for their problem.

In patients being evaluated for sexual activity who are judged to be intermediate risk by consensus statements,

**Figure 2** Prognostic risk score category of patients without sexual dysfunction. On comparing the risk scores between the groups, it was seen that there were no statistically significant differences between all three groups.



MPS is a cost-effective, reliable, and accurate diagnostic method to evaluate patients with cardiovascular disease.

### Study limitations

1. The main limitation of our study is that the number of patients is low. Studies with larger case groups are required.
2. Some problems encountered during the survey application:
  - ▶ The patient's own discomfort on being questioned about sexual activity
  - ▶ Having insufficient information about sexuality
  - ▶ Low priority given to sexual counseling
  - ▶ Too many patients and study load leading to insufficient time
  - ▶ Cultural differences
3. While it is not known whether the answers given by patients in the survey work in the clinical environment, we did not test the reliability of results obtained from the online survey study.
4. It is known that the presence of peripheral vascular disease has an association with SD. In our study, there were no patients with peripheral artery disease. Therefore, in this study, we make any comments.

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