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Evaluation of lower extremity perfusion in organ scintigraphy in patients who are planned for amputation

Amputasyon planlanan hastaların ekstremite perfüzyonunun değerlendirilmesinde radyonüklid organ perfüzyon sintigrafisinin değerlendirilmesi

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ÖZET

Giriş: Alt ekstremitelerin amputasyonuna karar vermede tek bir yöntem yeterli değildir. Bu nedenle, çalışmamızda, alt ekstermite değerlendirilmesinde Organ Perfüzyon Sintigrafisinin(OPS) katkısı araştırıldı.
Yöntem: Çalışmamız retrospektif olarak düzenlenmiş olup kliniğimize Ortopedi Kliniği tarafından amputasyon öncesi değerlendirme amaçlı başvuran ve Tc-99m sestamibi organ perfüzyon sintigrafisi yapılmış hastalar incelendi. Araştırmaya total olarak 21 hasta (18 erkek ve 3 kadın, yaş ortalamaları 67,2 ± 10,6) dahil edildi. Hastaların Tc-99m sestamibi Organ Perfüzyon Sintigrafisi sonuçları ile diğer inceleme yöntemleri (Dopler USG ve BTAnjio) ile karşılık olarak değerlendirildi. İstatiksel olarak OPS'nin tanı değeri diğer inceleme yöntemleri ile karşılaştırıldı.
Bulgular: Her iki gruptaki hastalar arasında demografik veriler, risk faktörleri ve eşlik eden hastalıklar açısından istatistiksel olarak anlamlı fark yoktu. Yirmi bir hastaya hem OPS hem de DUSG uygulanırken, sadece onbir hastada CTA yapıldı. Değerlendirmeler sonucunda, 21 hastanın 5'inde amputasyon gerçekleştirildi. Ampute edilen hastaların her üç testinde de sonuçlar pozitif saptandı.
Sonuç: Periferik arter hastalığının fonksiyonel bir sorun olduğu göz önüne alınırsa ağırlıklı morfolojik ve sınırlı hemodinamik verilerin klinik değerlendirme açısından yetersiz olduğu ve bu nedenle de fizyolojik ve fonksiyonel inceleme yöntemlerine ihtiyaç bulunduğu anlaşılmaktadır. Bu nedenle de OPS özellikte alt ekstreme perfüzyonun değerlerlendirilmesinde özellikle amputasyon planlanan hastalarda ilave olarak faydalanılabilecek değerli bir nükleer tıp yöntemidir.
Anahtar kelimeler: Alt ekstremite, periferik arter hastalığı, amputasyon, teknesyum Tc 99m Sestamibi, perfüzyon sintigrafisi, radyonüklid görüntüleme, dopler ultrason, radyografik tomografi, dijital kesit anjiografi

ABSTRACT

Introduction: No method alone is enough to take the amputation decision in the lower extremity. Therefore, in our study, the contribution of organ perfusion scintigraphy to the evaluation of lower extremity perfusion was investigated.
Methods: Our study was retrospectively designed and investigated patients applying for evaluation before amputation, and with Tc-99m sestamibi organ perfusion scintigraphy performed. The research included a total of 21 patients (18 male, 3 female, mean age 67.2 ± 10.6 years). The patients had OPS results and the results of other investigation methods (DUSG and CTA) comparatively evaluated. Statistically the diagnostic value of OPS was compared with the other investigation methods.
Results: There was no statistically significant difference between patients in both groups in terms of demographic data, risk factors and accompanying diseases. Twenty-one patients had both OPS and DUSG performed while only eleven patients had CTA performed. The results of the evaluations found that 5 of the 21 patients had amputation performed. The results were positive in all three tests of amputated patients.
Conclusion: Considering that peripheral arterial disease is a functional problem, it is understood that weighted morphological and limited hemodynamic data are inadequate for clinical evaluation and therefore physiological and functional examination methods are needed. For this reason, OPS is a valuable nuclear medicine method that can be used additionally in patients with amputation planned especially in the evaluation of lower extreme perfusion.
Keywords: Lower extremity, peripheral artery disease, amputation, Technetium Tc 99m Sestamibi, perfusion scintigraphy, radionuclide imaging, doppler ultrasonography, radiographic tomography, digital subtraction angiography

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INTRODUCTION

Lower extremity peripheral artery disease (LEPAD) is a disease characterized by narrowing or blockage of arteries in the lower extremities as a result of progressive atherosclerosis.

Peripheral artery disease (PAD) is a significant health problem with increasing incidence [1]. The clinical severity of PAD is closely related to the rate of blood vessels stenosis and whether collateral circulation provides sufficient perfusion. Patients initially observe pain during walking, with ischemic pains in the feet at rest developing as a result of continued reduction in blood flow. Advanced cases may develop ulceration and gangrene and if not treated this may lead to loss of the limb [2]. Atherosclerosis is a significant risk factor among risk factors for PAD. In addition to this, other risk factors include smoking, dyslipidemia, diabetes mellitus and hypertension [3].

General diagnostic approaches reveal predisposing factors and etiology causing the disease which is very important for appropriate treatment approaches [4].

In recent years advances in imaging and research techniques have increased the success rates of diagnosis and treatment of lower extremity ischemic diseases [5].

Unfortunately, in researching LEPAD no single method is sufficient to make the decision for amputation, however when used together they may be true aids to the clinician for medical and surgical management of the disease.

In 2011, the European Society of Cardiology published guidelines to ease the clinical decision-making process in diagnosis and treatment of peripheral artery diseases. This guideline states that in diagnosis approaches to LEPAD advanced tests and treatment approaches are important primarily to know the epidemiology and accompanying risk factors of the disease, that invasive and non-invasive investigation methods should be used to decide whether more advanced invasive procedures and surgical procedures should be undertaken and that close cooperation between doctors with different areas of expertise is required [6].

Good preliminary identification and differential diagnostic of current vascular pathologies is very important for treatment success. In lower extremity ischemic cases the importance of time for treatment success is great. For diagnosis of peripheral artery diseases, many non-invasive imaging methods are used, along with the nuclear medicine method of radionuclide organ perfusion studies [7].

Radiological imaging techniques can reveal anatomic narrowing of blood vessel structures, while nuclear medicine methods can determine whether perfusion in the leg is sufficient [8].

In nuclear medicine centers the technetium (Tc)-99m sestamibi (MIBI methoxy isobutyl isonitrile) kit is routinely used for myocardial perfusion scintigraphy imaging. Furthermore, it is used in organ perfusion scintigraphy. Tc-99 m sestamibi is a lipophilic cationic material which passes by passive diffusion through the cell membrane into the cell and up to 90% accumulates in mitochondria. The involvement of Tc-99m sestamibi in the cell is linked to perfusion, viability of the cell and mitochondrial activity. As a result of these characteristics many studies have used Tc-99m sestamibi to research tissue perfusion and viability [9,10].

In this study, the contribution of Organ Perfusion Scintigraphy to the evaluation of lower extremity perfusion was investigated.

METHODS

Patient Choice and Preparation

We retrospective investigated the data from twenty one patients who were to referred to our department for Organ Perfusion studies from May 2013-November 2015. All patients participating in the study were questioned about socio-demographic data, systemic diseases and medication use. This study was completed after receiving permission from the local ethics committee.

Demographic data, risk factors, accompanying diseases, disease duration, cause, affected side, operation history and amputation history of the patients were determined. The evaluation methods used for lower extremity perfusion research were investigated. All patients had body mass index (BMI) calculated using height and weight. The patients' hemoglobin, total cholesterol, HDL and LDL values were recorded during their hospital stay. The patients were separated into traumatic (Group 1) and non-traumatic (Group 2) groups and the correlation between clinical, laboratory parameters and accompanying diseases was researched.

Those who had previously traumatized to the lower extremity region, operation history and used drugs for perfusion were excluded from the study.

Additionally, invasive and non-invasive investigation methods for lower extremity perfusion and organ perfusion scintigraphy studies of the patients were evaluated together.

Organ Perfusion Scintigraphy (OPS) with Tc-99m Sestamibi

Tc-99m Sestamibi OPS study was completed in three phases; Phase 1 (perfusion studies), Phase 2 (reserve studies) and Phase 3 (static studies in 15th minute and 1st hour). Patients were placed in supine position with both lower extremities under the gamma camera.

Phase 1: To assess perfusion, 1-2 s dynamic images were obtained for 1 minute immediately after 15 mCi (555 MBq) Tc-99m labeled with sestamibi was injected in the antecubital vein.

Phase 2: To assess blood pool; immediately after the perfusion study, 30-120 second images were obtained to assess blood reserve.

Phase 3: Finally in the 15th minute after injection and in the 1st hours, five minute static images of the relevant area were obtained to complete the procedure.

Images were taken using a low energy high resolution collimator (LEHR) with double detector gamma camera system (GE, Infinia model).

Assessment of Imaging

All images obtained were evaluated by two nuclear medicine experts at different times. The evaluations were both visual and quantitative. Quantitative evaluation was performed with the aid of a computer using a quantitative perfusion program with total counts on the region of interest drawn on the images. The Region of Interest (ROI) was drawn on one side and mirror method was used for the contralateral side. The total ROIs obtained from both legs were used to calculate lower extremity perfusion reserves (PR %) using the formula given below. The perfusion reserve reference interval was between 50-80% [11].

PR% = ROI (Left or Right) / (Right ROI + Left ROI) x 100

Statistical analysis

The SPSS version 19.0 statistical software package was used for the research data. For statistical comparisons the Mann-Whitney and X2 tests were used. Significance level was accepted as $p<0.05$ for all tests.

RESULTS

Patient Characteristics

The 21 patients participating in the study were 18 men (85.7%) and 3 women (14.3%). The mean age of patients was 67.19±10.633 years (min: 46, max: 84). The demographic characteristics of patients included in the study are presented in Table 1. There was no statistically significant difference between patients in both groups in terms of demographic data, risk factors and accompanying diseases.

Of the 21 patients, 3 (14.3%) comprised the trauma group and 18 (85.7%) comprised the non-trauma group. In the non-traumatic patient group 52.3% had PAD while 27.8% had DM, while in the traumatic patient group 33.3% had PAD and 66.7% were traffic accident patients.

The distribution of etiological characteristics in the groups is presented in Table 2.

Perfusion assessment methods for lower extremities

All of the 21 patients had both Tc-99m sestamibi OPS and DUSG, while eleven patients had CTA performed. The results of the evaluation found that 5 of the 21 patients had performed amputation. The imaging methods and operation results of patients are presented in Table 3. Patients of normal and pathological organ perfusion studies were presented in Fig-1 and Fig-2.

Calculation of perfusion reserve of lower extremities (PR %)

When twenty-one patients with perfusion reserve calculation; five patients with amputations were performed and the patient was found to be less than 45% of the PR%. Perfusion reserves 45% -55% were considered suspicious (Table 3).

Table 1. Demographic characteristic of study population

Characteristics	Traumatic *n=3 (%)*	Non-traumatic *n=18 (%)*	P value
Age (mean ± SD)	68.7 ± 10.0	66.9 ± 11.0	0.801
BMI (mean ± SD) (kg/m^2)	32.4 ± 10.1	26.8 ± 4.7	0.291
Diabetes mellitus (%)	2 (66.7)	11 (61.1)	0.684
Hyperlipidemia (%)	1 (33.3)	1 (5.6)	0.271
Hypertension (%)	1 (33.3)	12 (66.7)	0.316
Smoking (%)	1 (33.3)	12 (66.7)	0.316
History of MI	0	1	0.857
History of CAD	0	4	0.511

M/F, Male/Female; BMI, Body Mass Index; MI, Myocardial Infarction; CAD, Coronary Artery Disease

Table 2. Etiological causes observed between groups

Diseases	Traumatic *n=3 (%)*	Non-traumatic *n=18* (%)
PAD	1 (33.3)	10 (55.6)
DM	0	5 (27.8)
Burger disease	0	1 (5.6)
Traffic accident	2 (66.7)	0
Industrial accident	0	0
Infection	0	2 (11.1)

Comparative evaluation of Tc-99m sestamibi OPS and Doppler Ultrasonography (DUSG)

The study included all patients with DUSG was performed and fifteen of these patients were evaluated as normal, while six evaluated to be pathological. It was decided to amputation of five patients were examined pathologically. In the decision amputation it showed similar results for both examination.

Comparative evaluation of Tc-99m sestamibi OPS and CTA

Computed tomographic angiography of the patients participating in the study was only done to eleven.

Patients 7/11 were assessed as positive while 4/11 were negative. It appeared that of 5 patients evaluated as positive on both tests, all had amputation performed (Table 4).

Figure 1A. Computed tomographic angiography of 65-year-old male patient.

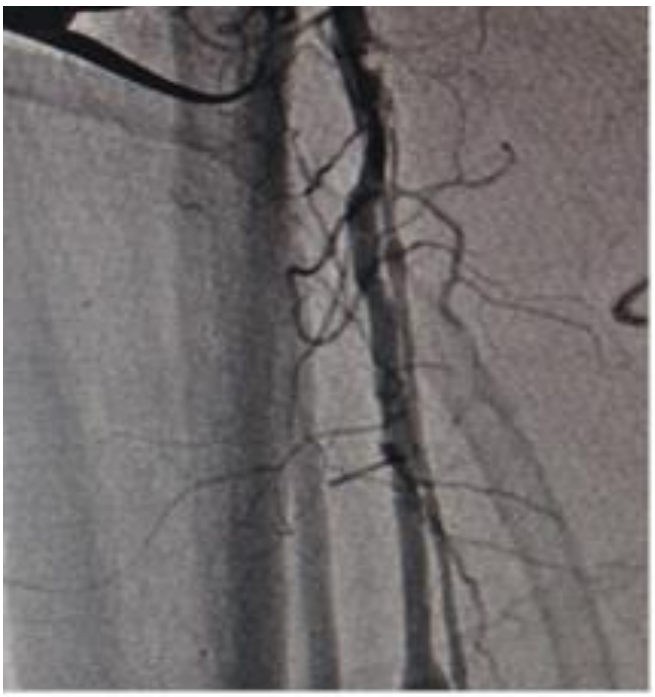

Figure 2A. The angiography of the patient appears to be open after balloon dilation of the vessel lumen

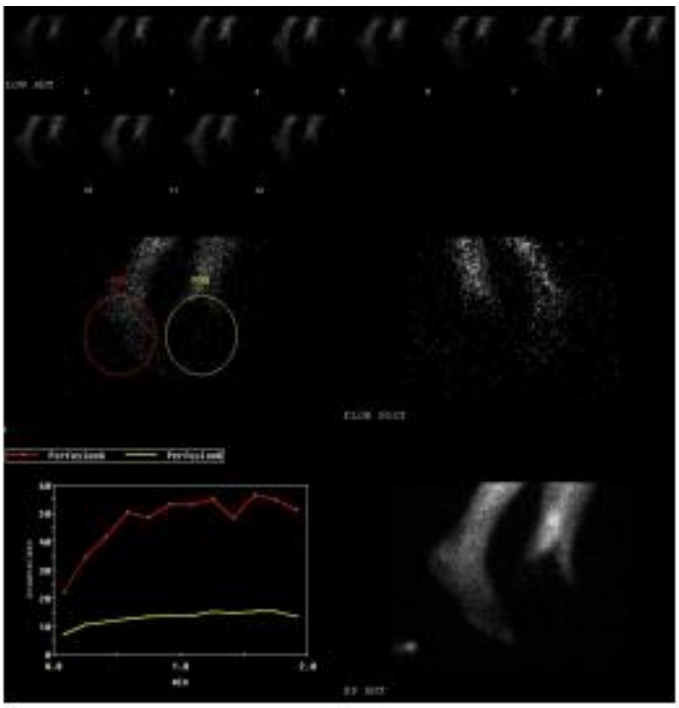

Figure 1B. Tc-99m sestamibi organ perfusion scintigraphy of 65-year-old male patient. Percutaneous Transluminal Angiography performed prior to treatment with the value determined by the left peroneal artery stenosis 90%. Perfusion scintigraphy in the work of the left lower extremity defect. Left lower limb perfusion reserve prior to treatment was <10%.

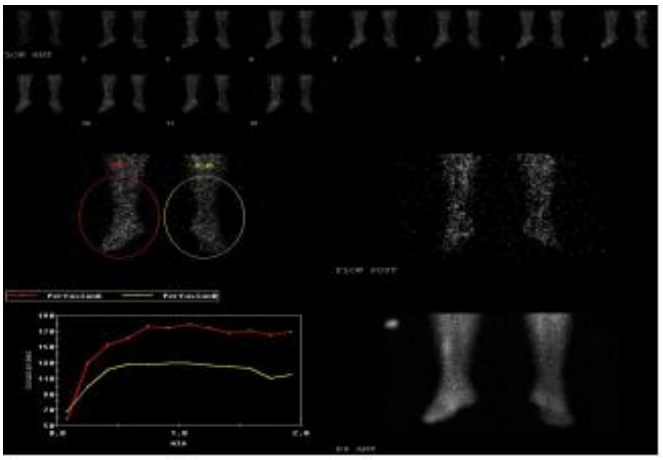

Figure 2B. The control organ perfusion studies performed after treatment (B). Left lower limb perfusion reserve after treatment was calculated as 75%.

Table 3. Comparison of organ perfusion scintigraphy, Doppler ultrasonography, computerized tomographic angiography and operation results.

Patient No	DUSG	OPS	CTA	AMP	PR(%)
1	negative	negative	negative	-	75
2	positive	positive	positive	+	42
3	negative	negative	no CTA	-	65
4	positive	positive	positive	+	38
5	positive	positive	positive	+	29
6	negative	negative	no CTA	-	70
7	negative	negative	negative	-	66
8	positive	positive	positive	+	40
9	negative	suspicious	no CTA	-	53
10	negative	negative	no CTA	-	76
11	negative	negative	no CTA	-	63
12	negative	suspicious	no CTA	-	52
13	negative	suspicious	negative	-	58
14	negative	suspicious	no CTA	-	47
15	positive	suspicious	no CTA	-	51
16	negative	suspicious	no CTA	-	49
17	negative	negative	no CTA	-	69
18	negative	suspicious	positive	-	54
19	negative	suspicious	positive	-	55
20	positive	positive	positive	+	27
21	negative	negative	negative	-	73

OPS, Organ perfusion scintigraphy; DUSG, Doppler Ultrasonography; CTA, Computed Tomographic Angiography; AMP, Amputation
Amputation ;(+): No Amputation (-)
PR, Perfusion Reserve

Table 4. Comparison of the results of other imaging techniques to those of organ perfusion scintigraphy

	DUSG Negative, *n*	DUSG Positive, *n*	CTA Negative, *n*	CTA Positive, *n*
OPS negative	8	0	4	0
OPS positive	2	5	0	5
OPS suspected	5	1	0	2

OPS, Organ perfusion scintigraphy; DUSG, Doppler Ultrasonography; CTA; Computed Tomographic Angiography

DISCUSSION

The aim of this study is to show whether research using Tc-99 m sestamibi for organ perfusion scintigraphy is a useful screening tool for assessment of pre-amputation in lower limb artery disease and to investigate the diagnostic value together with the other imaging findings in evaluation of patients with planned amputation.

In our study Tc-99m sestamibi OPS was found to be a useful method for evaluation of lower extremity perfusion and treatment decisions. Moreover, it was also found to contribute greatly to amputation planning with other investigation methods.

Currently many invasive and non-invasive assessment methods are used to research lower extremity artery patients. However, no single method is sufficient to research patients and make the decision for serious operations planned like amputation [12].

In addition to a good physical examination to research lower extremity artery disease, the first non-invasive test is Ankle Brachial Index (ABI). ABI is an economic and quick test practically applied in clinical practice. However, this test provides high false positive values linked to sclerotic blood vessel in diabetic patients and the elderly [13]. Thus, there is a need for other tests for diabetic patients and the elderly. There are studies reporting that radionuclide methods are useful to research lower extremity perfusion in diabetic patients [14, 15].

In previous studies conducted in diabetic patients, Duet et al. [16] reported that radionuclide perfusion scintigraphy was a more beneficial method compared to ABI. In our study, in diabetic patients, the ankle brachial index patients not achieving results be compared with organ perfusion scintigraphy.

In recent years different radionuclides have been used to research lower extremity peripheral artery diseases and comparison studies with different investigation methods are found. Some of these studies have attempted to emphasize the advantages and disadvantages of each of these methods.

Segall et al. [17] in a comparison study of lower extremity radionuclide perfusion scintigraphy and contrast angiography, reported that radionuclide perfusion scintigraphy was a beneficial technique to research peripheral artery diseases with sensitivity of 80% and specificity of 73%.

CTA is a non-invasive method imaging intravenous stents and bypass in addition to blood vessel structure. It used to research peripheral artery diseases. But, some difficulties linked to artifacts, its use is limited due to the high radiation level compared to other tests, potential risk of nephrotoxicity and insufficient imaging of proximal stenosis and small stenosis in the periphery [18].

In the presence of such conditions, Tc-99m sestamibi OPS has accepted superior aspects compared to CTA. The low radiation level, easy application and repeatability in each patient, along with non-invasive and inexpensive, due to it is chosen before CTA. In our study Tc-99m sestamibi OPS and CTA evaluated

patients with amputation performed with the same accuracy. As a result, it is a test that should not be ignored when deciding on advance testing and treatment of patients.

DUSG is a non-invasive test that both functionally and anatomically evaluates lower extremity blood vessel used in LEPAD research. Clinically it is easily performed, though assessment differences among operators, difficult evaluation of calcified veins and difficult evaluation of the whole body at the same time lead to the requirement for alternative additional tests [19].

In a study by Verim et al. [20], DUSG was shown to be a beneficial method in the diagnosis and monitoring of peripheral vascular diseases. In our study, evaluation of organ perfusion scintigraphy with DUSG provided additional information about both perfusion and vessel structure of lesions.

Organ perfusion scintigraphy is a non-invasive test, with significant advantages compared to other imaging methods due to providing accurate information on the level and severity of lesions, using lower ionizing radiation, being cheap and repeatable, and providing both physiological and functional information. [21].

A significant benefit of our study is that in addition to observing the physiological changes occurring in PAD with organ perfusion scintigraphy, this nuclear medicine method was shown to be very beneficial as a potential guide to evaluate patients before undergoing vascular interventions or amputation.

Another potential benefit is that it compares many imaging modalities to research peripheral vascular disease in the same study. Another benefit is that in patients with planned amputation, it is beneficial as it provides more information for treatment decisions for the majority of patients, confirms diagnosis and provides information about lesion location and severity, in addition to other investigation methods.

Limitations of the study

There are several major limitations of the study. Firstly, our study is retrospective and was completed with a small patient group. In the future, studies with larger groups are required. Secondly, monitoring of cases with vascular intervention or after amputation could not be followed. Studies including information from patients before treatment and after both procedures are needed. Finally, as our study is imaging based, to evaluate the diagnostic efficacy of our tests, all patients should not be compared with the standard reference test of catheter angiography.

CONCLUSION

If peripheral artery disease is considered a functional problem, clinical evaluation with mostly morphological and limited hemodynamic data is insufficient and as a result the need for physiological and functional investigation methods is understood. When evaluated with the benefit principle in choice of methods, the necessary criteria are be harmless and low cost. As a result organ perfusion scintigraphy is a required test that should not be ignored in the general diagnostic approach to lower extremity perfusion evaluation. When used with other non-invasive imaging methods of ABI and DUSG, it is clearly a useful method for diagnosis and monitoring of lower extremity peripheral vascular disease.

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