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The effect of end-systolic volume on ejection fraction in gated myocardial perfusion scintigraphy

Gated myokard perfüzyon sintigrafisinde sistol sonu volümün ejeksiyon fraksiyonuna etkisi

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SUMMARY

Objective: We aimed to investigate patient-related factors that might lead to calculation bias in the ejection fraction (EF), obtained by Myocardial Perfusion Scintigraphy (MPS). In this respect, relationships between EF and some biological and morphological parameters such as gender, left ventricular (LV) volumes, LV areas, beat per minute (BPM) were evaluated in 2 groups of patients (EF normal, above normal).

Method: Patients with hypertension, diabetes, CAD, MI, cardiomyopathy, heart failure, left bundle branch block, electrocardiogram (ECG) signs or suspicion of MI were excluded. 87 patients (37 male, 50 female, mean of age: 59 ± 12; 57 ± 11 years) who have visually and quantitatively normal MPS were included to the study. One day stress Tc99m-MIBI gated SPECT protocol was performed. A commercial software (QGS) was used for calculations. Patients were divided into two groups according to the average EF: 72.5 ± 10%; Group 1: EF>72% and Group 2: EF 50-72%.

Results: Statistically significant correlation (p=<0.001) was noted between EF and end-systolic volume (ESV) (r=-0.89), end-diastolic volume (EDV) (r=-0.75), maximum LV area (LVA max)(r=-0.79) and minimum LV area (LVAmin) (r=0.90) both in two groups; while there was significant a weak correlation with BPM (p<0.03). The ESV was <20 mL in all patients in Group 1. Therefore, patients in Group 2 were divided into two sub-groups, such that Group2a consisted of patients with ESV<20 mL and Group2b with ESV>20 mL. While significant correlation was observed between EF with ESV, EDV, LVAmax and LVAmin. values in 29 patients of Group 2b (p<0.001), there was no correlation in 18 patients of Group 2a (p>0.01).

Conclusion: Although, it is known that EF is overestimated in patients with ESV<20 mL, EF values were within normal range, in a group of patients with ESV<20 mL in our study. Therefore, we believe that EF values have some non-systematic bias, probably resulting from the calculation technique and partial volume effect that there is a need for correction parameters to improve the accuracy of the quantitative evaluation in MPS.

Keywords: Myocardial perfusion scintigraphy, ejection fraction, end-systolic volumes

ÖZET

Amaç: Myokard perfüzyon sintigrafisi (MPS) aracılığıyla hesaplanan ejeksiyon fraksiyonu (EF) değerindeki hata payına sebep olabilecek hasta kaynaklı nedenleri araştırmayı hedefledik. EF ile cinsiyet, sol ventrikül (SV) volümleri, SV alanları, kalp frekansı (DAS) gibi biyolojik ve morfolojik parametreler arasındaki ilişkiyi 2 grup hastada (EF normal; normalin üstünde) inceledik.

Yöntem: Kliniğimizde MPS için gelen hastalardan hipertansyion, diabet, KAH, MI, kardiyomyopati, kalp yetmezliği, sol dal bloğu, elektrokardiyogramda (EKG) MI bulgusu yada şüphesi olanlar çalışma dışı bırakıldı. MPS'si görsel ve kantitatif olarak normal raporlandırılan 87 hasta (37 E/erkek, 50 K/kadın; yaş ortalaması: 59 ± 12; 57 ± 11yıl) çalışmaya alındı. Tek gün stres Tc-99 m MIBI gated SPECT protokolü uygulandı. Hesaplamalarda ticari program (QGS) kullanıldı. Ortalama EF: %72,5 ± 10 olması üzerine, hastalar 2 gruba ayrıldı; EF>%72 olanlar 1. grup, EF: %50-72 olanlar 2. grup.

Bulgular: İki grupta EF değeriyle sistol sonu volüm (SSV) (r=-0,89), diyasol sonu volüm (DSV) (r=-0,75), en büyük SV alanı (EBSVA) (r=-0,79) ve en küçük SV alanı (EKSVA) (r=0,90) arasında istatiksel olarak anlamlı korelasyon saptanırken (p<0,001); DAS arasında zayıf korelasyon saptandı (p<0,03). Birinci gruptaki hastaların hepsinde SSV<20 mL bulundu. Bu nedenle 2. gruptaki hastalar SSV<20 mL (2a grup); SSV>20 mL (2b grup) olmak üzere iki alt guruba ayrıldı; 2b grubundaki 29 hastada EF ile SSV, DSV, EBSVA ve EKSVA değerleri arasında anlamlı korelasyon saptanırken (p<0,001); 2a grubundaki 18 hastada korelasyon saptanmadı (p>0,01).

Sonuç: SSV<20 mL olanlarda EF normalin üstünde hesaplandığı bilinmesine rağmen çalışmamızda SSV<20 mL olan bir grup hastada EF değeri normal hesaplandı. Bu nedenle EF değerlerinde sistemik olmayan bazı hatalar bulunduğunu; muhtemelen hesaplama tekniği ve parsiyel volüm etkisinden kaynaklandığını ve MPS de kantitatif değerlendirmenin doğruluğunun geliştirilebilmesi için düzeltme parametrelerine ihtiyaç olduğunu düşünüyoruz.

Anahtar sözcükler: Myokard perfüzyon sintigrafisi, ejeksiyon fraksiyonu, sistol sonu volüm

INTRODUCTION

In myocardial perfusion imaging, gated SPECT data acquisition with the option of calculating end-diastolic volumes (EDV), end-systolic volumes (ESV) and left ventricular ejection fraction (EF) has been established and validated[1]. Electrocardiographically gated SPECT allows myocardial perfusion imaging (MPS) with simultaneous analysis of regional wall motion and thickening, calculation of global function from ESV, EDV and EF[2]. A number of different software programs for determining left ventricular volumes by MPS have been developed. QGS (quantitative gated SPECT), Emory Cardiac Toolbox, Myo Metrix, Exini Heart and CARE Heart are some of them in which the quantification algorithms have been validated by cardiac MRI, employ varying algorithmic approaches to quantify LV volumes[3, 4, 5]. EDV, ESV, and EF are powerful and reliable predictors of long-term prognosis[6, 7]. They are prognostic parameters and have therapeutic relevance for different cardiac diseases[8, 9]. A number of studies since the 1990s have dealt with quantification of SPECT and functional parameters such as EF, EDV and ESV correlate well with those from left ventriculography, gated blood-pool studies and magnetic resonance imaging (MRI)[10]. However, it is well known that in a small LV volume the ESV is underestimated and EF is overestimated, and the errors are greater in women perhaps because of partial volume effect[11].

In our clinic, we also observed that some patients have higher EF rates than expected. On the other hand, EF values were in the normal range in some other patients with small ventricule volumes. Therefore, apart from a small LV volume of partial volume effect, we hypothesized that some biological and morphological parameters might lead to calculation bias in the EF, obtained by MPS. Thus, in the present study we aimed to evaluate the relationship between age, gender, BPM, EDV, ESV, area of LV with EF rates in patients either with normal or higher EF rates.

MATERIAL AND METHODS

Study population

A total of 87 patients were retrospectively included from consecutive series of patients, examined between December 2014 and January 2015 referred to our clinic for MPS for suspected coronary artery disease (CAD). All patients were instructed to avoid caffeine-containing products for at least 24h before the test, to stop calcium antagonists and β-blockers before 48h, nitrate preparations were withheld on the day of the MPS study. Two experienced physicians interpreted all examination results. The interpretations were done at the time of clinical reporting; clinical information and the results of the stress test were available to the physicians. Patients were included in the study group if they had no abnormality in stress perfusion imaging. Patients with hypertension, diabetes, CAD, MI, cardiomyopathy, heart failure, left bundle branch block, electrocardiogram (ECG) signs or suspicion of MI were excluded.

Gated SPECT imaging

All patients underwent stress 99mTc-MIBI gated SPECT using one day protocol. After 4-6h of fasting the patient underwent either a physiological stress (Bruce protocol) or a pharmacological stress test (oral dipyridamole).

At peak exercise, a bolus of 370MBq of 99 mTc-MIBI was intravenously injected. In the pharmacological stress test; 45 minutes after the 300 mg dpyridamole was administered orally, 370 MBq of 99 mTc-MIBI was intravenously injected. 30 minutes after 99 mTc-MIBI was injected; Gated SPECT was performed in the prone position using a dual-head gamma camera in the 90^0 setting (Dual-Head Variable-Angle ECAM; Siemens) equipped with high-resolution, low-energy collimators. The two heads were placed in an L-shaped configuration. Thirty two views over a 180^0 arc were obtained from the 45^0 right anterior oblique to the 45^0 left posterior oblique. Images were acquired for 25 sec per view with a zoom factor of 1.45 and gated at 8 frames per cardiac cycle using an R-wave trigger. The images were stored in 64×64 matrix in the computer. The reconstruction of gated data was done using filtered back-projection with a Butterworth filter (cut-off 0.4; power 5.0). No attenuation or scatter correction was used. After filtered back-projection, short-axis, vertical, and horizontal long-axis tomograms were generated. A commercially available software program QGS (Cedars-Sinai Medical Center, LosAngeles,CA,USA; 2009) was used to automatically calculate EF, EDV, ESV, BPM, LV area minimum and LV area maximum. Left ventricular ejection fraction was calculated as EDV-ESV/EDV×100. In the present study, patients were further divided into two groups; first group with EF ≥72% and second group with EF: 50-72%. Therefore, patients in Group 2 were divided into two sub-groups, such that Group 2a consisted of patients with ESV<20 mL and Group 2b with ESV>20 mL.

Statistical analysis

SPSS (version 20) was used for statistical calculations. All of the data were expressed in mean ±SD. Pearson's correlation analysis was used to test associations between variables. Unpaired Student's t test was used to test differences between groups, where appropriate. A $p<0.05$ was accepted as significant.

RESULTS

The 99 mTc-MIBI gated SPECT findings were within normal limits in all of 87 patients (37 male; mean age: 59 ± 12years; 50 female; mean age: 57 ± 11years).

The distribution of EF values in male and female patients showed differences; mean of EF was 72.5 ± 10% in all patients (n=87), mean of EF in female patients (n=50) was higher than male patients (n=37) (76.4 ± 4.7%vs67.2 ± 9.9%). No significant correlation was found between EF and age in male ($r=0.21$; $p>0.12$), also in female patients ($r=0.25$, $p>0.14$). There was a good correlation between the EF values and ESV ($r=-0.89$; $p<0.001$), EDV ($r=-0.75$; $p<0.001$), LV area max. ($r=-0.79$; $p<0.001$) and LV area min. ($r=0.90$; $p<0.001$), as expected. There was a weak correlation between BPM and EF ($r=0.24$; $p<0.03$). The mean of EF, BPM, ESV, EDV, LV area max. and LV area min. were shown in Table 1.

In our study, in accordance with the mean of EF being 72.5 ± 10%, patients were divided into two groups, those who had higher EF than normal were named as Group1 (EF>72%); those who had normal EF were named as Group2 (EF: 50-72%) (Figure1).

The mean of EF, BPM, ESV, EDV, LV area max. and LV area min. of all groups were shown in Table2.

31 (77%) of 40 patients were women, 9 (23%) were men in Group1. While a significant correlation was detected in values of EF and ESV($r=-0.93$; $p<0.001$), EDV($r=-0.76$; $p<0.001$), LV area max. (r=-

0.75; p<0.001) and LV area min. (r=0.88; p<0.001) between women and men; there was no significant correlation between BPM and EF (r=0.21; p<0.2). The correlation between the values of EF, BPM, ESV, EDV, LV area max and LV area min. in all groups were shown in Table 3. In Group 1, ESV values were found to be smaller than 20 mL in both women and men patients. Besides, EDV of all patients was below 70 mL except one patient.

Table 1: Functional parameters in the study patients obtained from QGS software (Mean ± SD). Note that ESV was calculated as if zero mL. in some patients.

Variables	All patients (n:87)	Male (n:37)	Female (n:50)	P value
EF (%)	72.5±10.0 (51-100)	67.2±9.9 (51-100)	76.4±4.7 (51-99)	<0.001
EDV (mL)	55.8±15.0 (26-108)	62.0±17.6 (26-108)	50.0±10 (32-74)	<0.001
ESV (mL)	16.7±10.1 (0-49)	21.8±10.8 (0-49)	12.9±7.6 (0-34)	<0.001
BPM (beat/min)	81.2±12.7 (55-111)	79.9±13.4 (55-111)	82.1±12.3 (54-110)	<0.5
LVareamin (cm^2)	62.9±15.0 (20-102)	69.7±16.2 (20-102)	57.8±11.8 (28-85)	<0.001
LVareamax (cm^2)	93.0±14.2 (57-138)	98.9±16.2 (57-138)	88.6±10.6 (66-110)	<0.001

EF: left ventricular ejection fraction. **EDV:** end-diastolic volume **ESV:** end-systolic volume **BPM:** Beats per minute. **LVarea min:** minimum left ventricular area. **LVarea max:** maximum left ventricular area

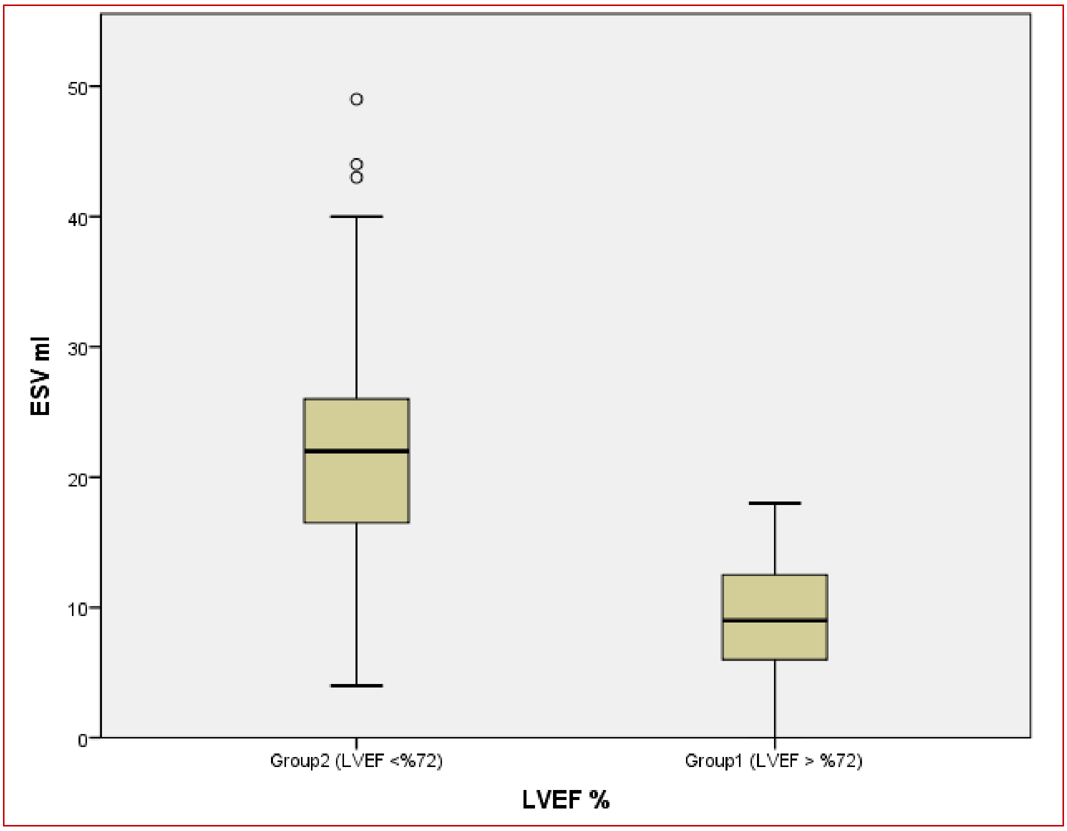

Figure 1: Comparison of end systolic volume distributions in the study groups; Group 1 (EF>72%) vs. Group 2 (EF: 50-72%)

Table 2: Distribution of the studied parameters according to patient groups.

Variables	Group I (≥EF%72) (no=40)	Group II (EF%50-72) Group 2a (n=18)	Group 2b (n=29)
EF (%)	81.7 ± 7.3	69.3 ± 3.1	61.6 ± 5.1
EDV (mL)	46.9 ± 9.7	53.3 ± 5.1	70.3 ±15.1
ESV (mL)	9.2 ± 4.8	15.1 ± 3.4	28.2 ± 7.7
BPM	83.2 ± 13.4	83.3 ± 11	76.3 ±11.5
LVarea min	51.9 ± 10.3	62.6 ± 6.9	79.2 ± 9.1
LVarea max	83.9 ± 10.0	79.2 ± 9.2	70.3 ± 15.0

EF: left ventricular ejection fraction. **EDV:** end-diastolic volume **ESV:** end-systolic volume **BPM:** Beats per minute. **LVarea min:** left ventricular area minimum cm². **LVarea max:** left ventricular area maximum cm².

Table 3: Correlation between the EF values and ESV, EDV, BPM, LV area max., LV area min. values in patient groups.

	ESV mL	EDV mL	BPM	LV areamax.	LV areamin.
	r	r	r	r	r
Group 1 (n:40) EF%	-0.93 (p<0.001)	-0.76 (p<0.001)	0.21 (p<0.2)	-0.75 (p<0.001)	-0.88 (p<0.001)
Group 2 (n:47) EF%	0.79 (p<0.001)	-0.58 (p<0.001)	0.20 (p<0.2)	-0.61 (p<0.001)	-0.76 (p<0.001)
Group 2a (n:18) EF%	-0.46 (p<0.05)	0.45 (p<0.05)	0.07 (p<0.8)	0.26 (p<0.3)	-0.28 (p<0.03)
Group 2b (n:29) EF%	-0.67 (p<0.001)	-0.47 (p<0.001)	-0.04 (p<0.9)	-0.51 (p<0.001)	-0.64 (p<0.001)

EF: left ventricular ejection fraction. **EDV:** end-diastolic volume. **ESV:** end-systolic volume. **BPM:** Beats per minute. **LVarea min:** left ventricular area minimum cm². **LVarea max:** left ventricular area maximum cm²

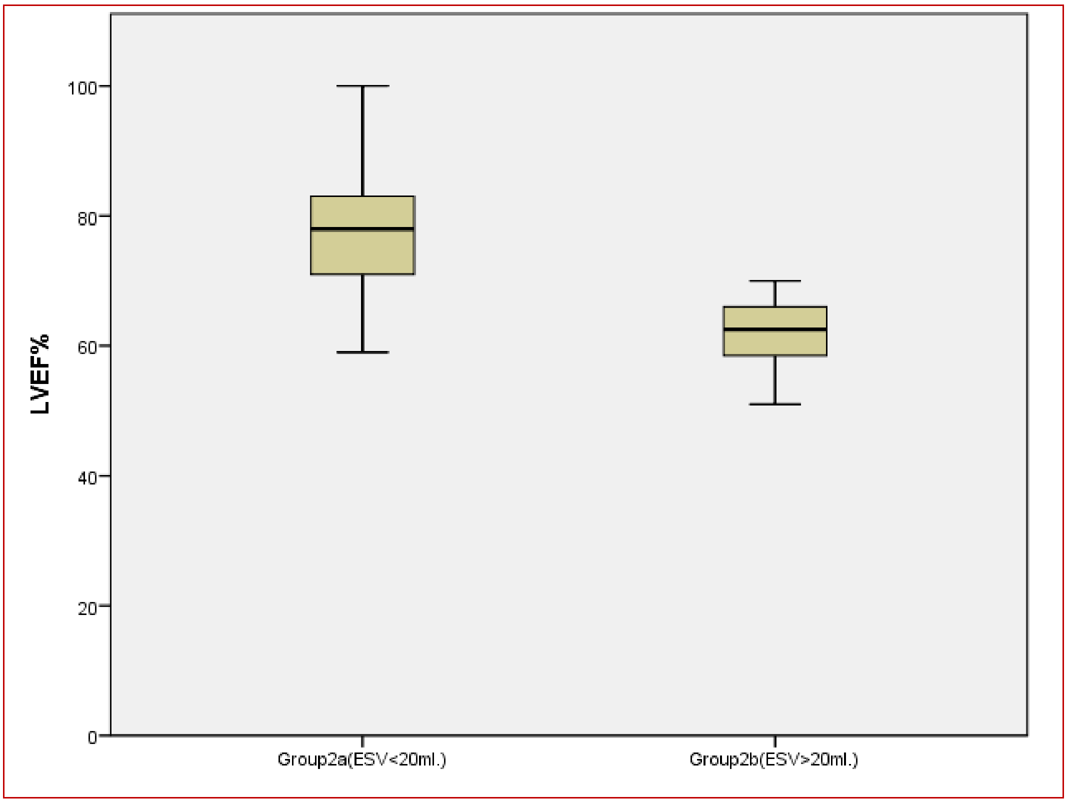

Figure 2: Comparison of EF% values in the study groups; Group 2a: ESV<20 mL, Group 2b: ESV>20 mL.

19 (40%) of 47 patients were women, 28 (60%) were men in Group 2. While a significant correlation was detected in values of EF and ESV (r=-0.79; p<0.001), EDV (r=-0.58; p<0.001), LV area max. (r=-0.61; p<0.001) and LV area min. (r=-0.76; p<0.001) between women and men; there was no significant correlation between BPM and EF (r= 0.20; p<0.2) (Table 3).

EF values in group1 were detected as over mean in all patients, Group 2 was divided into two subgroups according to the ESV values whether they are below or above 20 mL. Group 2a: ESV<20 mL, Group 2b: ESV>20 mL (Figure 2).

In Group 2a, 10 (55%) of 18 patients (EF mean: 69.33 ± 3.18%); were women, 8 (45%) were men (EF mean: 68.38 ± 4.17%). The mean of EF, BPM, ESV, EDV, LV area max. and LV area min. were shown in Table 2. There was a weak statistically significant correlation between the values of EF and ESV, EDV and no statistically significant correlation between the values of EF and LV area max., LV area min. and BPM (Table 3). However, there was statistically significant correlation between the values LV area max and EDV; LV area min and ESV in Group 2a without any gender discrimination (p<0.001).

In Group 2b, 9 (31%) of 29 patients (EF mean: 61.66 ± 5.06%) were women (EF mean: 63.78 ± 5.40%), 20 (%69) were men (EF mean: 63.78 ± 5.40%). The mean of EF, BPM, ESV, EDV, LV area max. and LV area min. were shown in Table 2. There was statistically significant correlation between the values EF and ESV, EDV, LV area max. and LV area min. between women and men. However, there was no statistically significant correlation between the values BPM and EF (Table3). Besides, there was statistically significant correlation between the values LV area max and EDV; LV area min and ESV in Group 2b without any gender discrimination (p<0.001).

DISCUSSION

Today, ECG-gated 99 mTc-MIBI SPECT myocardial perfusion scintigraphy is quite commonly used method in diagnosing cardiovascular disease, establishing prognosis, evaluating viability and left ventricular functions with calculation of EF. Therefore, the accurate determination of EF and left ventricular function plays an important role in the follow-up of the disease[2, 12]. Scintigraphic evaluation of the left ventricular functions is realized by the help of ready to use softwares. We calculated EF values with the QGS program which is one of the most widely used ones in our country and that we have been using it in our clinic for couple of months. Indeed, all programs use similar automated algorithms. For example, first step is to approximate the location of the LV in the image. And, the endocardial and epicardial surfaces are defined on each side of this centerline. The program draws an ellipsiod to these groups of voxel and uses asymmetric Gaussian curves defining endocardial and epicardial surfaces. So EF, EDV, ESV are calculated automatically[13].

Meanwhile, we observed that some patients have higher EF rates than expected. It is well known that in a small LV volume the ESV is underestimated and EF is overestimated, and the errors are greater in women perhaps because of partial volume effect. On the other hand, EF values were in the normal range in some other patients with small ventricule volumes. Therefore, apart from a small LV volume of partial volume effect, we hypothesized that some biological and morphological parameters might lead to calculation bias in the EF, obtained by MPS. We aimed in the present study to evaluate the relationship between EF and gender, ESV, EDV, BPM, LV area max. and LV area min. in 2 groups of normal patients; as with “normal” and “above normal EF” values, calculated by QGS. Our study showed differences in the distribution of EF values in male and female patients. The mean of EF value in female patients was found to be higher, as expected[11]. However, in group1; 77% of 40patients were women with ESV<20 mL and EDV<70 mL (except for one patient) but, there was no significant difference

between both genders with respect to EF values.
We observed a weak correlation between EF values with heart frequency ($r=0.24$; $p<0.03$). Like in the study of Itti et al.[14]. Rest/ redistribution 201 Tl gated SPECT protocol was applied to 75 patients with MI, EF values were calculated with QGS and Myo Track program and they could not find statistically significant correlation between BPM and EF values, as similar to our study. Sharir et al.[15] studied EF and LV volumes which have been calculated by the QGS program in diabetic, hypertension, revascularized patients. Our study consisted of only patients with normal MPS with no known risk factor. Our study results seem quite different as compared to theirs. Such as EF values were 67% in our study but 43% in their study and ESV values were 22% vs 75%. We believe that the probable reason is that the studied patient groups were very different. Indeed, no need to say that the clinical background of patients creates significant impact on left ventricular functions. However, it is hard to explain why were ESV values so small (even zero) in some patients in our study.

Nakajima et al.[16] compared EF, EDV and ESV values of patients with small hearts, using QGS and EXINI programs, with that of a digital phantom and with the data analysis results of the Japanese Society of Nuclear Medicine (JSNM) group, performed in 2007. The main outcome of the study was that the EF values calculated by the QGS program were found to be higher than those calculated by the EXINI program. EF values of patients with ESV<20 mL in our study and theirs were found to be higher than those with ESV>20 mL. In the study of Nakajima et al.[16], ESV<20 mL was taken as a threshold for the small heart-determination. The overestimation of EF values in patients with ESV<20 mL may result from the partial volume effect in small hearts. EF values calculated as higher than the normal is thought to be as a result of the perception of the ventricular volume smaller than the actual volume (partial volume effect) due to the short distance between ventricular walls.

Patrik et al.[17] also suggested in a smilar study that EDV value was calculated as lower than expected, so as EF value, because of the intermingling of voxels (partial volume effect) determining the endocardial are during the diastolic and systolic movement of the heart. In that study, EF values were found to be higher than normal in patients with EDV<70 mL who were thought to have small heart. In our study, all patients with EF≥72% had EDV<70 mL in Group 1, except one patient.

Various methods have been proposed to reduce the effect of small heart in many studies. For example, increasing zoom factor or changing filter type or changing cut-off value in butter worth filter. However, the use of these applications in routine is not practical and it has been reported that EF values were overestimated in these studies, as well[18].

In the present study, we investigated relationship between EF and the functional left ventricular volumes and size in patients with normal and above normal EF by correlation analysis. It is a well-known principle the statistics that among the parameters that are already associated with each other, using “correlation” analysis is irrelevant. EF is derived data from EDV and ESV. Hence, what we were already looking for was not the relationship between them. Instead, we were looking for where was the relationship broken. Surprisingly in our study, there was a weak significant correlation between EF values and ESV ($r=-0.46$; $p<0.05$), EDV ($r=0.45$; $p<0.05$) and no significant correlation between EF values LV area max. ($r=0.26$; $p<0.3$), LV area min. ($r=-0.28$; $p<0.3$) values of women and men patients in group 2a, unlike the other groups. Although, there was a significant correlation between LV area max. and EDV; LV area min. and ESV in group 2a, like the other groups. The most important point is that although ESV values were below 20 mL, EF values were calculated as normal in these patients. EF values might be actually low in these patients. However, calculated EF values as if were normal because they had small heart. Factors that cause this condition may be the technical reasons such as unsuitable cardiac ROI, miscalculation EDV or ESV or the patient-related factors other than the ischemia, such as bowel activity, heart failure, cardiomyopathy or cardio toxic chemotherapy.

In conclusion; we believe that EF values have some non-systematic bias, probably resulting from the calculation technique and that there is a need for correction parameters to improve the accuracy of the quantitative evaluation in MPS.

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