



A Different Scintigraphic Perspective on the Systolic Function of the Left Ventricle-I

Sol Ventrikülün Sistolik Fonksiyonuna Sintigrafik Olarak Farklı Bir Bakış Açısı-I

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Abstract

Objectives: The aim of this study was to analyze the systolic part of the left ventricular (LV) volume curve obtained by gated myocardial perfusion imaging with the formula used in exponential decay and to investigate the clinical value of the results.

Methods: One hundred fifty eight patients were retrospectively enrolled in the study. The study group was divided into three groups as normal, ischemia, and infarct. The systolic portion of the LV volume curve was also analyzed using the exponential decay formula. The scintigraphic parameter obtained using this formula is called the ejection constant (Ec).

Results: The Ec results were 1.8 ± 0.8 , 2.7 ± 0.9 , 3.5 ± 1 in infarct, ischemia, and normal groups, respectively, and the difference in Ec results between the groups was statistically significant ($p\leq 0.001$).

Conclusion: It appears that Ec may play a clinical role as a scintigraphic parameter in the evaluation of systolic functions of the left ventricle.

Keywords: Exponential decay, time-volume curve, the left ventricle, gMPI

Öz

Amaç: Bu çalışmanın amacı, üstel bozulmada kullanılan formül ile gated miyokard perfüzyon görüntüleme ile elde edilen sol ventrikül (LV) hacim eğrisinin sistolik kısmını analiz etmek ve sonuçların klinik değerini araştırmaktır.

Yöntem: Yüz elli sekiz hasta geriye dönük olarak çalışmaya alındı. Çalışma grubu normal, iskemi ve enfarktüs olmak üzere üç gruba ayrıldı. LV hacim eğrisinin sistolik kısmı da üstel bozulma formülü ile analiz edildi. Bu formülle elde edilen sintigrafik parametreye ejeksiyon sabiti (Ec) adı verilmiştir.

Bulgular: Enfarktüs, iskemi ve normal gruplarda Ec sonuçları sırasıyla $1,8\pm 0,8$, $2,7\pm 0,9$, $3,5\pm 1$ idi ve gruplar arasındaki Ec sonuçları farkı istatistiksel olarak anlamlıydı ($p\leq 0,001$).

Sonuç: Sonuç olarak, Ec'nin LV'nin sistolik fonksiyonlarının değerlendirilmesinde sintigrafik bir parametre olarak klinik bir rolü olabileceği görünmektedir.

Anahtar kelimeler: Üstsel azalma, zaman-hacim eğrisi, sol ventrikül, gMPS

Introduction

Electrocardiography (ECG)-gated myocardial perfusion imaging (gMPI) is the most widely used nuclear imaging modality for the diagnosis and management of coronary

artery disease because in addition to the assessment of regional myocardial perfusion, it allows the simultaneous evaluation of left ventricular (LV) volumes, synchronization of the onset of mechanical contraction of the left ventricle, and regional ventricular systolic and diastolic functions at

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post-stress gated examination (1,2,3,4,5). The 16-phase gMPI allows for the automatic generation of the time-volume curve of the left ventricle (6,7,8). The portion of the time-volume curve of the left ventricle corresponding to systole is non-linear (Figure 1) and shows a continuous exponential decrease. Since, in exponential decay, the decay factor relies on a percentage of the original amount, which means that the actual number by which the original amount might be reduced will change over time, it is different from linear decay in which the original number decreases by the same amount every time (9,10,11,12). Therefore, the systolic part of the LV volume curve can be analyzed with a formula of continuous exponential decay.

The aim of this study was to analyze the systolic part of the LV volume curve obtained by gMPI using the formula used in exponential decay and to investigate the clinical value of the results.

Materials and Methods

Patients

From March 2021 to March 2022, 158 patients (67 women, 42.4%, mean age: 62 years, age range: 31-79 years, 91 men 57.6%, mean age: 61 years, age range: 34-87) who were referred to our department for stress-rest gMPI for suspected coronary artery disease were retrospectively enrolled in the study. Patients had a history of one or more of the following findings: previous positive treadmill test, atypical chest pain, shortness of breath with or without atypical chest pain, typical chest pain, or respiratory distress alone. The height and weight of the patients were recorded to calculate the body surface area (BSA). Technical failure to evaluate the scans and infidelity

to instructions were the reasons for patients to be excluded from the study. Patients with bundle branch block, cardiac pacemaker, atrial fibrillation, valve disease, and images that were not evaluated for technical reasons were excluded from the study. According to our acquisition protocols, all patients were instructed to discontinue beta-blockers, calcium antagonists, and nitrates at least 24 h before testing. The University of Health Sciences Türkiye, Gülhane Scientific Research Ethics Committee approved the study protocol (decision no: 2022-278, date: 12.09.2022).

The study group was divided into three groups as normal, ischemia, and infarct, according to their history of heart disease and quantitative and qualitative evaluation of gMPI images. In the gMPI images of the normal group of 51 patients, the biological distribution of the radiopharmaceutical in the left ventricle was within normal physiological limits and the total stress score (SSS) was <4. In the ischemia group of 54 patients, reversible perfusion defects were detected in the gMPI images. Loss and reductions in radiopharmaceutical uptake detected in the left ventricle in stress gMPI images of the ischemia group were normalized in resting single photon emission computed tomography (SPECT) images. The SSS was ≥ 4 in this group. In the infarct group of 53 patients, perfusion defects detected in stress gMPI images persisted in resting SPECT images. In addition, past infarct findings were found in the histories or ECG records of these patients. The SSS was also ≥ 4 in this group. Demographic data of the subgroups of the study population are presented in Table 1.

Stress and Acquisition Protocols

One hundred forty one (~89%) patients underwent an exercise stress test and 17 (~11%) adenosine (Apoteket

Table 1. Demographic data of the study population

	Patient groups					
	Normal (51)		Ischemia (54)		Infarct (53)	
	W (27)	M (24)	W (24)	M (30)	W (14)	M (39)
Age (years)	63	57	62	63	62	63
Height (cm)	160.5	172.4	160	169.8	157	172.6
Weight (kg)	76.9	80.6	79	82.6	74	85
Diabetes	15	6	14	10	8	16
Hypertension	21	12	20	20	14	33
Hyperlipidemia	2	6	10	11	8	19
Family history	9	11	8	11	8	12
Infarct history	1	4	6	8	7	22
Stent history	2	4	9	10	8	21
Bypass history	0	1	4	8	2	8

W: Woman, M: Man

Produktion & Laboratorier AB, Formvagen, Sweden) pharmacologic stress tests. Depending on the patient's ability to exercise and to reach at least 85% of the maximal age-predicted heart rate, symptom-limited treadmill exercise test according to the standard Bruce protocol (stepwise increments of velocity and slope every 3 min) with continuous 12-lead ECG assessment or adenosine ($140 \mu\text{gr/kg/min}$ intravenously over 4 min) was chosen. Of the 141 patients who were submitted to the exercise stress test, 140 reached at least 85% of the expected maximal heart rate. Suboptimal exercise (75%) was administered to one patient in the infarct group where adenosine was contraindicated. According to our two-day stress-rest gMPI clinical protocol, each patient underwent stress gMPI for the first day. The intravenously injected dose of Tc-99m MIBI (Cardio-SPECT, Medi-Radiopharma, Budapest, Hungary) was 222-296 MBq (6-8 mCi) when the patients reached maximum exercise. All ECG-gated SPECT acquisitions were initiated 30 ± 10 min while the patients were in the supine position with arms placed over the head. The next day, rest SPECT imaging was performed 45 ± 15 minutes after the same dose of Tc-99m MIBI was applied to the subjects with perfusion defects on their stress images.

Daily quality control of the gamma camera was performed routinely before the first study of the day. A dedicated cardiac gamma camera (Discovery NM 530c, GE Healthcare, Chicago, Illinois, USA) equipped with a multiple pinhole collimator and 19 stationary cadmium-zinc-telluride detectors was used for patient acquisition. Each detector contained 32×32 pixelated 5 mm thick (2.46×2.46 mm) elements. A window of 15% was centered on the 140 keV gamma peak, and gating was performed with 16 frames per RR interval cycle. List mode files were acquired and stored. Images were reconstructed on the same workstation used for standard SPECT acquisition (Xeleris II, GE Healthcare, Haifa, Israel) using a new dedicated iterative algorithm. A Butterworth postprocessing filter (frequency 0.37, order 7) was applied to the reconstructed slices. Images were reconstructed without scatter or attenuation correction. The R-R acceptance window was set to 25%. Attenuation correction was not used.

Data Analysis

Scintigraphic images were analyzed visually and semi-numerically in consensus by 2 experienced nuclear medicine physicians who were unaware of the content of the study. The LV time-volume curves of the patients were obtained from stress-gMPI scans (Figure 1). Data from the gated SPECT studies of all patients were analyzed using Quantitative Gated SPECT and Quantitative Perfusion SPECT softwares (QGS, QPS, Cedars Sinai Medical center, Los

Angeles, CA, USA). Myocardial segmentation was based on a 20-segment model, and SSS was calculated based on 0-4 points in each segment (0, normal to 4, defect). The ejection fraction (EF), volumes of end-diastolic (EDV) and end-systolic (ESV) were automatically determined using QGS software, and heart rate as beats per minute (BPM) were noted.

Calculations

All continually and exponentially decreasing systems are scaled versions of a common constant represented by "e" (Euler's constant). In addition to a constant, four variables (percent change, time, the amount at the beginning of the time period, and the amount at the end of the time period) play roles in exponential functions. In exponential decreases, the original amount is reduced at a consistent rate over a period of time. The systolic portion of the LV volume curve was also analyzed using this formula, as it shows a continuous exponential decrease pattern.

Systole time was calculated for each patient based on their heart rate using the following method:

If the pulse rate of the patient is 60 beats/min, the duration of each beat is 1000 milliseconds (ms).

Cardiac cycle time (ms) = (1000 ms x 60)/BPM of the patient

Cardiac cycle time (ms) / 16 (total frame number) = Frame time (ms) (Figure 1)

Systolic frame number frame time (ms) = Systole time (ms)

Thus, each patient's systole time, and therefore, the ejection constant (E_c), was indexed to their own BPM.

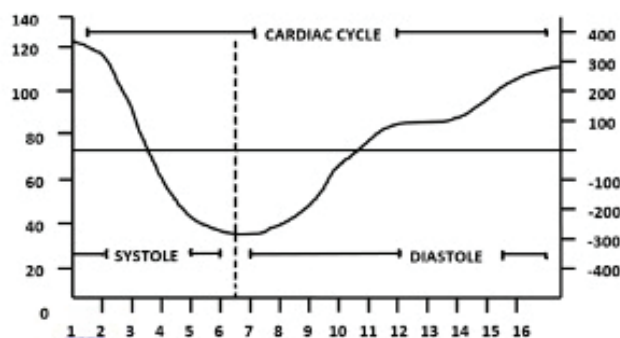


Figure 1. An example of the volume curve of the left ventricle over time in 16-frame gMPI, which was derived using QGS software. It shows that the cardiac cycle is divided into 16 frames. The systolic part of the time-volume curve can be seen as not linear
gMPI: Gated myocardial perfusion imaging, QGS: Quantitative Gated SPECT

Systole time in seconds (s) was used in the formula instead of "t".

The original continuous exponential decay formula is $A_f = A_i e^{-kt}$ where,

A_i = Initial amount or EDV in our study

A_f = Final amount or ESV in our study

e= Euler's constant (2.718...)

k= decay constant, or Ec in this study

t= Time or systole time (s) in this study

The exponential decrease analysis formula used to evaluate the systolic part of the LV volume curve in our study is as following.

$$ESV = EDV \times e^{-kt}$$

Using this formula, the LV emptying rate was calculated for each patient.

BSA is a more accurate indicator of metabolic mass and is used in various clinical settings, such as dosages for chemotherapy or determining the cardiac index, which relates a person's heart performance to their body size. The most widely used of these is the Du Bois formula, which is $BSA = 0.007184 \times W^{0.425} \times H^{0.725}$, where BSA is represented in m^2 , W is weight in kg, and H is height in cm. Each patient's BSA was calculated by using this formula and each result was divided by average BSA of $1.73 m^2$.

Ec is also indexed to BSA using the following method. Indexing measurements by body size is thought to establish limits of normality among individuals varying in body habits.

BSA indexing: Ec result of patient X (BSA of the patient/ $1.73 m^2$).

If the Ec is multiplied by 100, the unit of the result is given as percent reduction per second (Ec x 100= % decrease/second). It is necessary to change the name of the Ec to ejection rate, but we preferred not to multiply by 100 and to use the Ec in this study.

Statistical Analysis

Descriptive analysis was performed to examine the pertinent variables in the study group. Continuous variables are expressed as mean \pm standard deviation (SD). One-Way ANOVA was used to compare the results of the measurements between the groups. The linear relationship between the groups was investigated using the Pearson correlation test. The sensitivity and specificity of Ec in the differential diagnosis between the groups were investigated by receiver operating characteristic (ROC) curve analysis. All p values were two-tailed with a p value <0.05 set priori and used as the level of significance. Statistical analyzes were performed with using SPSS version 22.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

The demographic data of the study population and its subgroups are summarized in Table 1. There was no statistically significant difference between the groups in terms of age, gender, and BSA. The statistical results of the study are summarized in Table 2.

The differences in EF, ESV, EDV, and Ec (with or without BSA index) between the groups were statistically significant. (p<0,001). In post-hoc tests, it was revealed that this difference was due to the statistically significant difference in the mean of each group. There was no statistically significant difference between the groups in terms of other parameters (Table 2). The mean and SD of the Ec and EF results between the groups are compared in Figures 2, 3, respectively.

Table 2. Results data of the study groups

	Patients (158)	Patient groups			p
		Normal (51)	Ischemia (54)	Infarct (53)	
Age (years)	61 \pm 10	60 \pm 11	62 \pm 10	62 \pm 10	0.425
Height (cm)	166.5 \pm 8.9	166 \pm 8.7	165.3 \pm 8	168.3 \pm 9.8	0.199
Weigth (kg)	80.8 \pm 13.3	78.7 \pm 10.9	81 \pm 14	82.4 \pm 14.6	0.343
BSA (m^2)	1.9 \pm 0.2	1.9 \pm 0.2	1.9 \pm 0.2	2 \pm 0.2	0.303
EF (%)	56.3 \pm 14.2	64.9 \pm 9.6	58.2 \pm 12	45.8 \pm 13.4	<0.001
EDV (mL)	100.3 \pm 40.8	76 \pm 19	96.9 \pm 36.7	127 \pm 44.7	<0.001
ESV (mL)	48.8 \pm 35	27.2 \pm 11.9	43.6 \pm 28.8	74.8 \pm 39.2	<0.001
BPM	74 \pm 12	73 \pm 12	72 \pm 11	74 \pm 14	0.565
Ec*	2.4 \pm 1	3.2 \pm 1	2.4 \pm 0.9	1.6 \pm 0.7	<0.001
Ec	2.6 \pm 1.1	3.5 \pm 1	2.7 \pm 0.9	1.8 \pm 0.8	<0.001

BSA: Body surface area, EF: Ejection fraction, EDV: Volumes of end-diastolic, ESV: Volumes of end-systolic, BPM: Beats per minute, Ec: Ejection constant, Ec*: Not BSA indexed

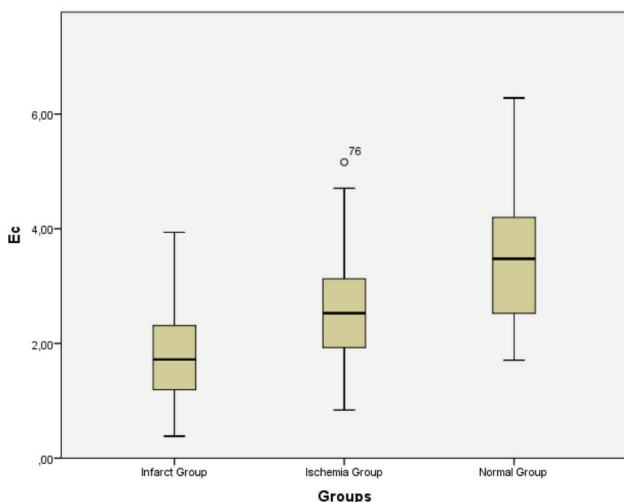


Figure 2. Box and whisker plots of Ec results among the groups
Ec: Ejection constant

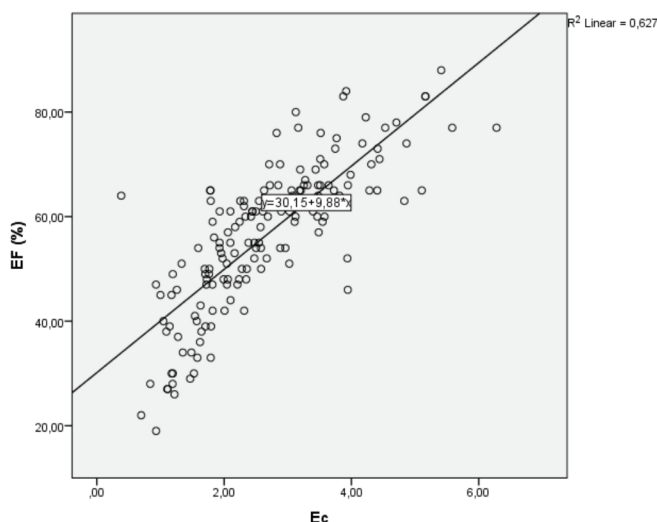


Figure 4. Scatter plot of the correlation between EF and Ec
EF: Ejection fraction, Ec: Ejection constant

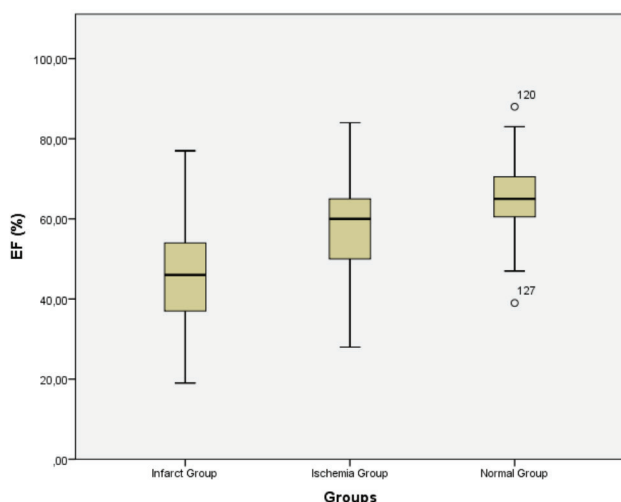


Figure 3: Box and whisker plots of EF results among the groups
EF: Ejection fraction

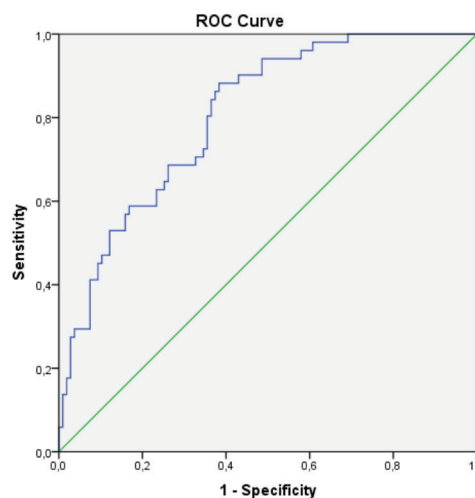


Figure 5. ROC curve between the normal group and others
ROC: Receiver operating characteristic

The correlation coefficient between Ec and EF was excellent ($r= 0.792, p<0.001$) (Figure 4).

If the value of 2.34 is taken as the cut-off, the sensitivity of Ec is 88% and the specificity is 62% in the differential diagnosis between the normal group and others (Figure 5). Area under the ROC curve is 0.805. If the value of 2.47 was taken as the cut-off, the sensitivity of Ec in the differential diagnosis between the ischemia and normal groups was calculated as 80% and the specificity as 50% (Figure 6). The area under the ROC curve is 0.719. If the value of 2.17 is taken as the cut-off, the sensitivity of Ec is 90% and the specificity is 74% in the differential diagnosis of normal and others (Figure 7). Area under the ROC curve is 0.892.

According to the ROC curves, it was noticed that the differential diagnosis of those in the normal group (Figure 8A) and the infarct group (Figure 8B) can be made more easily with Ec compared to those between the ischemia (Figure 8C) and normal groups. The underlying cause may be structural changes that change the shape of the systolic part of the LV time-volume curve more significantly than functional changes.

Discussion

In this study, because the systolic part of the LV volume curve obtained with gMPI shows a continuous exponential

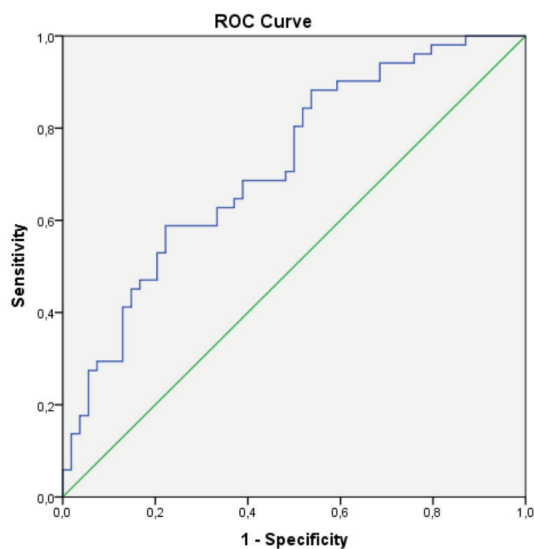


Figure 6. ROC curve between the ischemia and normal groups
ROC: Receiver operating characteristic

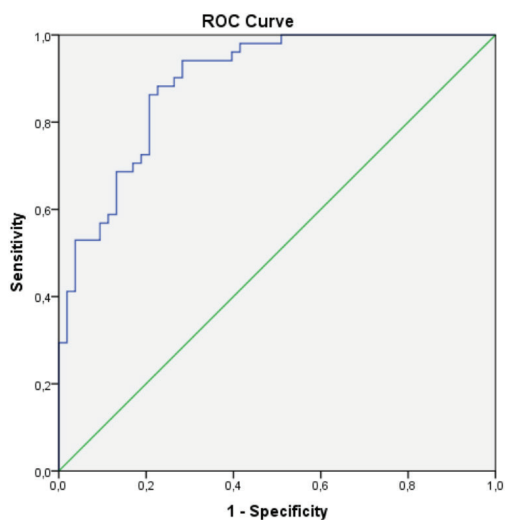


Figure 7. ROC curve between the normal and infarct groups
ROC: Receiver operating characteristic

decrease pattern, it was analyzed mathematically using the exponential decay formula. The parameter obtained using the formula used was named the E_c of the left ventricle. This parameter showed a statistically significant difference between the normal, ischemia, and infarct groups and correlated very well with the EF results of the patients in the study group.

EF is defined as the stroke volume indexed to the EDV, which is calculated from the input (EDV) and output (ESV) data and is one of the most frequently measured variables in clinical practice (13). In addition to contractility of the LV preload and afterload, EF is also affected by changes in heart rate (1). The exponential decay formula in this study gives the percent reduction per unit time, which is constant as the LV moves from EDV to ESV and is indexed to the heart rate and BSA (14,15). The percentage of decreasing volume of the left ventricle per unit time given by the formula seems to indirectly reflect the contraction or myocardial inotropy and afterload of the LV as a whole. We believe that E_c in the exponential decay formula is a scintigraphic parameter that will act like EF in the evaluation of the systolic functions of the left ventricle. The LV EF, a measure of LV systolic performance, reflects the contractility of the LV if abnormal afterload or valvular diseases are absent (16). According to our results, the presence of an excellent correlation between E_c and EF may support this idea.

The LV preload, which is the length of the muscle at the onset of contraction, is clinically assessed by measurements of the pulmonary capillary wedge pressure (6). LV preload can also be assessed from the LV filling pressure, LV EDV, or LV end-diastolic stress (17). In the healthy heart, increases in preload lead to an increase in stroke volume and cardiac output without major change in EF due to the Frank-Starling mechanism, in which myocyte stretch causes a more forceful systolic contraction (1,18). The exponential decay formula used in this study includes the EDV/ESV ratio; therefore, even the same amount of changes in the EDV and ESV values will change the results. On the basis of

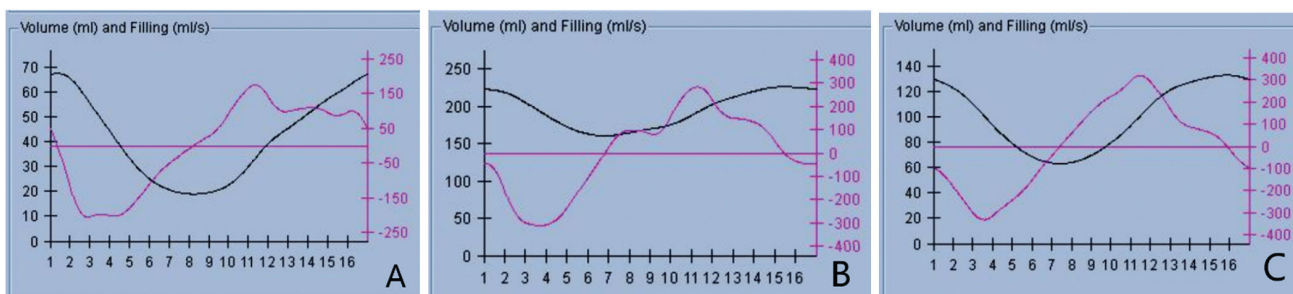


Figure 8. (A) Time-volume curve of a patient in the normal group. (B) Time-volume curve of a patient in the infarct group. (C) Time-volume curve of a patient in the ischemia group

these findings, the exponential decay formula appears to be sensitive to preload changes.

LV afterload may be defined as the tension or stress developed in the LV wall during ejection due to the force against which the myocardium contracts. LV afterload is determined by arterial pressure as well as the volume and thickness of the LV according to Laplace's law (19). Clinically, the level of LV afterload can be estimated by the systolic arterial pressure in the presence of a normal aortic valve (19,20). Afterload affects the workload of the heart and the contractility of the myocardium against this workload. This situation results in structural changes in the myocardium of the left ventricle. Accordingly, the parameters that determine the afterload according to Laplace's law also determine the shape of the systolic curve of the left ventricle. Even if EDV and ESV do not change under these conditions, the shape of the systolic part of the LV time-volume curve changes, and this change can be detected by the exponential decay formula used in this study. The exponential analysis of the systolic part of the LV volume curve seems to can evaluate the combined effect of parameters determining the afterload simultaneously. In fact, it has been reported that LV afterload is determined by complex, time-varying phenomena that affect the pressure and flow patterns produced by the pumping ventricle and cannot be expressed as a single numerical measure or defined in terms of pressure alone (20). However, exponential analysis of the systolic curve seems to have the potential to shed light on this issue.

In addition to contractility of the LV, preload, and afterload, EF is affected by changes in heart rate (1). Because heart rate affects the diastole duration of the cardiac cycle, it also affects the LV filling time or preload. Increased venous return increases ventricular filling, and increasing preload increases the active tension developed by the muscle fiber and increases the velocity of fiber shortening at a given afterload and inotropic state. Therefore, the time interval during ejection of the left ventricle in the exponential decay formula in this study has also been indexed to beat per minute of the LV. Thus, the differences caused by changes in heart rhythm are eliminated. Similarly, the results obtained using the formula were also indexed to the BSA of each patient. Thus, it has been aimed to eliminate the changes that will arise from the mass differences in the patients.

The presence of a statistically significant difference in the E_c results between the patient groups formed according to the presence of perfusion defects and whether they are reversible suggests that this parameter has diagnostic potential. In the ischemia group, myocardial stunning or

subendocardial ischemia caused by reversible perfusion defects probably played a role in the statistically significant difference between the normal and ischemia groups. In the infarct group with irreversible perfusion defects, the presence of myocardial fibrosis or hibernated myocardium, which are indicative of structural changes, may be responsible for an even more statistically significant difference between the normal and infarct groups. According to these results, structural and functional changes affecting inotropy of the left ventricle seem to gradually change the shape of the systolic part of the left ventricle time-volume curve. The presence of a very good linear correlation between EF and E_c may also support this view. Furthermore, sensitivity and specificity analyses of the results seem to support the existence of such a diagnostic potential.

Study Limitations

As a limitation of the study, although it was planned to obtain all parameters from scintigraphic data, the systole time could have been calculated more precisely using ECG, and E_c results would have been more precise.

Conclusion

Because the systolic part of the LV volume curve obtained using gMPI shows a non-linear decrease, it was analyzed using the exponential decrease formula. Thus, with a formula that includes output (ESV) and input (EDV), it was possible to examine the decreasing pattern of the volume curve as it progressed from EDV to ESV. The scintigraphic parameter obtained with this formula has been called the E_c , and it has been detected that this parameter showed a statistically significant progressive decrease trend in patients with reversible and irreversible perfusion defects compared with the normal group. Besides, it seems that E_c may have a clinical role as a scintigraphic parameter in the evaluation of systolic functions of the left ventricle.

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Ethics

Ethics Committee Approval: The University of Health Sciences Türkiye, Gülhane Scientific Research Ethics Committee approved the study protocol (decision no: 2022-278, date: 12.09.2022).

Informed Consent: Not applicable.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: A.Ö.K., A.Ç., Design: A.Ö.K., A.Ç., Data Collection or Processing: A.Ö.K., A.Ç., Analysis or Interpretation: A.Ö.K., A.Ç., Literature Search: A.Ö.K., A.Ç., Writing: A.Ö.K., A.Ç.

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