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Research Article

Reproducibility, Interobserver Variability and Comparison with Echocardiography (Echo) of Multigated Acquisition (MUGA) Scintigraphy in Rabbit Heart

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Abstract

Purpose: MUGA scintigraphy is accepted as the reference method in determination of left ventricular ejection fraction. Aim of this study is to investigate reproducibility, interobserver variability of this test in rabbit heart and to perform a comparison with echocardiography.

Materials and Methods: New Zell and six male, 5-6-month-old rabbits (approximately 3 kg in weight) were the subjects of this study. The MUGA scintigraphy and additionally Echo analysis were performed to the rabbits. Ejection fraction (EF) values obtained from both examinations and repeating MUGA exams and two different observers' results were compared by Paired Samples T test and $P < 0.05$ considered statistically significant. Additionally, a second set of MUGA acquisition were performed in order to obtain right ventricular EF values. In order to compare scintigraphy and echocardiography (Echo) results Bland Altman analysis was performed.

Results: According to the analysis of two different sets of the two studies obtained by two different observers there weren't significant difference between the EF values ($P > 0,05$). However, the left ventricular EF values derived from MUGA and Echo studies were not in agreement with each other according to Bland Altman analysis.

Conclusion: MUGA is an accurate method in the identification of the left or right ventricular EF values in the rabbits with good reproducibility and low interobserver variability. Although Echo has been the standard method for evaluation of the ventricular functions of the rabbits in previous studies our results showed that there is no agreement between MUGA and Echo results therefore MUGA might be a better test in the experimental studies including ventricular functions of the rabbits.

Keywords: Multigated Acquisition; Scintigraphy; Echocardiography; Rabbits

List of Abbreviations: Echo: Echocardiography, MUGA: Multigated acquisition, EF: Ejection fraction, ECG: Electrocardiograpy, SPECT: Single photon emission tomography, DTPA: Diethylene tyramine Penta acetic acid, MRI: Magnetic resonance imaging.

Introduction

The estimation of the left ventricular ejection fraction (EF) by MUGA is a reliable method in human. After *in-vivo* labelling the erythrocytes the acquisition is performed and automatic or semi-automatic processes might be applied. MUGA analysis requires synchronization with electrocardiography (ECG). Previously MUGA has been demonstrated to be an accurate, reproducible method with good interobserver agreement.

Although in routine practice Echo is a preferable method since it is easier and requires no radiation exposure comparative studies in human have showed that EF estimation by MUGA is superior to Eco and in agreement with angiographic method [1]. Therefore, in patients who needs more precise information like monitorization of cardiotoxic agents or cardiac complications of specific diseases MUGA is the method of choice [2,3]. The rabbit heart has similarities with human heart related to its coronary circulation therefore there are many reports about cardiac estimation in rabbits which includes Echo follow up as an example [4]. However, this is the first study including MUGA analysis in rabbit heart. Since reliability, sensitivity, repeatability is important in the experimental studies with small animal, in our experimental research we preferred to

perform MUGA scan in order to estimate rabbit heart. The aim of this study is to analyze the repeatability, inter-observer variability of MUGA and to compare MUGA and Echo results in rabbit heart.

Materials and Methods

Materials

Six male New Zealand White rabbits, 5-6-month-old, approximately 3 kg in weight were subject of this study. All animal protocols were approved by Institutional Animal care and use ethic committee. The study was conducted according to National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Anaesthesia

The animals were sedated by intramuscular administration of 35 mg/kg ketamine before all the imaging procedures.

Scintigraphy

MUGA scintigraphy's were performed after labelling of red blood cells by intravenous injection of the pyrophosphate agent and Tc-99m from against ear veins by direct administration. The imaging was performed in 30 - 40º left anterior oblique position by a double head SPECT gama camera (Infinia ll, Israel, GE) with low energy general purpose collimator. The acquisition was synchronized with ECG, by dividing cycles into 8 frames. The imaging was repeated several minutes after the first acquisition in two rabbits. Additionally, MUGA scintigraphy was repeated in another day with the same procedure and the same acquisition parameters except for the angle of the detector (30-40º right anterior oblique position). These acquisitions were also repeated after complement of the first imaging in all rabbits.

Process

Semiautomatic processes of all images were performed by an experienced nuclear medicine physician and additionally by another observer in a blind manner to all the data sets. Additionally, automatic processes were performed to the images. Left ventricular EF and right ventricular EF values were obtained from the analysis (Figure 1, 2).

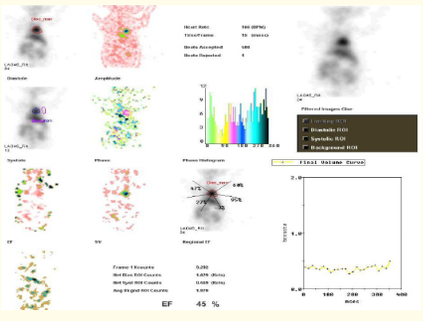

Figure 1: Left Ventricular Ejection Fraction Estimation by Systolic and Diastolic Region of Interests.

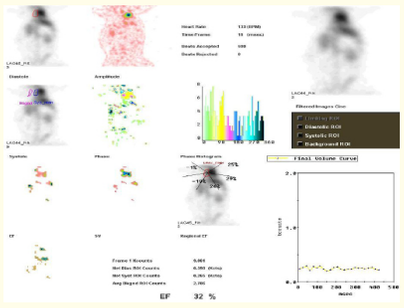

Figure 2: Right Ventricular Ejection Fraction Estimation by Systolic and Diastolic Region of Interests.

Echocardiography

Transthoracic echocardiography (Figure 3) was performed by VIVID I (GE) portable Echocardiogram with a 7S probe while the animals were sedated and in supine and left lateral position.

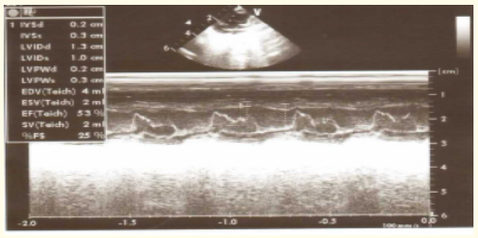

Figure 3: Transthoracic Echocardiography Image of Left Ventricular with Corresponding Dataset.

The systolic and diastolic ventricular dimensions and wall thicknesses were measured by M-mode echocardiography in the parasternal long axis and ejection fraction and shortening fraction was calculated by Teicholz formula. Right ventricular EF and the shortening fraction were calculated in subcostal position by measuring the systolic and diastolic dimensions and area by modified Simpson method by 2D echocardiography due to the geometrical discrepancy of the right ventricle for Teicholz formula.

Statistical Analysis

Ejection fraction (EF) values obtained from the MUGA scintigraphy, repeated MUGA exams and two different observers' results were compared by Paired Samples T test and the P value < 0.05 considered statistically significant. In order to compare scintigraphy and Echo results Bland Altman analysis was performed

Results

According to the analysis of the MUGA exams; the left ventricular EF values obtained by two different observers weren't significantly different (mean: 44 ± 10 versus 42 ± 12) (P = 0,309) (Fig-

ure 4a). An animal died just after the first episode of scintigraphy and therefore other investigations were performed in five rabbits. The mean left ventricular EF values obtained from first and second datasets of MUGA scintigraphy's obtained in two different days with different angles of the detector weren't significantly different (mean: 48 ± 4 versus 46 ± 2) (P = 0,627) (Figure 4b). Additionally, there were no significant difference between right ventricular EF values that were obtained from second acquisition and repeated examination analysed by two different observers (mean: 54 ± 7 versus 47 ± 12) (P = 0,795; 0,154; 0,52 respectively).

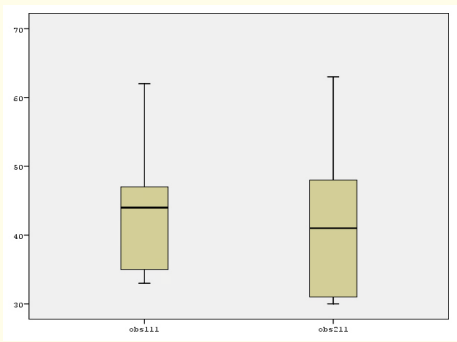

Figure 4a: Graphic Demonstration of the EF Values of Two Observers that weren't Significantly Different.

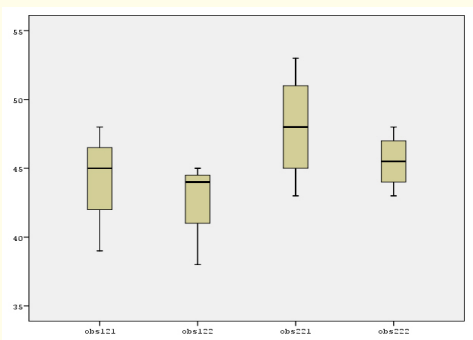

Figure 4b: Comparison of EF Values Obtained by different MUGA Exams and Analysis..

Discussion

Multigated acquisition scintigraphy has been previously documented to be more accurate and reproducible method than Echo in the EF analysis [5]. Additionally, a previous report has showed that MUGA is sufficiently sensitive to demonstrate the subtle changes in EF which Echo might overestimate [6].

Additionally, in another previous study the myocardial damage due to the iron deposition in the sickle cell anaemia have been evaluated by MUGA [7]. In another study, the efficacy of a drug in beta Thalassemia major patients have been investigated by means of the MUGA [8]. Besides MUGA has been a preferable method in the patients prior to cardioverter-defibrillator implantation which causes cost saving by identifying the appropriate patients [9]. However, the most common indication of MUGA has been considered to be the cardiac side effects of chemotherapy agents and comparative studies have indicated that MUGA is much more sensitive than Echo in the determination of the EF in these patients [1,2,6,10].

Estimation of the ventricular functions in experimental studies might be another indication of the MUGA. Our results showed repeatability and interobserver variability of MUGA in the rabbits firstly. In our study, we also demonstrated that Echo might not be an appropriate modality in especially left ventricular EF calculation in the rabbits. This is an important finding since previous observations in rabbit heart have been based on Echo findings although it has been known that Echo is a user dependent method and sometimes repeatability is poor which leads to poor reliability. Additionally, Echo analysis might be influenced with the different geometric characteristics of the rabbit heart. In a previous study including mice, rats, rabbits, dogs and human volunteers, different strain rates have been found in especially long axis in different sized hearts [11]. Additionally, MUGA provides information regarding right ventricular dysfunction which has been considered as an important parameter in patients with anamnesis of infer posterior myocardial infarct in a previous study [12]. Right ventricular EF is an important parameter in special circumstances.

In our study, the right ventricular EF results obtained from MUGA and Echo were not different from each other. This might be a consequence of geometrical properties of the rabbit heart which makes right ventricular estimation easier by Echo. Thus, in our opinion right ventricular estimation by Echo is as accurate as MUGA. The myocardial perfusion single photon emission tomography (SPECT) imaging also provides an EF measurement and additionally wall motion might be evaluated by means of the Gated analysis which is an adjunct analysis of the myocardial perfusion SPECT. However, there are different results about reliability of this method. Although a previous comparative study with MUGA has showed that EF calculation and wall motion analysis by Gated SPECT is feasible, another study has indicated that MUGA or Echo should be preferred over SPECT in the estimation of the EF [13,14]. In a previous comparative study with SPECT, MUGA and contrast ventriculographic LV function measurements obtained from MUGA and SPECT have found to be in correlation with contrast ventriculographic [15]. Another comparative study including Tc-99m DTPA human serum albumin MUGA-SPECT protocol and contrast ventriculography have demonstrated the superiority of MUGA in the estimation of LV function and wall motion to contrast ventirculography in a non-invasive manner [16]. We also documented in this study that MUGA is a precise method however automatic processes are not reliable compared to semiautomatic process since we observed important differences between EF values obtained by two methods.

Previous comparative studies about MUGA and contrast enhanced harmonic Doppler, non-contrast Echo and MRI analysis in human have documented correlation of these methods in the left ventricular estimation [17-19]. However, in an animal model which has been performed to obtain information about status of the myocardial damage during septal ventricular pacing in canine heart; the researchers have based their results to the MUGA imaging and intracardiac electrograms [20]. Although there are exceptional examples of MUGA studies in the small animal [21,22] there is an important lack of MUGA applications in experimental studies in especially the rabbits although MUGA is an accurate method in the estimation of ventricular functions and detecting subtle changes in EF related to ongoing pathologies and/or new treatment modalities. Limitations of this study are relatively small number of subjects (n = 6) and death of one of the rabbits during the study. Also, the application of the MUGA additional to myocardial perfusion SPECT could achieve more information however this methodology requires special camera for small animal. In this experimental research, we documented that MUGA is a reproducible method with low interobserver variability. MUGA analysis is a more suitable method for the estimation of ventricular functions in especially experimental studies in rabbits.

Highlights

Multigated acquisition is a sensitive and accurate method in evaluation of cardiac movements and quantificatitative values like ejection fraction in human. This research documented that MUGA is an applicable and accurate method for evaluation of rabbit heart for experimental studies.

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Volume 1 Issue 1 June 2017