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The Evaluation of Doxorubicin Cardiomyopathy By Signal Averaged Electrocardiography

Doksorubisin Kardiyotoksisitesinin Sinyal Ortalamalı Elektrokardiyografi ile Değerlendirilmesi

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ABSTRACT

Purpose: Signal-averaged electrocardiography detects low-amplitude signals designated as late potentials which are strongly related to myocardial damage. We aimed to search for the possible relation between the myocardial effects of doxorubicin and signal-averaged electrocardiographic parameters.

Material and Methods: Fortyeight patients who received doxorubicin included chemotherapy were enrolled. Signal-averaged electrocardiographic parameters were detected by using 3 parameters; filtered QRS (fQRS), the square root of the voltage obtained during the last 40 milliseconds of the duration of fQRS (RMS40), the duration starting from the last 40 miliseconds of fQRS till the decrease of voltage under 40 microvolts. (HFLA40). Ejection fractions of the patients were measured by echocardiographic evaluation.

Results: Median age was 44 (27-70) years. Mean cumulative doxorubicin dosage was 475.56±98.45 mg. Mean values of the measured signal-averaged electrocardiographic parameters were as follows; fQRS: 78.27±10.74 miliseconds, RMS40:115.10±50.23 and HFLA was 21.95±8.39 microvolts . The doses of doxorubicin showed a positive correlation with fQRS (r=0.28, p=0.02) and a negative correlation with RMS40 (r=-.31,p=0.03). There was no correlation between the doxorubicin dosage and the ejection fraction of the patients (r=.18, p=0.22).

Conclusion: Our results suggested that significant correlations are present between fQRS and RMS40 and cumulative doxorubicin dosages. Therefore, signal-averaged electrocardiographic parameters may be of value for predicting the prognosis of the patients who have received doxorubicin included chemotherapy.

Key Words: Signal-averaged electrocardiography, doxorubicin, cardiotoxicity

ÖZET

Giriş: Sinyal ortalamalı elektrokardiyografi miyokardiyal hasarla oldukça ilişkili olan geç potansiyeller olarak adlandırlan düşük amplitüdlü sinyalleri saptar. Bu çalışmadaki amacımız, doksorubisinin miyokardiyal yan etkileri ile sinyal ortalamalı elektrokardiyogram arasındaki potansiyel ilişkiyi araştırmaktır.

Materyal ve Method: Doksorubisin içeren kemoterapi alan 48 hasta çalışmaya dahil edildi. Sinyal ortalamalı elektrokardiyografi, 3 parametre kullanılarak ölçüldü: filtrelenmiş QRS (fQRS), fQRS süresinin son 40 milisaniyesi boyunca saptanan voltajın karekökü (RMS40), fQRS in son 40 milisaniyesinden başlayarak 40μV altına düştükten sonraki geçen süre (HFLA40). Hastaların ejeksiyon fraksiyonları, ekokardiyografi ile ölçüldü.

Tartışma: Bulgularımız, kümülatif doksorubisin dozları ile fQRS ve RMS40 arasında anlamlı korelasyon olduğunu düşündürmektedir. Bu yüzden sinyal ortalamalı elektrokardiyografik parametreler doksorubisin içeren tedaviler alan hastalarının prognozunu belirlemede değerli olabilir.

Sonuçlar: Ortalama yaş 44 (27-70) yıl idi. Ortalama kümülatif doksorubisin dozu 475.56±98.45 mg idi. Ölçülen sinyal ortalamalı elektrokardiyografik parametrelerin ortalama süreleri şöyleydi: fQRS:78.27±10.74 milisaniye, RMS40: 115.10±50.23 ve HFLA: 21.95±8.39 mikrovolt idi. Doksorubisin dozu ile fQRS arasında pozitif korelasyon saptanırken (r=0.28, p=0.02), RMS40 arasında negatif korelasyon mevcuttu (r=-.31,p=0.03). Doksorubisin dozu ile ejeksiyon fraksiyonları arasında korelasyon saptanmadı (r=.18, p=0.22).

Anahtar Kelimeler: Sinyal ortalamalı elektrokardiyografi, doksorubisin, kardiyotoksisite.

INTRODUCTION

Doxorubucin have been used for the treatment of a wide range of cancer types especially for breast cancer and lymphoma. It's most important side effect is cumulative cardiac toxicity. These toxic effects can be grouped in three categories: acute, chronic and late-onset. Acute toxicity is generally temporary and occurs during doxorubicin infusion or within the first week of infusion. Chronic cardiotoxicity is seen in the first year and late-onset toxicity is seen after the first year of treatment. In late-onset toxicity, the patients are initially asymptomatic however later may show ventricular dysfunction, heart failure and arrhythmias during the later stages[1,4]. As the drug-related heart failure, in chronic and late toxicities, is associated directly with the irreversible myocardial damage caused by the formation of free radicals[5,6]. early recognition of the abnormalities is very important. For the early diagnosis, cardiac biopsy[7] and radionuclide examination (Multiple Gated Acquisition Scan (MUGA))[8] are also used, but their usage in clinical practice is limited because of the required invasive procedures and their costs. Cardiac systolic and diastolic functions detected by echocardiographic examinations are commonly used in daily practice, but since the decrease in EF reflects severe cardiac damage, it would be of limited value for early diagnosis.

In the heart, late potentials resemble the waves with low amplitudes and high frequencies which originate from the damaged cardiac tissue[9]. In patients treated with doxorubicin, myocardial damage can either be occured in the right or left side of the heart, however left ventricle is more frequently affected than right ventricle[10,11]. Major pathological change in the myocardium is the separation of the myocardial bundle and deformation of parallel orientation by fibrosis[12]. These changes lead the ventricular activation to spread over the end of QRS wave during the sinus rhythm and therefore the late potentials occur. Late potentials are closely related to the total myocardial mass[13]. Since the late potentials have dense frequencies and low voltages, their signal-interference ratios are low. That is the reason why they cannot be measured at the scale of 12 led ECG. The dense frequencied waves can be recorded by using a high-transitioned filter. After all ECG complexes are captured, the mean values are measured. This electrocardiographic evaluation is called SAECG. In SAECG the signal-interference ratio is changed in favor of the signal and this process enables the identification of very low voltaged waves[14]. It is suggested that these waves can give information about the predisposition to arrhythmias and show correlation with the myocardial damages. SAECG is noninvasive and practical.

It is well known that in the patients at the post-infarction period[15] and in the patients with non-ischemic dilated cardiomyopathy (CMP)[16], presence of the late potentials show the increased risk for severe arrhythmias and sudden cardiac death. We thought that late potentials may also be used for early diagnosis of the cardiac damage caused by doxorubicin. Therefore, we investigated

the correlation between the total dose of doxorubicin, SAECG parameters and the echocardiographic findings[17,19].

MATERIALS AND METHODS:

This study was conducted with 48 patients who received doxorubicin for breast cancer (n=43), Non-Hodgkin lymphoma (n=3) and Hodgkin lymphoma (n=2) at our center from 2002 to 2009 and who do not have any known heart diseases. The patients admitted to the Medical Oncology Outpatient Clinic who received doxorubicin treatment previously, with no cardiac complaints and with echocardiographic EF measurements over 50 % were included in this study. The doses of doxorubicin which the patients received during all the therapy regimens were summed and this value was accepted to be the total doxorubicin dose. After a careful analysis of the group, the correlation between the dosage of doxorubicin and SAECG values and the effects of the factors related to the dosage of doxorubicin were evaluated. The patients with hypertension, diabetes mellitus, history of known atherosclerotic heart disease and anti-arrhythmic drugs usage were excluded. A detailed systemic examination, electrocardiographies and the blood pressures of the patients were noted. Signal-averaged electrocardiographies and echocardiographies were also recorded.

Echocardiography (ECHO)

All patients underwent a M-Mode, 2D and tissue Doppler examination using GE Wingmed® device in the left lateral decubitus position. Left ventricular ejection fraction was calculated using the Modified Simson method. The measurements were done by the same person for once. EF values of 50 % or more were accepted as normal. If left ventricular EF was detected below 50 %, doxorubicin-related systolic dysfunction was considered.

Signal-Averaged Electrocardiography (SAECG)

SAECG measurements were made by the same person. None of the patients had baseline values and each patient had only one measurement.

In all patients, signal-averaged ECGs were obtained using Tepa branded ECG master USB, Class II-BF type Petas® software and winecgpro® software, in which X, Y and Z orthogonal leads were used in the supine position. They were filtered within the frequency ranges of 40-250. The signals recorded from the three axes were averaged by using the computer . The averages of the signals were evaluated using Hi-Res® software. Using Simson method [9], 3 parameters were noted and the presence of 2 out of these 3 parameters was considered as late potential. These three parameters are the duration of fQRS over 114 ms, (HFLA40> 38 ms) the square root of the voltage obtained during the last 40 milliseconds of fQRS (RMS40 <20μV) and the duration starting from the last 40 miliseconds of fQRS till the decrease of voltage under 40 microvolts (HFLA40> 38 ms). While RMS40 could not be recorded in one patient due to the technical reasons, it was recorded in the other 47 patients. fQRS and HFLA values were measured in all patients.

Statistical Analysis: For the statistical evaluation of the data, SPSS 18 software was used. The categorical measurements were summarized as number and percentage and the numeric measurements were summarized as mean and standard deviation (median and minimum-maximum, when required). In the group, the correlations between doxorubicin dosage, SAECG measurements and ECHO parameters were examined using Spearman Rank Correlation. In all analysis, the level of statistical significance was considered as $p<0.05$.

RESULTS

A total of 48 patients with a median age was 44 (27-70) years were enrolled for the study. Forty four patients (91.7%) were female and 4 patients (8.3%) were male. 43 patients had the diagnosis of breast cancer (89.6%), 3 patients had Non-Hodgkin lymphoma (6.3%), 2 patients had Hodgkin lymphoma (4.2%) and none of the patients had recurrence of their diseases. The mean total doxorubicin dose was 475.56±98.45mg. Demographic data is shown in Table 1.

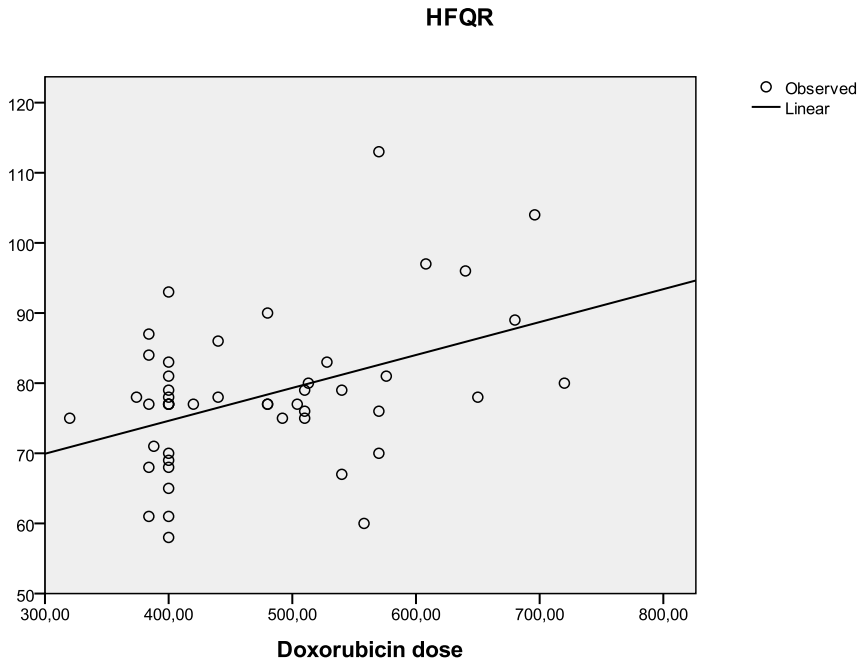
Mean cumulative doxorubicin dosage was 475.56±98.45 mg. Mean values of the measured signal-averaged electrocardiographic parameters were as follows; fQRS: 78.27±10.74 miliseconds, RMS40:115.10±50.23 and HFLA was 21.95±8.39 microvolts. For groups, echocardiographic values and data of SAECG are given in Table 2. Mean EF values were in normal ranges (65.19±4.01 %) and there were no findings of heart failure. Statistical analysis showed a positive correlation between the total dosage of doxorubicin and fQRS (r=0.33, p=0.021) (Figure 1), and a negative correlation between the total dosage of doxorubicin and RMS40 (r=-0.31, p=0.03), however no correlation between the total dosage of doxorubicin and HFLA (r=0.05, p=0.28) (Figure 2). There were no correlations found between EF and the total doxorubicin dose (r=.18, p=0.22), EF and HFQR (r=.21,p=0.13), EF and RMS40 (r=-.06,p=0.66) and EF and HFLA (r=.12,p=0.39).

Table1: Demographic data of the patients

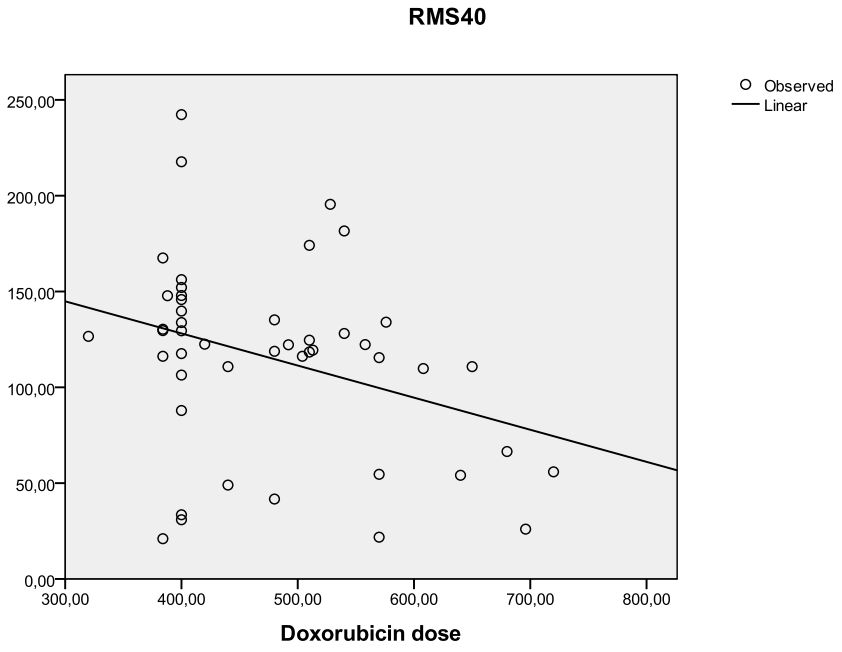
	GROUP (N:48)
Age (years; median (min-max))	44 (27-70)
Gender (Male/Female; N, %)	4 (8.3 %) / 44 (91.7 %)
Breast cancer (N, %)	43 (89.6 %)
Non-Hodgkin Lymphoma (N, %)	3 (6.25 %)
Hodgkin Lymphoma (N, %)	2 (4.16 %)
Dosage of doxorubicin (mg)	475.5 ± 98.4 mg

Table 2: Signal average and echocardiographic data according to group

f QRS (N: 48); miliseconds	78.27±10.74
RMS40 (N:47)	115.10±50.23
HFLA(N: 48); milivolts	21.95±8.39
EF(N: 48); %	65.19±4.01



Graphic 1. The curve showing the correlation between doxorubicin dosage and filtered QRS (p:0.021, r:0.287)



Graphic 2. The curve showing the correlation between doxorubicin and RMS40 (p:0.03, r:-0.31)

DISCUSSION

In our study, there was a statistically significant positive correlation between fQRS and the total dose of doxorubicin and a negative correlation between RMS40 and the total dose of doxorubicin. To our knowledge, our study is the first one which used SAECG to determine the relation between the total dose of antracyclines and myocardial function. Substances like brain natriuretic peptid (BNP) are frequently used for evaluating anthracyclin toxicity, but serum BNP levels can change by factors like age, gender, and obesity[20,22]. This parameter's level may change hourly or weekly[23]. Besides, it appears that there is no considerable change in the plasma BNP levels with treatment of cumulative doxorubicin doses of maximum 400 mg/m^2. In the doses higher than 400 mg/m^2 a considerable change in the serum BNP levels had been observed and this has been correlated with the neurohormonal effects caused by the ventricle functions that are affected by anthracyclins[24]. Since serum BNP level is affected by age, sex and obesity, for the early documentation and follow up of the cardiac toxicity due to anthracyclines, serum BNP level seems a non-reliable parameter.

Another widely used marker to evaluate the cardiac injury caused by the anthracyclins is cardiac troponin (cTPN). But it is neither sensitive nor enough to determine myocardial damage accurately[25]. Fink et al. have reported that cTPN levels did not differ at the 72nd hour of doxorubicin infusions[26]. After the beginning of the acute cardiac symptoms, the sensitivity of the serum cTPN levels was 98.2 %[27] and 33 % in the 12nd and 49 % in 4th hours. These studies showed that serum levels of BNP and cTPN could easily be affected by various factors and therefore cannot be used precisely to show doxorubicin induced cardiotoxicity.

Development of cardiac toxicity is absolutely not a rule and in the literature it was reported that no cardiac toxicity was present at the total dose of 1000mg/m^2 doxorubicin administiration. But in some patients a total dose of doxorubicin 180 mg/m^2 is enough to see the cardiac toxicity[28]. A number of patients seem to be oversensitive for antracyclin side effects but there is no method to determine the sensitivity of patients for the drug.

Anthracyclines can cause acute, chronic and late-onset myocardial damage. They can lead to subclinical or clinical cardiac abnormalities at a dose of 250 mg/m^2 [29] or even at lower doses[30]. These abnormalities may progress in time and lead to dilated or restrictive cardiomyopathy and fatal arrhythmias[2,17,18,31]. It is reported that rate of heart failure development is 0.14 % at a total dose of 400 mg/m^2, 7 % at 550 mg/m^2 and 18 % at 700 mg/m^2 [32]. Although the negative effect of the doxorubicin on the heart function is well-known, the studies conducted by Vonhoof and Henderson[32,33] have failed to show pathological abnormalities with cardiac biopsies, even at the doses above 1000 mg/m^2. The early diagnosis of development and presumably increasing toxicity is very important. In the study performed by Friedman et al., doxorubicin toxicity was seen even at the doses as low as 180 mg/m^2 and as demonstrated in the subsequent biopsies, higher doses cause more progressive and greater damage[28]. In the study performed by Ewer et al.[34] no similar relationship existed between cumulative adriamycin dose and ejection fractions measured at rest or between biopsy results and ejection fractions. In patients who underwent serial endomyocardial biopsies and serial ejection fraction determinations, the correlation between changes in histopathological grade and ejection fraction was poor.

In the studies conducted by Mason et al.[35] and by Bristow et al.[7] only pathologic assessment of doxorubicin induced myocardial damage showed a progressive stepwise increase in severity at higher dose of doxorubicin. Doxorubicin administration was associated with a dose–related

increase in the degree of myocyte damage and patients with catheterization proven heart failure had a significantly greater amount of myocyte damage on biopsy than dose-matched control subjects.

The reliability of fQRS and RMS40 in showing myocardial damage and destruction of myocardium due to arrhythmias were clearly demonstrated in the study performed by Gomes et al. and it was suggested that fQRS and RMS40 could be used for the surveillance of cardiac toxicity[15]. This study also has shown that the increase in fQRS and the decrease in RMS40 were associated with a shortened life span. The relationship between the fQRS and RMS40 and the cardiac disorders, as shown by Gomes et al., establishes more reliable data about cardiac morphology and functions, when used together with the ECHO[15]. In our study, statistical analysis showed a positive correlation between cumulative dose of doxorubicin and fQRS and a negative correlation with RMS[40]. Therefore, we suggest that SAECG may be important for the early diagnosis of cumulative cardiac toxicity. Doxorubicin-induced myocardial toxicity is insidious and myocardial functions are preserved up to a critical level of structural damage[34]. When a critical level of myocardial damage occurs, myocardial performance decline irreversibly[36]. Therefore, we believe that, as shown in the studies performed by Torti et al[37], in the individuals with a prolonged fQRS and a shortened RMS40, anthracyclines may be used weekly rather than each 3 weeks, to provide a less toxic treatment. Our study has limitations to reach a firm conclusion, because the definitive correlation between fQRS, RMS40 and HFLA40 and the grade of toxicity in the myocardium are not clear. So the evaluation of the toxicity caused by doxorubicin may not have predictive value for prognosis.

In conclusion, we found a positive correlation between the cumulative dose of doxorubicin and the SAECG parameters such as FQRS and RMS40 in the patients receiving doxorubicin. The importance of this relation is that for the patients without cardiac symptoms and normal echocardiographic EF measurements, a parameter for the follow-up of cardiac toxicity may be important for the management strategies.

There are two reasons which may suggest the significance of our data: 1- A relationship similar to the one between doxorubicin dosage and myocardial biopsy was found between SAECG and doxorubicin dosage noninvasively 2- The myocardial biopsy may reveal different results for left and right ventricule however no such difference is present with SAECG. For these reasons we suggest that SAECG could be a reliable method for evaluating the side effects of doxorubicin on myocardium.

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