

CLINICAL STUDY

Frequency-domain analysis of the signal-averaged electrocardiogram in hematological malignancies survivors

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Abstract: *Objectives:* The aim of the presented study was to evaluate the frequency-domain signal-averaged ECGs (SAECG) abnormalities in childhood and adolescence acute leukemia and lymphoma survivors treated either with or without anthracyclines (ANT) containing chemotherapy in comparison with healthy volunteers.

Background: The late development of chemotherapy-induced myocardial complications becomes an issue as the number of childhood cancer survivors is increasing. Underlying cardiac impairment may progress to serious cardiac diseases. Therefore, an early identification of myocardial injury is essential.

Patients and methods: Study population was divided into two treatment groups: ANT group (31 patients previously treated with ANT), and non-ANT group (32 patients who underwent chemotherapy without ANT, both more than 5 years ago). SAECG was added to routine cardiology examination in the whole population study and 32 controls. Using the frequency-domain analysis within the QRS complex a ratio (AR) of 20–50 (Hz)/0–20 (Hz) was calculated.

Results: AR 20–50/0–20 in SAECG was significantly higher in ANT and non-ANT groups, relative to controls (262.5 p<0.00001 vs 135.9 p<0.001 vs 74.7). The difference between both patient groups was also evident p<0.01.

Conclusion: Significant differences in frequency-domain SAECG parameters between patients (with or without anthracyclines) and controls might indicate the increased risk of electrical instability particularly in anthracycline-treated patients (Tab. 2, Fig. 1, Ref. 34). Full Text (Free, PDF) www.bmj.sk.

Key words: anthracyclines, cardiotoxicity, hematological malignancy, signal-averaged electrocardiography.

Anthracyclines (i.e., doxorubicin, daunorubicin, idarubicin, epirubicin, mitoxantrone) remain the key treatment component in children with cancer, including leukemias, Hodgkin's disease, non-Hodgkin's lymphoma, as well as solid tumors (e.g. osteosarcoma, Wilms tumor, neuroblastoma) (1, 2). Their use is however limited by cardiac toxicity. It is described in acute, chronic and late-onset forms (3, 4). Anthracycline cardiotoxicity is exponentially dose-dependent, albeit myocytes damage may occur regardless of the cumulative dose and may be observed even after the initial dose treatment (5–7). Negative cardiovascular effects were described also in other non-anthracycline agents (cyclophosphamide, ifosfamide, mitomycin, vinca alkaloids) used in the management of hematological malignancies (1, 4, 8).

The improvement in childhood cancer survival has significantly elevated the occurrence of late cardiac morbidity and mor-

tality (9, 10). Several years following anticancer therapy the underlying cardiac impairment may progress to dilated or restrictive cardiomyopathy, congestive heart failure or life-threatening arrhythmias (2). Therefore, the essential problem in prevention, identification and treatment of cardiotoxicity in cancer survivors is based on early identification of myocardial injury (2, 7).

The exploration of means of early detection of late cardiac changes is in progress. Signal-averaged electrocardiography (SAECG) is a non-invasive diagnostic method used in cardiac pathologies that affect the electrophysiology of myocardium (11, 12). Cytostatic therapy-induced myocardial fibrosis can alter the frequency spectrum of the QRS complex in SAECG (13). Frequency-domain abnormalities reflect the fractionated activation fronts that lead to abnormal ventricular conduction. Such conditions generally represent a risk for the development of malignant ventricular arrhythmias and sudden cardiac death (14, 15). There is an evidence of abnormalities in the frequency content of ECG signal in anthracycline-induced cardiotoxicity (13, 15–17). According to available literature, frequency-domain analysis data in patients following chemotherapy without anthracyclines are missing.

The aim of the presented study was to evaluate frequency-domain SAECG abnormalities in childhood and adolescent acute leukemia and lymphoma survivors treated with or without anthracyclines-containing chemotherapy in comparison to healthy volunteers.

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Tab. 1. Baseline characteristics of both study populations and control group. Values are presented as median (range).

	Group (n=31)	nonANT Group (n=32)	Control Group (n=32)
Sex M/F	17/14	15/17	16/16
Diagnosis (number of patients)	ALL (23) AML (4) Hodgkin's disease (2) NHL (2)	ALL (32)	
Age at diagnosis (yrs)	8 (1–17)	5 (2–10)	
Yrs after completion of CHT	11 (5–22)	15.5 (6–25)	
Age at study (yrs)	22 (18–31)	22.5 (17–31)	23 (20–27)
Chemotherapy	Doxorubicin Daunorubicin Rubomycin Epirubicin	Vincristine Methotrexate Cyclophosphamide 6-Mercaptopurine L-Asparaginase	
ANT cumulative dose (mg/m ²)	200 (75–600)	0	
Number of irradiations			
CNS	18	19	
Mediastinal	1	0	
Dose of radiation (Gy)			
CNS	18 (12–24)	18 (14.8–24)	
Mediastinal	21	0	

ANT – anthracyclines, ALL – acute lymphoblastic leukemia, AML – acute myeloid leukemia, NHL – non-Hodgkin lymphoma, CHT – chemotherapy, yrs – years

Patients and methods

Study population

From January 2006 till May 2009, a total of 63 consecutive, asymptomatic, event-free survivors of childhood and adolescent acute leukemia (ALL, AML) and lymphoma (Hodgkin's disease, non-Hodgkin lymphoma), more than 5 years after the completion of therapy were enrolled in this study. All patients were treated and followed at The Pediatric Oncology Department, Children's University Hospital, Bratislava (Slovak Republic) and later at the oncology out-patient clinic of The National Cancer Institute, Bratislava (Slovak Republic). Study population was divided into two treatment groups according to anthracycline exposition: group ANT (n=31) – patients previously treated with chemotherapy containing anthracyclines, and group non-ANT (n=32) – survivors who underwent chemotherapy without anthracyclines (including vincristine, methotrexate, cyclophosphamide, 6-mercaptopurine, L-asparaginase). No concomitant diseases that could have potentially modified the study results were observed. One patient (3.2 %) received mediastinal radiotherapy in addition to anthracyclines.

At the time of enrolment, all patients were at complete remission for at least 5 years. Liver and renal parameters were normal in all patients. The control group consisted of 32 healthy age-wise and sex-wise matched volunteers. Characteristics of both study populations and control group are shown in Table 1.

Patients, as well as controls were enrolled in the study upon the obtainment of written informed consent. Basic demographic

data and oncologic medical history were documented at enrollment. The patients enrolled in study population including the controls were subsequently seen by general cardiologists to evaluate any symptoms of cardiovascular diseases and to perform general examination. At the same time standard ECG, SAECG tracing were assessed. The work has been approved by the ethical committee of the Faculty of Medicine, Comenius University, Bratislava, Slovak Republic.

Signal-averaged ECG recording and frequency domain analysis

The signal-averaged electrocardiography (SAECG) was recorded and calculated from X, Y and Z orthogonal leads using a 1200 EPX High Resolution Electrocardiograph (Arrhythmia Research Technology (ART), Austin, TX, USA). The X leads were positioned at the fourth intercostal space in both midaxillary lines, the Y leads were positioned on the superior aspect of the manubrium and on the left iliac crest, and the Z leads were positioned at the fourth intercostal space with the second electrode directly posterior on the left side of the vertebral column. Approximately 300–600 beats were averaged to obtain the low-noise level. We used only low-noise recordings (below 0.7 V). The recorded signals were amplified, digitized, averaged and filtered with a bidirectional four-pole Butterworth filter.

The SAECG recordings were analyzed using the software ART, Late Potential Analysis Version 2.01 for frequency-domain analysis. Fast Fourier transform (FFT) analysis was performed in an interval of 140 ms starting on the QRS onset using a composite lead (vector sum of leads X, Y and Z). Four-term Black-

Tab. 2. Frequency-domain parameters (AR 20–50/0–20) of signal-averaged ECG in the control group, patients without anthracycline chemotherapy (nonANT Group) and patients with anthracycline chemotherapy (ANT Group). Values are presented as median (range). AR – area ratio 20–50/0–20.

Frequency-domain analysis	Control group	NonANT Group	ANT Group	p
AR 20–50/0–20 Hz	74.7 (9.3–159.6)		262.5 (24.7–900.7)	0.000001
AR 20–50/0–20 Hz	74.7 (9.3–159.6)	135.9 (10.6–315.7)		0.0004
AR 20–50/0–20 Hz		135.9 (10.6–315.7)	262.5 (24.7–900.7)	0.003
Abnormal AR % (number/all)	3.1% (1/32)	43.8% (14/32)	69.0% (20/29)	

man-Harris window was used to reduce spectral leakage. Results were expressed as a ratio of the area under the spectral plot between 20 (Hz) and 50 (Hz) divided by the area under the spectral plot between 0 (Hz) and 20 (Hz) (area ratio (AR) 20–50/0–20).

Statistical analysis

Characteristics of the study population as age at diagnosis, years after completion of chemotherapy, age at study are summarized as median and range. Data of SAECG analysis are presented as median and range. XLstatistics version 5 was used for Statistical analyses. SAECG parameters between studied groups were compared by the Kruskal-Wallis ANOVA test for nonparametric variables. A probability value of $p < 0.05$ was considered statistically significant.

Results

Medical history, physical examination and standard 12-lead ECG did not reveal any signs of cardiac impairment in all study groups including controls. No concomitant diseases that could have potentially modified the study results were observed.

Two frequency-domain tracings from ANT group of survivors were excluded due to the high-noise level obtained during the recording. For the purpose of this study, AR was considered abnormal when above the upper limit of the 97.5th percentile of controls.

The median (range) AR 20–50/0–20 of frequency-domain analysis was 262.5 (24.7–900.7) in ANT group of patients, 135.9 (10.6–315.7) in non-ANT patients and 74.7 (9.3–159.6) within the control group. The frequency-domain analysis revealed abnormal AR values in 69.0 % (20/29) of anthracycline-treated patients and in 43.8 % (14/32) of patients who had not undergone anthracycline therapy. AR of the patient with mediastinal irradiation in addition to anthracyclines was abnormally elevated. Except for one case (3.1 %, 1/32) all frequency domain parameters in the control group were normal. AR values of 20–50/0–20 were significantly higher in ANT group ($p < 0.00001$) as well as in non-ANT chemotherapy group ($p < 0.001$) when compared to controls. The difference between both patient groups was also evident ($p < 0.01$). The results of frequency-domain SAECG analysis within the QRS complex are shown in Table 2 and Figure 1.

Discussion

The elevated risk of cardiac dysfunction in childhood cancer survivors places its early detection to focus. The previous results of frequency-domain SAECG analysis in assessment of subclinical anthracycline-induced myocardial alterations in children after anthracycline therapy were encouraging (13, 15–17). In our study, the frequency-domain SAECG abnormalities were evaluated in childhood and adolescence hematological malignancies survivors treated with or without anthracyclines-containing chemotherapy.

The late development of anthracycline-induced myocardial complications becomes more common as the number of childhood cancer survivors is constantly increasing (4). It is of concern that the late onset of cardiac toxicity can be subclinical for years and may culminate in cardiomyopathy, heart failure or se-

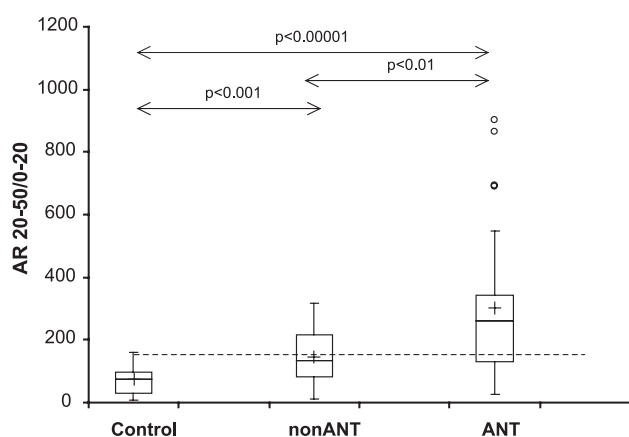


Fig. 1. Comparison of AR 20-50/0-20 of signal-averaged ECG in the control group, i.e. in patients without previous anthracycline-included chemotherapy (nonANT Group), and in patients with past anthracycline chemotherapy (ANT Group). Each box-plot represents 25th and 75th percentile (boxes), the lowest and highest values (error bars), mean (+), median (black band), outliers (O). Horizontal line indicates upper limit of normal AR values. For the purpose of this study, AR was considered abnormal when above the upper limit of the 97.5th percentile of controls.

rious arrhythmias (2, 4). Moreover, clinicians are facing the problem that additional cytostatic drugs (cyclophosphamide, ifosfamide, cisplatin, busulfan, mitomycin, vinca alkaloids, fluorouracil, cytarabine, amsacrine, asparaginase, etoposide, teniposide, paclitaxel, docetaxel, trastuzumab) can trigger cardiac damage as well (1, 4, 8).

The first International Workshop on Anthracycline Cardiotoxicity that took place in Italy in 2006 emphasized the urgent clinical research of strategies that could identify early signs of cardiac deterioration in patients who underwent chemotherapy (7). Monitoring schemes for cardiotoxicity involve regular electrocardiographic and echocardiographic assessments (2). The main limitation of these measures is that they are unable to detect preclinical functional changes of myocardium (13, 18). According to Cooper et al, endomyocardial biopsy is reasonable for patients with unexplained heart failure associated with suspected anthracycline-induced cardiomyopathy (19). Cardiac troponins and natriuretic peptides are monitored in frame of cardiac health follow-up (20–23).

The signal-averaged ECG has been introduced as a non-invasive method that can be useful in various cardiac conditions that disrupt the electrical stability of the heart (11, 12, 24). Fast-Fourier transform analysis of signal-averaged ECG provides the signal processing in the frequency domain (25). This technique enables the whole QRS complex to be examined throughout a wide range of different frequencies. The process may discover electrophysiological correlations of diffuse structural cardiac alterations that are below the resolution of a 12-lead ECG (25).

In the last decades, altered frequency spectrum of the QRS complex was detected in patients in risk of ventricular tachyarrhythmias (25–27). Currently there are further proofs of SAECG use in the detection of abnormal myocardial electrical activity (28–30).

Anticancer therapy-induced diffuse separation of myocytes by interstitial fibrosis may lead to electrical instability of the heart. Abnormalities in the frequency spectrum of the QRS complex can reflect fragmented ventricular activation – a potential substrate for arrhythmogenesis. Several studies documented an increased incidence of persistent frequency-domain abnormalities in patients with anthracyclines (13, 15, 17) and indicated the protective effect of dexrazoxane on electrophysiological myocardial properties (16). SAECG in children with left ventricular dysfunction following anthracycline therapy was differentiated from those without left ventricular dysfunction (11). According to available literature, the data of using frequency-domain analysis in patients who underwent chemotherapy without anthracyclines are missing.

In our study we used frequency-domain SAECG analysis (AR 20–50/0–20) in evaluating the long-term abnormalities in childhood and adolescent acute leukemia and lymphoma survivors treated with or without anthracyclines-containing chemotherapy in comparison with healthy volunteers. The usefulness of AR of 20–50/0–20 in assessment of cardiomyopathy was previously documented by its significant correlation with histopathological cardiac changes (13, 25, 31). However, other area ratios (e.g. 40–100 (Hz)/0–100 (Hz) or 60–120 (Hz)/0–120 (Hz)) might be

also valuable (15, 17). Both groups of our leukemia and lymphoma survivors (with and without anthracyclines) revealed significant elevations in AR values when compared to the control group. The difference between both patient groups was also evident ($p < 0.01$).

Based on our results, it is not clear whether SAECG abnormalities signal the late cardiotoxicity. Nevertheless, higher AR might suggest an increased electrical instability that arises irrespective of received chemotherapy. It was previously demonstrated by Lipshultz et al that all long-term survivors of childhood cancer are at an increased global risk of premature cardiovascular disease regardless of anthracycline or cardiac irradiation exposure (20). It is of concern that the degree of SAECG abnormalities in anthracycline group was significantly increased when compared to patients with anthracycline-free protocols. This may highlight the particular risk of inhomogeneous ventricular activation in anthracycline-treated patients.

It remains inconclusive whether the frequency-domain SAECG abnormalities in our patients resulted from a loss of myocytes during anthracycline cardiotoxic therapy, long-term alterations in myocytes metabolism, or whether anthracyclines mediated the effect on non-muscle cells or other mechanisms. The possible course of late SAECG abnormalities development in our non-ANT patients is not clear as well. Vincristine, cyclophosphamide and L-asparaginase used within the non-ANT protocols may be associated with acute cardiac toxicity (1). They can induce cardiac necrosis and/or ECG changes immediately or just after the treatment. Long-term toxicity has not been described yet. Therefore, we cannot explain whether late SAECG changes are based on progression of acute myocardial changes or are signs of new pathologies developing *de novo* by separate mechanisms.

The incidence of anthracycline-induced cardiotoxicity depends on the cumulative dose, but there appears a wide variability in individual toxicity of the drugs (6, 7). In adults, a cumulative anthracycline dose beyond 550 mg/m² raises rapidly the development of cardiac dysfunction (32). Children are much more susceptible to anthracyclines. Doses higher than 300 mg/m² were associated with an increased risk of heart failure 15 years after the completion of therapy (33). Other studies indicate that adverse cardiac effects can occur regardless of the amount of doxorubicin exposure (4), even after the initial administration (5).

The median of cumulative anthracycline dose used in our ANT group was low (median 200 mg/m²). Albeit considered safe, this dose has led to the development of abnormally elevated AR in the majority of our ANT patients.

The incidence and severity of cardiotoxicity is also related to mediastinal radiotherapy in general (1, 8). Poutanen et al recorded that children with additional irradiation in the cardiac region are at higher risk of abnormal cardiac outcomes (34). In our study, there was only one patient who had received adjunct mediastinal therapy in addition to anthracyclines, as well as showed abnormal AR value. We assume that the irradiation could have potentiated the adverse cardiac effect of anthracyclines in this patient. Thus, patients after mediastinal irradiation should be considered as a separate group during the further follow-up.

Conclusion

Anticancer therapy leads to the occurrence of late frequency-domain SAECG abnormalities in survivors of hematological malignancies. Significant differences in frequency-domain SAECG parameters between patients (with or without anthracyclines) and controls might indicate an increased risk of electrical instability, particularly in anthracycline-treated patients.

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