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Possible Prognostic ECG Indices for Cardiac Injury Associated with Experimentally Induced Chronic Doxorubicin-Cardiomyopathy in Dogs

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Abstract

DOXORUBICIN (DOX) induced- cardiomyopathy is a predictable outcome for doxorubicin administration in dogs treated for various malignancies. Early detection of cardiac alterations is a mandatory step to prevent permanent and irreversible cardiac damage. Many tools have been employed to detect those alterations including echocardiography (ECHO), electrocardiography (ECG) and cardiac biomarkers analysis. ECG is a cost-effective tool used to scan for DOX induced-cardiomyopathy in dogs. To this point, no detection criteria has been established for chronic DOX-cardiotoxicity in dogs using ECG. Five adult healthy male dogs were employed to receive six consecutive doses of DOX (30 mg/ m^2) which was repeated with three-weeks interval. Baseline physical, ECHO, ECG and serum biochemical examinations were conducted before the first DOX application. Serial ECG evaluation was carried out just prior to the next DOX session then three weeks after discontinuing DOX therapy. Lead II of the ECG was standardized for all measurements including heart rate, rhythm, duration and amplitude of the P wave and QRS complex, duration of the PR, QT and QTc intervals, existence and amplitude of the J wave, polarity and amplitude of the T wave, mean electrical axis and the position of the ST segment. No cardiac arrhythmias were detected except for sinus tachycardia. The most detected ECG alterations were ST depression or/ elevation, T wave flattening and inversion as well as prominent J wave. In conclusion, ST interval and T wave changes along with prominent J wave could represent important indicators for chronic DOX-cardiomyopathy in dogs.

Keywords: Cardiomyopathy, Dogs, Doxorubicin, Electrocardiography.

Introduction

Doxorubicin (DOX) is a widely known anthracycline chemotherapeutic agent that work effectively on a wide variety of malignancies including lymphoma, hemangiosarcoma, osteosarcoma, histiocytic sarcoma, and carcinomas in dogs and humans [1-5]. Owing to its lethal and dose-dependent cardiotoxic effect [1], DOX therapy can be limited in some breeds of dogs possessing high risk of cardiac diseases [3-4]. Moreover, DOX is known for its early onset- (acute) or late-onset and chronic cardiotoxic effect which is usually irreversible and has poor outcomes [2, 4, 6-8]. Acute DOX-induced cardiotoxicity has been detected in dogs as transient and immediate changes by developing arrhythmias and hypotension occurring within minutes of IV DOX infusion [4, 6, 9]. Unlike acute cardiotoxicity, chronic DOX cardiotoxicities are usually associated with cumulative administration of doses exceeding 240 mg/ m2 in dogs. Thus, most institutions administrate DOX at a dose rate of 30 mg/ m2 for dogs with body weight ≥15 kg and 1 mg/kg for dogs not exceeding 15 kg given each 21 days, however, they rarely exceed a total cumulative dose of 180 mg/ m^2 [4, 6, 10].

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The DOX-induced cardiomyopathy is characterized by left ventricular structural and functional changes as detected by echocardiography (ECHO) in close resemblance to dilated cardiomyopathy in dogs [1, 4, 6, 8]. Pre-DOX scanning using proper physical, ECHO and electrocardiographic examination (ECG) is a crucial procedure to preclude animals with pre-existing heart abnormalities which represented 10 % of dogs admitted for chemotherapy in a previous study [11]. Since the presence of cardiotoxocity is a limiting point for administration of DOX therapy, sequential screening using ECHO, ECG and serum cardiac biomarkers evaluation as cardiac troponin-I (cTnI), became very important to detect arrhythmias, left ventricular and right ventricular dysfunction even in the absence of clinical signs [1, 6, 11, 12].

In consideration to the adverse effects associated with DOX therapy in dogs, early detection of the cardiac alterations became mandatory before permanent and irreversible damage of the heart develops [6]. One of the important yet inexpensive tools that is used to detect these alterations is the ECG [2, 6]. In clinical settings, ECG has been employed mainly for detection acute rather than chronic cardiotoxicity induced during or shortly after DOX application in dogs. The most detected ECG abnormalities included ventricular premature beats, atrial premature beats, bradycardia in addition to other nonspecific alterations in the QRS wave, QT interval, T wave and ST segment [4, 10, 11, 13, 14]. For years, experimental models served to detect ECG abnormalities associated with long term administration of DOX therapy. An early study documented that serial ECG evaluations after multiple DOX infusion with a total cumulative dose of 90 mg/m2, showed that dogs experienced progressive prolongation of the QT interval and reduction of R-R duration and T wave amplitude [15]. Another study noted that only minor ECG changes were detected after repeated DOX application in dogs including ST segment, T wave reduction and QRS prolongation associated only with marked left ventricular dysfunction [16]. In human medicine, the same ECG abnormalities were reported in 11 to 30% of the patients [11, 17]. A recent study in humans stated that there are ECG indices that could possibly predict the late onset chronic doxorubicin cardiotoxicity or the so-called cancer therapy related cardiac dysfunction (CTRCD). The most common findings included T wave changes either by flattening or inversion, and QT prolongation [2].

To this point, no detection criteria has been established for chronic DOX- cardiotoxicity in dogs similar to their human counterparts. Thereby, we suggest that sequential observation of ECG fluctuations at the baseline and prior to each subsequent DOX infusions could yield important information regarding chronic cardiac toxicity. This study aims at [1] investigating chronic dose-dependent effect of DOX therapy in dogs using sequential ECG evaluations and [2] identifying early ECG indicators for chronic DOX-induced cardiomyopathy.

Material and Methods

Animals- Five adult apparently healthy intact-male mixed breed dogs of the same age and body weight range were recruited in the study. Selection criteria included normal physical examination, ECHO, ECG, CBC and serum biochemical analysis at the time of selection. Before starting the experiment, all animals were allowed to adapt at least one month from selection, during which they received proper deworming and defleaing medications. Each dog was housed separately in a clean cage and was fed specially formulated diet for dogs, while the water was available ad libitum. The study was performed at the small animal housing facility at the Department of internal medicine, Faculty of Veterinary Medicine- Damanhur University. All study procedures were approved by Institutional Animal Care and Use Ethical Committee, Faculty of Veterinary Medicine, Damanhur University (Approval number: DMU/VetMed- 2025/004).

Experimental procedures- Doxorubicin HCl (Adricin®, Hikma, Cairo, Egypt) was administrated at a dose rate of 30 mg/m2 via slow IV infusion after reconstitution in 20 ml of sterile dextrose (5%) as recommended by the manufacturing company. Infusions were repeated at a three-week interval until six doses were achieved (cumulative dose of 180 mg/ m2) [4, 6, 10]. Prior to each infusion, IV injection of Chlorpheniramine maleate (0.5 mg/ kg) (Avil®, Sanofi-Aventis, Cairo, Egypt) was insured to prevent anaphylactic reaction to the DOX infusion [4]. Each dog was scanned by ECG before the first IV infusion of DOX and then every three weeks prior to each infusion. After the final dose of DOX, all animals were re-evaluated after three weeks from discontinuing the chemotherapy. The first evaluation before the DOX administration served as control values for all dogs.

ECHO examination- ECHO examination was performed before the first DOX infusion without sedation after gentle restraining of the dogs in right and left lateral recumbency on a special cut-out table using a phased array transducer with a frequency range of 2-8 MHZs (Hitachi Aloka F31, Japan). Offline analyses were conducted from stored images for cine loops of three cardiac cycles to evaluate the cardiac structure and function. M-mode derived left

ventricular internal dimensions obtained from the right parasternal short-axis views at the level of papillary muscle in both diastole and systole were obtained and fractional shortening was calculated. EF % was calculated from Simpson's method of disc-derived end diastolic and systolic volumes from the right parasternal long axis- four chamber view. The left atrial to the aortic root ratio was measured from the right parasternal short axis view at the level of left atrium. All measurements, ratios and indices were compared to weight dependent-reference ranges [18- 20].

ECG- A standard 6-lead electrocardiogram was recorded after the dogs were positioned in right lateral recumbency. Lead II of the ECG was standardized for all measurements made from three consecutive P-QRS-T complexes then the values were averaged. The Heart rate (HR) and rhythm was recorded. The ECG evaluation included measuring duration and amplitude of the P wave and QRS complex, duration of the PR and QT intervals, existence and amplitude of the J wave, polarity and amplitude of the T wave, mean electrical axis and the position of the ST segment was recorded. Correction of the QT interval (QTc) to the heart rate was done using the logarithmic formula as previously described. Paper speed for the ECG was set at 50 mm/s, and the voltage calibration scale was set as 0.5 or 1 cm per one mV depending on the wave amplitude. Any abnormalities in the leads were documented for each visit and the ECG measurements obtained were compared to previously published ranges [21].

Blood sample collection- Blood samples were collected from each dog before the first DOX infusion. Samples were collected from the right cephalic vein in plain tubes for serum biochemical analysis. Serum biochemical analysis was conducted to measure cardiac enzymes including creatine kinase (CK) and its isoenzyme (CK-MB), and biomarkers including cardiac troponin-type I (cTnI), to exclude any myocardial injury before the DOX application.

Statistical analysis- All data including demographic data, ECHO data, ECG data, blood and serum biochemical analysis were analysed using IBM SPSS version 22.0.0.0. The baseline ECHO, blood and serum biochemical analysis data were expressed as mean ± standard deviation (SD). Homogeneity of variances was evaluated using Levene's test. The Shapiro Wilk test was used to test the normality of variables.

The data that violated the normality or homogeneity of variance assumptions, were analysed with the Kruskal Wallis test. P values less than 0.05 were considered statistically significant.

Results

Data were collected from all dogs except for one dog that suddenly died before the last post-DOX evaluation. The population's age ranged between 1.5- 2 years old. The baseline ECHO data of the five dogs were well within the normal ranges. The mean left ventricular internal dimensions in diastole and systole were 32.7 mm (±SD: 3.77) and 22.18 mm (±SD: 3.32) respectively, while the mean interventricular septal and free wall thicknesses were 6.58± 0.41 mm and 7.70± 1.31 mm in diastole, and 11.76± 1.30 mm and 12.18± 0.96 mm in systole respectively. The systolic function as indicated by the FS % and EF % were 32.30± 3.83 and 61.42± 6.03 respectively. The left atrial to the aortic root ratio was 1.16± 0.04. All dogs had normal baseline serum biochemical values. Serum CK and CK-MB concentrations were 110± 19.69 U/L and 14.93± 1.13 U/L respectively. Serum cTnI level was 3.62± 1.81 ng/L.

The demographic and ECG data were analysed using Kruskal-Wallis test as they were neither homogenous nor normally distributed. Both data were summarised in Table 1. There was no difference between the groups in the body weight, BSA as well as the ECG parameters except for the HR. The HR was significantly higher after the fourth and fifth DOX infusion (Median± IQR: 140± 50 and 140± 25 bpm respectively) than the first post-DOX examination (Median± IQR: 100± 20 bpm) at a p value $\leq$ 0.05, while there was no significance between the other post-DOX evaluations.

The Alterations of ST segment position and amplitude of deviation, T wave polarity and amplitude and J wave existence and amplitude for each dog at every post-DOX evaluation were documented and summarised in Table 2. In all groups, the ST segment showed normal baseline appearance either isoelectric, depressed or elevated by less than 0.2 mV. In the following post-DOX evaluation, there were fluctuations in the position of the ST segment which showed persistent depression or elevation by more than 0.2 mV (n= 3/5 dogs) starting from 4^{th} or 5^{th} post-DOX evaluation (Fig. 1. A and 1. B).

In all baseline ECG examinations, the T wave showed positive morphology then exhibited alterations in its morphology (positive, negative or biphasic), while it maintained a normal range of amplitude. In two out of five dogs, flattening of the T wave was observed at the 3rd post-DOX evaluation before turning negative (Fig. 1. A). In four out of five dogs, the T wave was negative by the last post-DOX evaluation (Fig. 1. B).

The J wave was either absent or appeared as a small component (amplitude range of 0.05- 0.1 mV) at the baseline evaluation. Prominent J wave of amplitude > 0.1 mV was noticed starting from the 1st post-DOX evaluation and persisted to the end of the study (Fig. 1. B).

Discussion

This experimental study demonstrated a detailed observation for the ECG fluctuations along a course of DOX therapy in dogs. The most prominent ECG changes were abnormal ST segment, T wave and prominent J waves. Some of those changes started at as early as 30 mg/ m2 of DOX therapy.

In our study, the HR was significantly higher in the late post-DOX evaluations than the first post-DOX evaluation, where the heart rate was at the upper limit of/ or exceeding the normal range for adult dogs (> 160 bpm) [21]. That increase in the HR started at a dose rate of 60 mg/ m2, then subsequently got higher till the last DOX infusion. Previous studies that conducted serial ECG examination for canine patients receiving DOX therapy alone or in combination with other drugs for treatment of various malignancies, reported supraventricular tachy-arrythmias at a dose range of 30- 150 mg/m2. Although only sinus tachycardia was detected in the current study, however, they were concluded within the same dose range as reported before [11-22]. The reason for these variable findings could be attributed to the fact that patients included in those studies were receiving other drugs or even were of dog breeds predisposed to heart diseases.

The ST segment represents the time taken for ventricular contraction and early repolarisation and it's normally found as isoelectric or above /or below the baseline by < 0.2 mV [22]. In all dogs, the baseline readings showed normal ST segment. ST segment abnormalities either by depression or elevation were detected at a cumulative dose of 60 mg/ m2, which progressively worsened with each DOX infusion in three out of five dogs. Those results were consistent with previous human and animal studies that reported similar ST segment abnormalities [11,15-17, 23]. Our results disagreed with a previous study that reported no change in ST segment with long term DOX application [6].

In all groups, the T wave showed normal morphology and amplitude before the DOX therapy. T wave flattening was detected in two dogs, which agreed with previous findings [16] followed by inversion. This specific pattern of T wave flattening then inversion was recently reported in human with CTRCD [2]. This trend was also observed in humans receiving radiotherapy and it was hypothesized it was caused by myocardial fibrosis [2, 24]. In our study, four out of five dogs showed a negative morphology by the end of evaluation which was consistent with a previous report [15]. Unlike the current study, the T wave maintained a normal morphology and polarity in a similar experimental study in dogs [6].

J wave or Osborn wave is a broadly known positive component at the R-ST junction with an amplitude ≥0.1 mV in more than one limb lead [25, 26]. Early reports have detected the J wave in correlation to pathological conditions in dogs [25-27]. However, more recent studies interpreted the J wave as a normal ECG finding in the canine species [26, 28]. In addition, the Osborn wave is still correlated to genetically predisposed and fatal arrhythmias in humans known as Brugada syndrome and early repolarization syndrome [29, 30]. In our study, the J wave was absent or barely detectable (amplitude < 0.1 mV) at the baseline evaluation of all dogs, however, it became progressively prominent (amplitude > 0.1mV) with each subsequent dose. To date, there are no studies reporting the presence of the J wave as an ECG finding to anticancer therapy in dogs or humans. Moreover, there is no strong explanation for its presence except for what might be a difference in action potential between both the ventricular endocardium and epicardium during early repolarization [25]. Since, chronic DOX cardiotoxicity were found to be realted to altered myocardial repolarization by inducing inhomogenous prolongation of the activation recovery interval of both ventricular epicardium [2, 16, 31], hence those changes could be a causal effect to the increase of the J wave amplitude. More importantly, the coexistence of prominent J waves, inverted T waves and elevated ST segment is a deadly combination of the so known Brugada syndrome, which predisposes to fatal arrhythmias and sudden cardiac deaths in humans [29, 30]. Those findings were evident in the dog that failed to survive in the current report. All other ECG parameters as amplitude and duration of the P wave and QRS wave, duration of the QT, QTc, R-R and PR interval were normal and no arrhythmias were detected in this report which disagreed with the previous studies [4, 6, 11, 13- 16].

One limitation of this study was the small number of animal population examined along the course of DOX therapy. Also, these animals were presumptively diagnosed with chronic DOX-cardiomyopathy only based on pre- DOX exclusion of other cardiac diseases using ECHO examination without necropsy findings. Moreover, no serial ECHO examinations were conducted to detect any structural or functional changes of the heart to correlate to the current ECG alterations.

Conclusion

The current report demonstrated a detailed ECG observation during long term DOX applications. ST interval, T wave changes along with prominent J wave could represent important indicators for chronic DOX-cardiomyopathy in dogs. These results encourage future studies to revalidate the findings on larger population of canine patients receiving DOX therapy in cooperation with other diagnostic modalities.

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Declaration of Conflict of Interest

The authors declare that there is no conflict of interest.

Ethical of approval

All study procedures were approved by Institutional Animal Care and Use Ethical Committee, Faculty of Veterinary Medicine, Damanhur University (Approval number: DMU/VetMed- 2025/004).

TABLE 1. Electrocardiographic data for all animals at baseline and every 21 days prior to each of six DOX sessions. Median (IQR) and Min.- Max. values were reported for each evaluation.

	Baseline	First dose	Second dose	Third dose	Fourth dose	Fifth dose	Sixth dose
Population (n)	5	5	5	5	5	5	4
Evaluation day	0	21	42	63	84	105	126
Cumulative dose of DOX (mg/ m^2)	0	30	60	90	120	150	180
Body weight (kg)	20 (7)	20 (5)	20 (5)	18 (5)	20 (6)	18 (5)	20 (-)
	(12- 20)	(15- 20)	(14- 20)	(14- 19)	(14- 20)	(15- 20)	(15- 21)
BSA (m^2)	0.744 (0.173)	0.744 (0.130)	0.744 (0.117)	0.694 (0.132)	0.744 (0.143)	0.694 (0.117)	0.744 (-)
	(0.529- 0.744)	(0.614- 0.744)	(0.587- 0.744)	(0.587- 0.719)	(0.587- 0.744)	(0.614- 0.744)	(0.614- 0.769)
Heart rate (bpm)	120 (29)	100 (20)	125 (35)	140 (40)	140 (50) *	140 (25) *	120 (-)
	(80- 125)	(80- 100)	(100- 140)	(100- 160)	(120- 200)	(120- 160)	(100- 140)
P amplitude (mV)	0.20 (0.20)	0.20 (0.10)	0.2 (0.10)	0.2 (-)	0.2 (0.1)	0.2 (-)	0.2 (-)
	(0.10- 0.40)	(0.10- 0.20)	(0.20- 0.40)	-	(0.1- 0.2)	-	-
P duration (ms)	40 (5)	40 (20)	40 (5)	40 (-)	40 (10)	40 (10)	40 (-)
	(30- 40)	(20- 40)	(40- 50)	-	(20- 40)	(20- 40)	-
QRS amplitude (mV)	1 (0.15)	1 (0.75)	1.2 (0.4)	1 (0.5)	1.4 (0.7)	1.6 (0.8)	1.4 (-)
	(0.8- 1)	(0.8- 1.8)	(1.2- 1.6)	(0.8- 1.8)	(0.9- 1.8)	(0.8- 1.8)	(1- 1.6)
QRS duration (ms)	60 (10)	60 (10)	50 (15)	40 (15)	40 (10)	40 (10)	40 (-)
	(40- 60)	(40- 60)	(40- 60)	(40- 60)	(40- 60)	(40- 60)	(40- 60)
PR interval (ms)	100 (40)	100 (30)	100 (10)	100 (10)	100 (20)	100 (10)	100 (20)
	(80- 120)	(80- 120)	(80- 100)	(100- 120)	(80- 100)	(80- 100)	(80- 100)
R-R interval (ms)	520 (70)	550 (170)	480 (110)	440 (160)	400 (80)	420 (80)	480 (-)
	(440- 540)	(440- 680)	(400- 540)	(400- 600)	(320- 460)	(400- 520)	(440- 500)
QT interval (ms)	220 (20)	200 (20)	200 (50)	190 (30)	180 (10)	200 (20)	200 (-)
	(200- 220)	(200- 220)	(180- 240)	(180- 220)	(180- 200)	(180- 200)	(200- 220)
QTc (ms)	213 (16)	210 (11)	215 (47)	203 (23)	192 (30)	209 (28)	210 (-)
	(207- 225)	(201- 216)	(183- 249)	(191- 220)	(188- 222)	(184- 219)	(207- 226)
MEA (°)	74 (9)	70 (73)	52 (63)	64 (35)	62 (34)	67 (28)	71 (-)
	(71- 85)	(0- 81)	(0- 74)	(15- 73)	(40- 81)	(30- 77)	(58- 85)

For any constant data, actual values were reported rather than descriptive analysis. "*" is used to indicate the significant difference between the first and the fourth as well as between the first and the fifth post- DOX infusion at a *p value* < 0.05.

BSA: body surface area, DOX: doxorubicin and n: overall number of animals.

TABLE 2. Changes in ST segment, T wave and J wave for each animal at baseline and every 21 days prior to each of six DOX sessions.

ECG findings	Day of evaluation	Animal				
		1	2	3	4	5
ST segment (amplitude of deviation (mV), position)	0	ISO	0.1 (□)	ISO	0.05 (□)	0.1 (□)
	21	ISO	ISO	0.1 (□)	ISO	ISO
	42	ISO	ISO	0.2 (□)	0.1 (□)	ISO
	63	ISO	ISO	ISO	ISO	ISO
	84	0.2 (□)	0.2 (□)	0.05 (□)	0.1(□)	ISO
	105	ISO	0.1 (□)	ISO	0.2 (□)	0.2 (□)
	126	ISO	0.2 (□)	0.1 (□)	Dead	0.2 (□)
T wave (amplitude (mV), polarity)	0	0.15 (+ve)	0.2 (+ve)	0.2 (+ve)	0.2 (+ve)	0.1 (+ve)
	21	0.3 (+ve)	0.3 (+ve)	0.2 (+ve)	0.2 (+ve)	0.2 (+ve)
	42	0.2 (+ve)	0.2 (+ve)	0.2 (+ve)	0.2 (-ve)	0.2 (+ve)
	63	0.1 (+ve/-ve)	Flat	Flat	0.2 (+ve)	0.1 (+ve)
	84	0.3 (-ve)	0.3 (-ve)	0.1 (+ve/-ve)	0.2 (-ve)	0.2 (+ve)
	105	0.1 (+ve/-ve)	0.3 (-ve)	0.2 (-ve)	0.3 (-ve)	0.2 (+ve)
	126	0.1 (-ve)	0.3 (-ve)	0.2 (-ve)	Dead	0.2 (+ve)
J wave (amplitude (mV) if present)	0	0.05	-	-	0.05	0.1
	21	0.1	0.2	-	0.1	0.2
	42	0.1	0.2	0.2	0.1	0.2
	63	0.1	0.1	0.2	0.2	0.1
	84	0.2	0.2	0.1	0.15	0.2
	105	0.2	0.2	0.1	0.2	0.2
	126	0.2	0.2	0.1	Dead	0.2

Actual values were reported for ST deviation, T wave and J wave amplitudes. " ISO, □ and □" were used to indicate isoelectric location, elevation and depression of ST segment respectively. "+ve, -ve and +ve/ -ve" were used to indicate positive, negative and biphasic morphology of T wave.

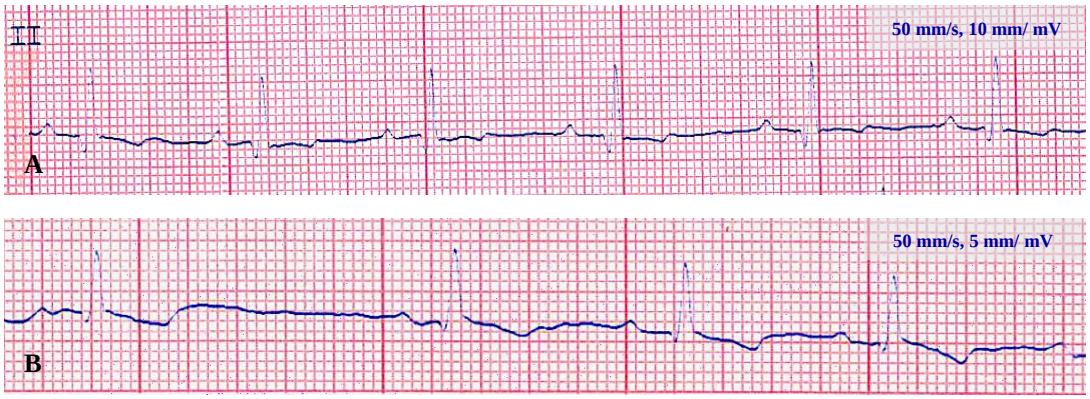

Fig.1. (A)Lead II reading from the 3rd post DOX infusion showing flattening of the T wave (amplitude: 0.05 mV) and isoelectric ST segment. (B) Lead II reading from the 6th post DOX infusion showing a slurred J wave (0.2 mV), depressed ST segment (0.2 mV) and negative T wave (> 0.2 mV).

References

1. Morita, T., Uchida, N. and Kimura, M. Effects of chemotherapy treatment with doxorubicin on right ventricular function in dogs. *Journal of Veterinary Medical Science*, **86**(8), 885-891(2024).
2. Kinoshita, T., Yuzawa, H., Natori, K., Wada, R., Yao, S., Yano, K., Akitsu, K., Koike, H., Shinohara, M., Fujino, T. and Shimada, H. Early electrocardiographic indices for predicting chronic doxorubicin-induced cardiotoxicity. *Journal of Cardiology*, ***77***(4), 388-394(2021).
3. Pino, E.H.M., Weber, M.N., de Oliveira, L.O., Vieira, L.C., Dos Santos, K.H., Liu, I.P., Gomes, H.M., Trindade-Gerardi, A.B., Moreira, J.C. and Gerardi, D.G. Evaluation of cardioprotective effects of carvedilol in dogs receiving doxorubicin chemotherapy: A prospective, randomized, double-blind, placebo controlled pilot study. *Research in Veterinary Science*, **135**, 532-541(2021).
4. Hallman, B.E., Hauck, M.L., Williams, L.E., Hess, P.R., Suter, S.E. Incidence and risk factors associated with development of clinical cardiotoxicity in dogs receiving doxorubicin. *J. Vet. Intern. Med.*, **33**, 783–791(2019). [Medline] [CrossRef]
5. Simunek, T., Sterba, M., Popevol´a, O., Adamcov´a, M., Hrdina, R., Gersl, V. Anthracycline-induced cardiotoxicity: overview of studies examining the roles of oxidative stress and free cellular iron. *Pharmacol. Rep.*, **61**, 154–171 (2009).

6. de Souza, R.C.A. and Camacho, A.A. Neurohormonal, hemodynamic, and electrocardiographic evaluations of healthy dogs receiving long-term administration of doxorubicin. *American journal of Veterinary Research*, **67**(8), 1319-1325(2006).

7. Billingham, M.E., Mason, J.W., Bristow, M.R. and Daniels, J.R. Anthracycline cardiomyopathy monitored by morphologic changes. *Cancer. Treat. Rep.*, **62**, 865-872(1978).

8. Onishi, T., Fukuda, Y., Miyazaki, S., Yamada, H., Tanaka, H., Sakamoto, J., Daimon, M., Izumi, C., Nonaka, A., Nakatani, S. and Akaishi, M. Guideline Committee of the Japanese Society of Echocardiography. Practical guidance for echocardiography for cancer therapeutics-related cardiac dysfunction. *J. Echocardiogr.*, **19**, 1–20(2021). [Medline] [CrossRef]

9. Postorino, N.C., Susaneck, S.J., Withrow, S.J.,Macy, D.W. and Harris, C.. Single agent therapy with adriamycin for canine lymphosarcoma. *J. Am. Anim. Hosp. Assoc.*, **25**, 221–225(1989).

10. Gillings, S.L., Johnson, J., Fulmer, A. and Hauck, M. Effect of a 1-hour IV infusion of doxorubicin on the development of cardiotoxicity in dogs as evaluated by electrocardiography and echocardiography. *Vet. Ther.*, **10**, 46-58 (2009).

11. Ratterree, W., Gieger, T., Pariaut, R., Saelinger, C. and Strickland, K. Value of echocardiography and electrocardiography as screening tools prior to doxorubicin administration. *J. Am. Anim. Hosp. Assoc.*, **48**(2), 89-96 (2012).

12. Pino, E.H.M., Weber, M.N., de Oliveira, L.O., Vieira, L.C., Dos Santos, K.H., Liu, I.P., Gomes, H.M., Trindade-Gerardi, A.B., Moreira, J.C. and Gerardi, D.G. Evaluation of cardioprotective effects of carvedilol in dogs receiving doxorubicin chemotherapy: A prospective, randomized, double-blind, placebo controlled pilot study. *Research in Veterinary Science*, **135**, 532-541(2021).

13. Mauldin, G.E., Fox, P.R., Patnaik, A.K., Bond, B.R., Mooney, S.C. and Matus, R.E., Doxorubicin-lnduced Cardiotoxicosis Clinical Features in 32 Dogs. *Journal of Veterinary Internal Medicine*, **6**(2), 82-88(1992).

14. Xin, Y., Zhang, S., Gu, L., Liu, S., Gao, H., You, Z., Zhou, G., Wen, L., Yu, J. and Xuan, Y. Electrocardiographic and biochemical evidence for the cardioprotective effect of antioxidants in acute doxorubicin-induced cardiotoxicity in the Beagle dogs. *Biological and Pharmaceutical Bulletin*, **34**(10), 1523-1526(2011).

15. Hanai, K., Takabe, K., Manabe, S., Nakano, M., Kohda, A. and Matsuo, M. Evaluation of cardiac function by echocardiography in dogs treated with doxorubicin. *The Journal of Toxicological Sciences*, **21**(1), 1-10(1996).

16. Danesi, R., Del Tacca, M., Bernardini, N., Cardini, G. and Bellini, O.. Evaluation of the JT and corrected JT intervals as a new ECG method for monitoring doxorubicin cardiotoxicity in the dog. *Journal of pharmacological methods*, **21**(4), 317-327(1989).

17. Goorin, A.M., Borow, K.M. , Goldman A., Williams, R. G. , Henderson, I .C. , Sallan, S. E. , Cohen, H. and , Jaffe, N., Congestive heart failure due to adriamycin cardiotoxicity: its natural history in children. *Cancer*, **47**(12), 2810–6281(1981).

18. Visser, L.C., Ciccozzi, M.M., Sintov, D.J. and Sharpe, A.N. Echocardiographic quantitation of left heart size and function in 122 healthy dogs: a prospective study proposing reference intervals and assessing repeatability. *Journal of Veterinary Internal Medicine*, **33**, 1909-1920(2019). https://doi.org/ 10.1111/jvim.15562

19. Boon, J.A. Veterinary echocardiography: "Evaluation of size, function and hemodynamics", 2nd edition, Willey-Blackwell, West Sussex, UK, pp: 153-171(2011).

20. Cornell, C.C., Kittleson, M.D., Torre, P.D., Häggström, J., Lombard, C.W., Pedersen, H.D., Vollmar, A. and Wey, A. Allometric scaling of M-mode cardiac measurements in normal adult dogs. *Journal of Veterinary Internal Medicine*, **18**, 311-321. (2004) https://doi.org/10.1111/j.1939-1676.2004.tb02551.x

21. Willis, R., Oliveira, P. and Mavropoulou, A. Guide to canine and feline electrocardiography: " Electrocardiography", first edition, John Wiley & Sons, pp: 35- 65(2018) .

22. Gallay-Lepoutre, J., Belanger, M.C. and Nadeau, M.E. Prospective evaluation of Doppler echocardiography, tissue Doppler imaging and biomarkers measurement for the detection of doxorubicin-induced cardiotoxicity in dogs: A pilot study. *Research in Veterinary Science*, **105**, 153-159(2016).

23. Pereira Neto, G.B., Andrade, J.N.B., Sousa, M.G. and Camacho, A.A. Holter electrocardiography in dogs showing doxorubicin-induced dilated cardiomyopathy. *Arquivo Brasileiro de Medicina Veterinária e Zootecnia*, **58**, 1037-1042(2006).

24. van Acker, S.A., Kramer, K., Voest, E.E., Grimbergen, J.A., Zhang, J. and van der Vijgh, W.J., van der Vijgh, W. J. and Bast, A., Doxorubicin-induced cardiotoxicity monitored by ECG in freely moving mice. A new model to test potential protectors. *Cancer Chemother Pharmacol.*, **38**, 95–101(1996).

25. Osborn, J. J. Experimental hypothermia; respiratory and blood pH changes in relation to cardiac function. *Am. J. Physiol.*, **175**, 389–398(1953).

26. Elsharkawy, S.H. and Torad, F.A. Prominent J wave in cats with hypertrophic cardiomyopathy. *Journal of Veterinary Medical Science*, **83**(7), 1093-1097(2021).

27. Sridharan, M. R. and Horan, L. G. Electrocardiographic J wave of hypercalcemia. *Am. J. Cardiol.* **54**, 672–673(1984).

28. Rudling, E. H., Schlamowitz, S., Pipper, C. B., Nilsson, E., Höllmer, M., Willesen, J. L., Berendt, M., Fredholm, M., Gulløv, C. H., Christiansen, M. and Koch, J. The prevalence of the electrocardiographic J wave in the Petit Basset Griffon Vendéen compared to 10 different dog breeds. *J. Vet. Cardiol.*, **18**, 26–33(2016).

29. Sarkozy, A., Chierchia, G. B., Paparella, G., Boussy, T., De Asmundis, C., Roos, M., Henkens, S., Kaufman, L., Buyl, R., Brugada, R., Brugada, J. and Brugada, P. Inferior and lateral electrocardiographic repolarization abnormalities in Brugada syndrome. *Circ. Arrhythm. Electrophysiol.*, **2**, 154–161(2009)

30. Tsuda, T., Hayashi, K., Konno, T., Sakata, K., Fujita, T., Hodatsu, A., Nagata, Y., Teramoto, R., Nomura, A., Tanaka, Y., Furusho, H., Takamura, M., Kawashiri, M. A., Fujino, N. and Yamagishi, M.: J waves for predicting cardiac events in hypertrophic cardiomyopathy. *JACC Clin. Electrophysiol.*, **3**, 1136–1142(2017).

31. Kharin, S., Krandycheva, V., Tsvetkova, A., Strelkova, M. and Shmakov, D. Remodeling of ventricular repolarization in a chronic doxorubicin cardiotoxicity rat model. *Fundam Clin Pharmacol*, **27**,364–372(2013).

أهم مؤشرات رسم القلب الكهربائي للكشف عن اصابة عضلة القلب الناتج عن اعتلال عضلة القلب التجريبي المترتب على استخدام الدوكسوروبيسين في الكلاب

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الملخص

الدوكسوروبيسين لمعالجة مختلف الأورام الخبيثة. إن الكشف المبكر عن التغيرات القلبية خطوة إلزامية لمنع الأضرار الدائمة وغير القابلة للعلاج في عضلة القلب. تم استخدام العديد من الأدوات لاكتشاف هذه التغيرات بما في ذلك فحص القلب بالموجات فوق الصوتية (ECHO)، رسم القلب الكهربائي (ECG) وتحليل مؤشرات إصابة عضلة القلب. يعد تخطيط القلب الكهربائي أداة فعالة من حيث التكلفة، لفحص الإصابة الناتجة عن الدوكسوروبيسين في الكلاب. وحتى الآن، لم يتم وضع معايير للكشف عن التسمم القلبي المزمن والناتج عن استخدام الدوكسوروبيسين في الكلاب باستخدام رسم القلب الكهربائي. تم استخدام خمسة كلاب ذكور بالغين بعد التأكد من خلوها من أي إصابة، لتلقي ست جرعات متتالية من الدوكسوروبيسين (٣٠ ملغ/ متر مربع) التي تم تكرارها بفاصل زمني قدره ثلاثة أسابيع. تم إجراء فحوصات إكلينيكية، فحص القلب بالموجات فوق الصوتية، رسم القلب الكهربائي وفحوصات كيميائية حيوية قبل تطبيق أول جرعة من الدوكسوروبيسين. تم تقييم رسم القلب الكهربائي بشكل متسلسل قبل كل جلسة متتالية من الدوكسوروبيسين ثم بعد ثلاثة أسابيع من إنهاء العلاج. تم توحيد الاليكترود الثاني في رسم القلب الكهربائي لجميع القياسات بما في ذلك معدل ضربات القلب، الإيقاع، مدة واتساع الموجة P و مركب QRS، مدة PR و QT و QTc، و وجود واتساع الموجة J، القطبية واتساع الموجة T، المحور الكهربائي المتوسط وموقع مقطع الST. لم يتم الكشف عن أي اضطرابات في إيقاع القلب باستثناء تَسرُّع القلب الجيبي. كانت التغيرات الأكثر اكتشافًا في تخطيط القلب هي انخفاض أو ارتفاع مقطع الST، تسطح وانقلاب الموجة T بالإضافة إلى الموجة J البارزة. في الختام، قد تمثل التغيرات في مقطع الST والموجة T بالإضافة إلى الموجة J البارزة مؤشرات هامة للتسمم القلبي المزمن الناتج عن الدوكسوروبيسين في الكلاب.

الكلمات الدالة: اعتلال عضلة القلب، الكلاب ، الدوكسوروبيسين، رسم القلب الكهربائي.