Arch Med Vet **46, 63-68 (2014)** **DOI: 10.4067/s0301-732x2014000100009**

ORIGINAL ARTICLE

Assesment of the TEI index of myocardial performance in dogs with doxorubicin-induced cardiomiopathy

Evaluación del índice de desempeño miocárdico de TEI en perros con cardiomiopatía inducida por doxorrubicina

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RESUMEN

El desarrollo de una cardiomiopatía dosis dependiente es la principal limitación para el uso de doxorrubicina en protocolos de quimioterapia tanto en seres humanos como en animales. En estos casos, la función global del miocardio puede ser cedida, teniendo como resultado signos atribuibles a la insuficiencia cardíaca congestiva. En este estudio, nosotros investigamos la capacidad del índice de desempeño miocárdico de Tei para identificar disfunción de miocardio en perros sanos tratados con doxorrubicina a una dosis cumulativa de 210 mg/m^2 en un periodo de 147 días, comparándolo con otros indicadores ecográficos estándar de función sistólica y diastólica. Nuestros resultados indicaron que el índice de Tei, el tiempo de relajación isovolumétrica, el período de pre-eyección, y la relación período de pre-eyección/tiempo de eyección ventricular izquierda pudieron identificar los efectos cardiotóxicos de doxorrubicina en la función cardíaca cuando sólo 60 mg/m^2 habían sido administrados, mientras los parámetros estándar sistólicos y diastólicos, incluso el diámetro sistólico del ventrículo izquierdo, la fracción de eyección y la fracción de acortamiento, necesitaron por lo menos 120 mg/mg^2 para empeorar. Se concluye que la terapia prolongada con antraciclinas perjudica las funciones sistólica y diastólica, que pueden ser documentadas antes adicionándose el índice de Tei a la evaluación ecográfica estándar en animales que reciben doxorrubicina.

Palabras clave: cardiotoxicidad, antraciclinas, disfunción cardiaca, quimioterapia.

SUMMARY

The development of a dose-dependent cardiomyopathy is the main limitation for the use of doxorubicin in chemotherapy protocols in both humans and animals. In this setting, the global myocardial function may be compromised resulting in signs of congestive heart failure. In this study, we investigated the ability of the Tei index of myocardial performance to identify myocardial dysfunction in healthy dogs receiving doxorubicin to a cumulative dose of 210 mg/m^2 over 147 days, comparing it with other standard echocardiographic indicators of systolic and diastolic function. Our results indicated that the Tei index, the isovolumic relaxation time, pre-ejection period and the pre-ejection period-to-left ventricular ejection time ratio were able to identify the cardiotoxic effects of doxorubicin on cardiac function when only 60 mg/m^2 had been administered, while the standard systolic and diastolic parameters, including left ventricular diameter at systole, ejection fraction, and fractional shortening needed at least 120 mg/mg^2 to deteriorate. We concluded that prolonged anthracycline therapy compromises both systolic and diastolic functions, which may be documented earlier by including the Tei index evaluation to the standard echocardiographic assessment of animals receiving doxorubicin.

Key words: cardiotoxicity, anthracycline, cardiac dysfunction, chemotherapy.

INTRODUCTION

Doxorubicin is an anthracycline drug indicated for the treatment of several neoplasms. Its mechanism of action is not completely understood, but it is likely tobe related with toxic oxidative metabolites, which are not as well metabolized by the heart as they are by other organs (Olson and Mushlin 1990). Although indicated in both medical and veterinary practices, doxorubicin has a limited use owing to the development of a dose-dependent cardiomyopathy that can lead to congestive heart failure (Susaneck 1983, Maudlin *et al* 1992, Souza and Camacho 2006).

Because doxorubicin cardiotoxicity tends to be related to the cumulative dose and dosing schedule (Ganz *et al* 1996), several protocols have been proposed to minimize the toxic effects on the heart. In our laboratory, when doxorubicin was given to healthy dogs at 30 mg/m^2 each 21 days until a cumulative dose of 240 mg/m^2 was achieved, signs of congestive heart failure developed 165 days after chemotherapy started. However, an increase in the left ventricular diameter at systole and diastole, and reductions in both fractional shortening ($FS_{\%}$) and ejec-

Accepted: 18.04.2013.

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tion fraction ($EF_{\%}$) were documented much earlier, at 91 days post initiation (Silva and Camacho 2005).

In human beings, it has been demonstrated that diastolic dysfunction also occurs during anthracycline-based chemotherapy (Tjeerdsma *et al* 1999). Nonetheless, only few veterinary studies have evaluated diastolic parameters in animals treated with doxorubicin. Several methods may be used to investigate diastolic function. Standard echocardiography can be used to assess the isovolumic relaxation time (IVRT), and flow deceleration times through the analysis of atrioventricular flows. Moreover, the Tei index (TEI), an index of myocardial performance useful in estimating ventricle function, demonstrated to correlation with indicators of diastolic function, including the diastolic peak (-dP/dt) and *tau* in people with ischemic heart disease (Tei *et al* 1997). Also, in a porcine model, this index showed a direct correlation with the ventricular stiffness constant, and it was inversely related to the ejection fraction, thereby supporting its clinical use not only as an indicator of diastolic performance, but as a measure of global ventricular function (Lacorte *et al* 2003). TEI is defined as (Isovolumic contraction time + Isovolumic relaxation time)/Left-ventricular ejection time, as reported elsewhere (Tei 1995, Tei *et al* 1995).

Therefore, the goal of this study was to assess the Tei index in healthy dogs receiving doxorubicin, and to compare this index with some standard echocardiographic indicators of systolic and diastolic functions.

MATERIAL AND METHODS

ANIMALS

Seven mature mongrel dogs of either sex, with mean weight of 17.6 kg, were enrolled in the study. The dogs were housed in individual cages and were given free access to water and provided with commercially available dog food twice a day during the entire period of the experiment. The study was conducted in accordance with the guidelines outlined in the National Institutes of Health Guide for the Care and Use of Laboratory Animals, and was previously approved by the institutional Commission on Ethics and Animal Welfare under protocol 1538/06. Health status of the animals was assessed prior to the beginning of the experiment based on results of both physical and laboratory examinations.

INDUCTION OF DOXORUBICIN CARDIOMYOPATHY

To induce the cardiomyopathy, 30 milligrams of doxorubicin per m^2 of body area were given intravenously at 21-day intervals (M30, M60, M90, M120, M150, M180, and M210) until a cumulative dose of 210 mg/m^2 was achieved.

ASSESSMENT OF CARDIAC FUNCTION

A transthoracic echocardiographic examination was performed in every dog using a 5.0 MHz mechanical sector transducer. Echocardiographic images were recorded with a simultaneous lead II electrocardiogram for offline measurements. A single experienced veterinary cardiologist was responsible for all echocardiographic studies.

To obtain better images, hair was clipped between the right 3rd and 6th intercostal spaces, and left 2nd and 7th intercostal spaces. Generous coupling gel was applied to these areas of the thorax immediately before echocardiography was started. Measurements were taken by using two-dimensional-guided M-mode on the standard right parasternal short-axis view at chordae tendineae level for measurement of left ventricular end-systolic (LV_s) and end-diastolic (LV_d) dimensions, which were used for calculation of $EF_{\%}$ and $FS_{\%}$. With dogs positioned in left lateral recumbency, either apical four-chamber view or apical five-chamber view images were acquired. Gain and filter settings were adjusted individually to reduce background noise and result in clear flow signals. To acquire inflow and outflow velocity spectra during the same cardiac cycle, the Doppler sample volume was placed midway between mitral inflow and left ventricular outflow in the apical five-chamber view. Left-ventricular ejection time (LV_{ET}) was determined as the duration of left ventricular outflow profile, and TEI was calculated by using the formula $(A - LV_{ET})/LV_{ET}$ where A is the time interval between the end and the onset of transmitral flow (Tei and others 1995).

The apical five-chamber view was also used to measure the pre-ejection period (PEP) from the electrocardiogram Q wave to the onset of the left-ventricular outflow. IVRT was measured as the interval between aortic valve closure and the onset of mitral inflow. Also, the PEP-to-LV_{ET} ratio (PEP/LV_{ET}) was calculated. Mitral peak velocities of early (E) and late (A) diastole were acquired at the tips of the mitral valve leaflets, and were used to calculate the E-to-A ratio (E/A). Based on aortic flow spectra, stroke index (SI) and cardiac index (CI) were also calculated. These parameters were chosen because they are indicators of either systolic or diastolic function included in the standard echocardiogram and may be measured easily without the need of advanced echo modalities, such as tissue doppler imaging.

All echocardiographic measurements were recorded at baseline and at 21-day intervals until a cumulative dose of 210 mg of doxorubicin per m^2 of body area was achieved. M-mode measurements were performed in accordance with the recommendations of the American Society of Echocardiography. At least three consecutive beats were measured and averaged for each parameter. All Doppler parameters were recorded using pulsed-wave Doppler, and special care was taken to perform these measurements with the Doppler beam as parallel as possible to the presumed direction of blood flow.

STATISTICAL ANALYSES

The mean and standard deviation of all echocardiographic measurements were calculated. A repeated measures analysis of variance was applied to the various echo measures to investigate differences over time. When the differences were determined by the analysis of variance to be significant, the *post hoc* Tukey-Kramer multiple comparisons test was used to further investigate differences. The software Prism for Windows v. 5.04 (Graphpad Software, San Diego CA, USA) was used for all statistical analyses, and significance was set at $P < 0.05$.

RESULTS

No complications were seen during the induction of doxorubicin cardiomyopathy. Although several alterations have been detected over time in the echocardiographic examinations, the dogs enrolled in the study presented no clinical signs at all, but a mild reduction in body weight during the induction period.

Table 1 gives the results of echocardiographic parameters. Significant differences along time are reported. A significant increase in LV_s, PEP, IVRT, PEP/LV_{ET}, and TEI was observed along doxorubicin therapy. Also, significant decreases were seen in $EF_{\%}$ and $FS_{\%}$. Although not statistically significant, an increase was documented for LV_d, as well as a decrease for E/A, SI and CI in accordance with the infusion of cumulative doses of doxorubicin. On the contrary, LV_{ET} remained relatively unchanged during therapy.

The Tei index values at M60 showed differences from the baseline values, meaning that 60 mg of doxorubicin resulted enough to cause changes in myocardial performance as revealed by such parameter. Interestingly, $EF_{\%}$ attained significant difference from the baseline value only at M120, whereas for $FS_{\%}$, a significant change was only documented at M150. Regarding diastolic function, significant changes were observed in IVRT at M60. Differently the E/A did not differ significantly from its baseline value at all times, but some animals showed an inverse mitral E/A at M150.

DISCUSSION

Although it was not the primary aim of this study to describe the myocardial morphologic and functional alterations owing to doxorubicin, it is clear that this drug produces cardiotoxicity in a dose-dependent fashion (Maudlin *et al* 1992). As far as the cumulative dose of 120 mg of doxorrubicin/m^2 was achieved, most dogs included in this investigation demonstrated significant alterations in the indicators of systolic function. As the infusion of the drug progressed, several parameters changed statistically as compared to baseline values. When the cumulative dose of 210 mg/m^2 had been given, an important systolic dysfunction was documented in all dogs based on echocardiographic indicators. This is in agreement with previous studies that demonstrated the progressive cardiotoxicity of doxorubicin, resulting in both clinical and echocardiographic findings similar to those of idiopathic dilated cardiomyopathy (Silva and Camacho 2005, Souza and Camacho 2006). Interestingly, none of the animals of this study developed signs of severe heart failure, such as pulmonary edema, as reported by Maudlin and colleagues (1992), whose investigation showed that heart failure may arise in dogs as soon as 90 mg of doxorubicin/m^2 had been given. This finding may be attributable to variations in individual responses to anthracycline therapy (Souza 2004, Silva and Camacho 2005).

According to the echocardiographic indicators of cardiac function, a marked deterioration in systolic and diastolic functions occurred as the cardiomyopathy progressed. Thus, the greater the cumulative dose of doxorubicin, the highest the degree of myocardial dysfunction documented. It is well known that such cardiotoxicity develops because arachidonic acid metabolites, histamine, platelet-activating factor, and free radicals are released into the cardiac muscle, leading to functional damage and myocardial remodeling (Toyoda et al 1998, Sousa and Camacho 2007). In this regard, our results are similar to those described by Souza (2004) and Silva and Camacho (2005) along the induction of doxorubicin cardiomyopathy. These authors also identified a progressive increase of the left ventricular diameter at systole, with diminished contractility. However, a major problem of using both shortening and ejection fractions to estimate contractility rely on the influence played by preload and afterload on them, therefore making them less specific in quantifying systolic function (Ferraris 2007, Boon 2011). Also, because the ejection fraction in this investigation was calculated using the unidimensional left ventricular measures in systole and diastole processed by Teichholz´s corrected cubic equation, the values of $EF_{\%}$ are proportional to those of $FS_{\%}$ (Henik 2002). Nonetheless, because $PEP\text{-to-}LV_{ET}$ ratio is inversely proportional to myocardial contractility (Sousa et al 2007), its increase observed herein is consistent with a reduction in contractility.

Regarding diastolic function, our results demonstrated some degree of impairment after the cumulative dose of 90 mg/m^2 was reached. Although in many veterinary studies the diastolic function has historically been left aside, diastolic dysfunction has been documented in human patients treated with doxorubicin for breast cancer (Tjeerdsma *et al* 1999). Interestingly, Marchandise *et al* (1989) and Stoddard *et al* (1992) have demonstrated that diastolic dysfunction might occur prior to systolic dysfunction, making it an earlier indicator of doxorubicin cardiotoxicity. In this study, the diastolic impairment was demonstrated by the prolongation of IVRT, as well as by the reduction of the E/A. Although the majority of pre-

Table 1. Echocardiographic parameters (mean ± SD) in dogs being given doxorubicin (n = 7).
Parámetros ecocardiográficos (promedio ± SD) en perros con doxorubicina (n = 7).

Parameter	Baseline	M30	M60	M90	M120	M150	M180	M210	P
	0 mg	30 mg	60 mg	90 mg	120 mg	150 mg	180 mg	210 mg	ANOVA
LV_s	2.23 ± 0.08	2.28 ± 0.24	2.33 ± 0.28	2.47 ± 0.11	2.47 ± 0.24	2.69 ± 0.20*	2.79 ± 0.16*	2.95 ± 0.12*	< 0.0001
LV_d	3.51 ± 0.34	3.66 ± 0.26	3.53 ± 0.18	3.42 ± 0.33	3.46 ± 0.33	3.48 ± 0.23	3.53 ± 0.21	3.73 ± 0.12	0.3688
$EF_{\%}$	66.7 ± 4.5	64.3 ± 10.0	62.6 ± 11.0	57.0 ± 10.1	51.7 ± 10.5*	45.3 ± 7.0*	43.8 ± 5.4*	42.0 ± 5.8*	< 0.0001
$FS_{\%}$	36.1 ± 3.5	34.8 ± 7.2	33.3 ± 7.8	29.5 ± 6.8	28.0 ± 7.2	22.8 ± 3.9*	20.7 ± 2.3*	19.1 ± 3.0*	< 0.0001
PEP	34.2 ± 5.6	40.2 ± 4.7	48.2 ± 8.7*	48.6 ± 8.0*	49.8 ± 4.3*	50.0 ± 8.7*	53.3 ± 8.7*	66.7 ± 11.3*	< 0.0001
LV_{ET}	218.0 ±15.4	220.1±6.6	222.7±9.0	215.0±6.9	207.5±3.5	211.7±9.9	216.5±8.1	220.1±10.2	0.0736
IVRT	31.6 ± 9.0	37.9 ± 5.5	43.3 ± 8.2*	46.7 ± 8.6*	48.1 ± 6.8*	49.8 ± 5.1*	54.7 ± 2.8*	57.8 ± 4.7*	< 0.0001
PEP / LV_{ET}	0.15 ± 0.03	0.18 ± 0.02	0.24 ± 0.05*	0.22 ± 0.03*	0.20 ± 0.03	0.24 ± 0.05*	0.24 ± 0.05*	0.32 ± 0.05*	< 0.0001
E / A	1.41 ± 0.29	1.30 ± 0.20	1.29 ± 0.16	1.31 ± 0.19	1.31 ± 0.04	1.26 ± 0.33	1.20 ± 0.34	1.17 ± 0.20	0.6927
SI	50.1 ± 7.9	53.1 ± 9.8	46.3 ± 12.4	42.2 ± 10.1	45.5 ± 8.9	38.1 ± 4.9	36.0 ± 4.3	40.8 ± 4.7	0.0046
CI	5.3 ± 1.8	6.1 ± 0.4	4.7 ± 0.7	4.4 ± 1.4	5.0 ± 1.6	4.8 ± 1.5	4.7 ± 1.3	4.7 ± 0.7	0.3102
TEI	0.26 ± 0.04	0.35 ± 0.04	0.43 ± 0.08*	0.44 ± 0.04*	0.43 ± 0.06*	0.48 ± 0.05*	0.49 ± 0.05*	0.59 ± 0,09*	< 0.0001

LV_s: left-ventricular diameter at systole (cm); LV_d: left-ventricular diameter at diastole (cm); $EF_{\%}$: ejection fraction (%);$FS_{\%}$: fractional shortening (%); PEP: pre-ejection period (milliseconds); LV_{ET}: left-ventricular ejection time (milliseconds); IVRT: isovolumic relaxation time (milliseconds); PEP/LV_{ET}: PEP-to-LV_{ET}-ratio; E/A: Mitral E-to-Mitral A-ratio; SI: stroke index (milliliters/beat x m^2); CI: cardiac index (L/min x m^2); TEI: Tei index of myocardial performance

* Statistically different from Baseline value (P < 0.05)

vious studies using this model of cardiomyopathy only focused on systolic function, some clinical signs actually may be attributable to the diastolic impairment, which was well documented in this investigation. The diastolic compromise may result from foci of myocardial fibrosis caused by ultra-structural lesions promoted by the anthracycline therapy (Susaneck 1983, Marchandise *et al* 1989, Stoddard *et al* 1992). Although right ventricular diastolic function have not been evaluated in this research, it is likely that the same alterations observed for the left ventricle occurred on its right counterpart, since the cardiotoxicity of doxorubicin affects the whole heart (Toyoda *et al* 1998, Sousa and Camacho 2007).

According to the Tei index of myocardial performance, a global cardiac dysfunction was documented in the dogs of this investigation. This index is calculated using both isovolumic contraction time and isovolumic relaxation time, as well as the left ventricular ejection time, therefore allowing the assessment of systolic and diastolic function concurrently (Tei 1995, Pellet *et al* 2004). Besides being very simple to calculate, this index performs independently of ventricular geometry, and is likely less influenced by heart rate, arterial pressure, preload and afterload, being especially useful to evaluate remodeled hearts (Tei *et al* 1995, Sousa *et al* 2007). The cardiac dysfunction documented by the Tei index in this study is in agreement with the other echocardiographic indicators of systolic and diastolic function, which also changed along the induction of doxorubicin cardiomyopathy. However, the changes in the Tei index were identified much earlier than the standard indicators of cardiac function, making it especially useful for monitoring the cardiotoxicity of anthracycline therapy.

The main limitations of this study rely on the small number of animals enrolled, as well as the absence of a more detailed echocardiographic evaluation of diastolic function, including tissue doppler imaging and strain to better characterize diastolic dysfunction. In conclusion, this investigation showed that the prolonged therapy with doxorubicin impairs both systolic and diastolic functions, and the Tei index may be used as an easily calculated non-invasive indicator of global cardiac function.

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