

Assessment of electrocardiographic parameters in healthy dogs undergoing dobutamine stress testing

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Summary

The electrocardiographic effects of dobutamine stress testing (10 to 40 $\mu\text{g}/\text{kg}/\text{minute}$) were investigated in five conscious healthy dogs. We studied the changes in the duration and amplitude of P wave, PR interval, duration of QRS complex, R wave amplitude, QT interval, and heart rate. Development of arrhythmias and ST segment abnormalities were also recorded. It was observed that dobutamine significantly affects atrioventricular-nodal conduction and total electrical systole time at higher infusion rates. Only a single episode of sustained ventricular tachycardia was observed, which was promptly restored to sinus rhythm shortly after dobutamine infusion was discontinued. No ST segment abnormalities were detected. Dobutamine stress testing was concluded to play a role in some ECG parameters at higher infusion rates.

Keywords: dobutamine stress testing, electrocardiogram, arrhythmia, catecholamines, electrophysiology

Veränderungen elektrokardiographischer Parameter bei gesunden Hunden während Dobutamin Stressuntersuchungen

Bei fünf unsedierten gesunden Hunden wurden die Auswirkungen einer Dobutamin Stressuntersuchung (10 bis 40 $\mu\text{g}/\text{kg}/\text{Min}$) auf das EKG studiert. Untersucht wurden Veränderungen der Dauer/Amplitude der P-Welle, des PR-Intervalls, des QRS-Komplexes, der R-Zacke, des QT-Intervalls sowie der Herzfrequenz. Zusätzlich wurde auf das Auftreten von Arrhythmien und ST-Segment Veränderungen geachtet. Es wurde festgestellt, dass Dobutamin bei höheren Infusionsraten die Überleitung im AV-Knoten und die Dauer der totalen elektrischen Systole signifikant beeinflusst. Bei einem Hund wurde eine Episode einer anhaltenden ventrikulären Tachykardie beobachtet, welche sofort zu einem Sinusrhythmus konvertierte, nachdem die Dobutamin Infusion gestoppt worden war. Veränderungen am ST-Segment wurden keine festgestellt. Aus diesen Beobachtungen wird geschlossen, dass während einem Dobutamin Stress-Test bei höheren Dosierungen EKG-Veränderungen auftreten.

Schlüsselwörter: Dobutamin, Stress, Elektrokardiogramm, Arrhythmie, Katecholamine, Elektrophysiologie

Introduction

Exercise stress testing is routinely used in human beings to increase cardiac workload and assess heart function. However, several patients are unable to undergo exercise testing due to neurologic, respiratory, orthopedic, and age-related limitations. Several drugs have been proposed for stress studies. Owing to the property of increasing myocardial oxygen demand by way of enhancing contractility, dobutamine has been recognized as an alternative to exercise testing (Sawada et al., 1991; Pelikka et al., 1995). In human beings, therefore, it is possible to determine regional wall motion abnormalities and perform a better evaluation and early identification of cardiac function

disorders in comparison with echocardiography at rest (Sawada et al., 1991; Mazeika et al., 1992).

Dobutamine is a synthetic positive inotropic agent developed for short-term intravenous infusion. Its effects include augmentation of myocardial contractility via beta-1 receptor stimulation, though little effect on systemic vasculature can occur as a result of beta-2 and alpha-1 receptor agonist effects (Leier et al., 1979; Leier and Unverferth, 1983; Pelikka et al., 1995). Although often referred to as a positive inotropic agent, at doses sufficiently high dobutamine has also a chronotropic effect mediated through beta-1 receptor stimulation (Vatner and Baig, 1979; Craw-

ford, 1999). Since the hemodynamic effects of dobutamine are directly correlated with its dose and plasma concentration, dobutamine stress echocardiography demands the infusion of substantially higher doses of the drug than are used therapeutically (Pelikka et al., 1995; Mcentee et al., 1998). However, despite considered an acceptable pharmacologic stress agent for evaluation of cardiac function, dobutamine has the undesirable effect of precipitating arrhythmias (Hanson et al., 1997).

Although stress echocardiography is considered more trustworthy and informative, electrocardiographic evaluation during dobutamine stress test was demonstrated to be an objective and reliable procedure, which accurately predicts the results of standard stress testing (Martinez-Martinez et al., 1997; Martinez-Martinez et al., 2004). It has also been documented that electrocardiography has an incremental diagnostic value when used during dobutamine stress echocardiography (Shaheen et al., 1998).

In dogs, the diagnosis of dilated cardiomyopathy remains difficult if paroxysmal arrhythmias or echocardiographic evidence of ventricular dilatation and hypokinesia are not present (Calvert, 1995). During the subclinical phase, the baseline values of cardiac performance in healthy and affected dogs overlap, therefore making the diagnosis difficult prior to development of overt echocardiographic abnormalities (Calvert, 1992; Mcentee et al., 1999). Stress testing is still not frequently used in veterinary medicine, despite a clear demand for it exists indeed. The inotropic challenge with dobutamine might disclose echocardiographic abnormalities attributable to heart disease in the early stages of heart failure. Since dobutamine stress testing demands the infusion of substantially higher doses of dobutamine and this drug can precipitate arrhythmias, this study was conceived to investigate the effects of increasing doses of dobutamine on the electrocardiographic parameters, as well as the abnormalities in cardiac rhythm and ST segment in conscious healthy dogs.

Materials and Methods

Animals

Five adult female mongrel dogs were used. Dogs' mean weight was 19.5 kg. 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 guidelines outlined in the National Institutes of Health *Guide for the Care and Use of Laboratory Animals*. The animals were determined to be healthy based on results of physical, echocardiographic, and laboratorial examinations prior to the beginning of the experiment.

Drug administration

A 20F catheter was inserted into the left cephalic vein for administration of dobutamine. Every dog was individually placed in right lateral recumbency and baseline electrocardiogram (Time zero, T0) was recorded at rest for at least one minute. Just prior to the infusion, dobutamine (Dobtan – União Química – Embu-Guaçu – Brazil) was diluted in 5% dextrose in water (Solução de Glicose a 5% – JP Indústria Farmacêutica – Ribeirão Preto – Brazil) to a final concentration previously calculated in accordance with the animal's weight, in order to administer similar volumes to every animal. The solution was delivered intravenously by an infusion pump (Digi-bomb – Fundação Adib Jatene – São Paulo – Brazil) at a starting rate of 2.5 µg/kg/minute for five minutes to check the development of adverse reactions by the animal. At 15-minute intervals, the dosage was increased to (T1) 10 µg/kg/minute; (T2) 20 µg/kg/minute; (T3) 30 µg/kg/minute; and (T4) 40 µg/kg/minute.

Electrocardiography

A 6-lead computerized electrocardiogram (ECG-PC – TEB – São Paulo – Brazil) was monitored continuously and recorded as described elsewhere (Tilley, 1995). Recordings were performed five minutes after each stage of infusion started in order to allow plasma concentration of dobutamine to stabilize. We measured the following parameters: duration of P wave (Pms), P wave amplitude (PmV), duration of PR interval (PRms), duration of QRS complex (QRSms), R wave amplitude (RmV), duration of QT interval (QTms), and heart rate (HR). Changes in ST segment were also investigated, as well as the development of arrhythmias. For the parametric parameters, each value represents the average of at least five individual measurements.

Statistical analysis

The results are expressed as the means \pm SD. All data were submitted to ANOVA and Tukey-Kramer's post hoc testing to demonstrate differences in relation to baseline values (T0). Values of $P < 0.05$ were considered significant.

Results

Table 1 shows the results of resting and dobutamine stress electrocardiograms. No dog reacted adversely to the initial infusion of dobutamine. Hence, the test was performed in every animal included in this study. No ST segment depressions or elevations were observed.

Table 1: Electrocardiographic data in healthy dogs ($n = 5$) undergoing the infusion of increasing doses of dobutamine. Data expressed as mean \pm SD.

| Parameters | T0 | T1 | T2 | T3 | T4 |
|------------|-------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|
| | Baseline | 10 $\mu\text{g}/\text{kg}/\text{min}$ | 20 $\mu\text{g}/\text{kg}/\text{min}$ | 30 $\mu\text{g}/\text{kg}/\text{min}$ | 40 $\mu\text{g}/\text{kg}/\text{min}$ |
| Pms | 50.80 \pm 6.18 | 50.40 \pm 4.33 | 54.80 \pm 12.47 | 55.20 \pm 14.85 | 50.80 \pm 4.26 |
| PmV | 0.19 \pm 0.06 | 0.19 \pm 0.08 | 0.24 \pm 0.06 | 0.25 \pm 0.07 | 0.24 \pm 0.05 |
| PRms | 96.00 \pm 13.00 | 97.40 \pm 6.58 | 84.00 \pm 11.79 | 74.80 \pm 12.65* | 66.80 \pm 7.19* |
| QRSms | 70.80 \pm 4.26 | 72.00 \pm 8.88 | 64.00 \pm 5.87 | 70.00 \pm 10.44 | 70.00 \pm 13.37 |
| RmV | 1.42 \pm 0.20 | 1.59 \pm 0.35 | 1.67 \pm 0.37 | 1.55 \pm 0.42 | 1.68 \pm 0.36 |
| QTms | 220.60 \pm 6.42 | 218.60 \pm 11.37 | 208.00 \pm 5.38 | 201.20 \pm 7.88* | 202.80 \pm 10.68* |
| HR | 85.60 \pm 15.20 | 97.60 \pm 22.52 | 114.00 \pm 17.16 | 144.80 \pm 13.21* | 157.20 \pm 26.86* |

Pms: duration of P wave; PmV: P wave amplitude; PRms: PR interval; QRSms: duration of QRS complex; RmV: R wave amplitude; QTms: duration of QT interval; HR: heart rate.

* Statistically different from baseline value (T0) ($P < 0.05$)

Complications of dobutamine stress testing included the development of sustained ventricular tachycardia in one dog (Fig. 1) when receiving 20 $\mu\text{g}/\text{kg}/\text{minute}$. In this instance, the immediate termination of dobutamine infusion was enough to restore sinus rhythm. Soon afterwards, the test was restarted with no further complications. The duration of P wave (Pms) and QRS complex (QRSms) did not change significantly during dobutamine infusion. Also, when P wave and R wave amplitude (PmV and RmV) were analyzed, no differences were determined to exist among dobutamine stage values (T1 to T4) and baseline value (T0).

With the infusion of dobutamine, a decrease ($P = 0.0006$) occurred in PR interval (PRms). When this data were submitted to Tukey-Kramer's test, it was verified that the dobutamine stage values differed from baseline value at T3 and T4. Such finding was also observed for QT interval (QTms), which shortened significantly ($P = 0.0044$) at T3 and T4. Accordingly, heart rate (HR) increased significantly ($P < 0.0001$) from T3 to T4.

Discussion

In human beings, Hanson et al. (1997) demonstrated that the probability of developing nonsustained ven-

tricular tachycardia during dobutamine stress testing was 4%. Asymptomatic ventricular ectopic activity has been associated with dobutamine in 3% to 15% of human patients receiving this drug, although ventricular tachycardia similar to the case we describe appears to occur rarely (Tisdale et al., 1995). The proposed arrhythmia mechanism suggests that the increased myocardial contractility and changes in ventricular refractoriness and repolarization adversely affect myocardial oxygen balance, myocardial perfusion, and electrical stability (Stump et al., 2000).

The decrease in PR interval was probably attributable to the dromotropic effect of dobutamine. In human beings, a significant reduction in atrioventricular-nodal conduction time has been observed during the infusion of dobutamine (Bischoff et al., 1979; Leppo, 1996). The absence of changes in the duration of QRS complex and R wave amplitude was likely due to an unchanged ventricular depolarization phase even under the infusion of higher doses of dobutamine. Such findings are in contrast with results of Mcentee et al. (1998), who observed changes in ventricular depolarization phase when administering similar doses of dobutamine to healthy dogs.

The QT interval is inversely related to heart rate (Luo et al., 2004). In this study, therefore, it is probable that QT shortened due to an increase in heart rate. A significant increase in heart rate started at 30 $\mu\text{g}/\text{kg}/$

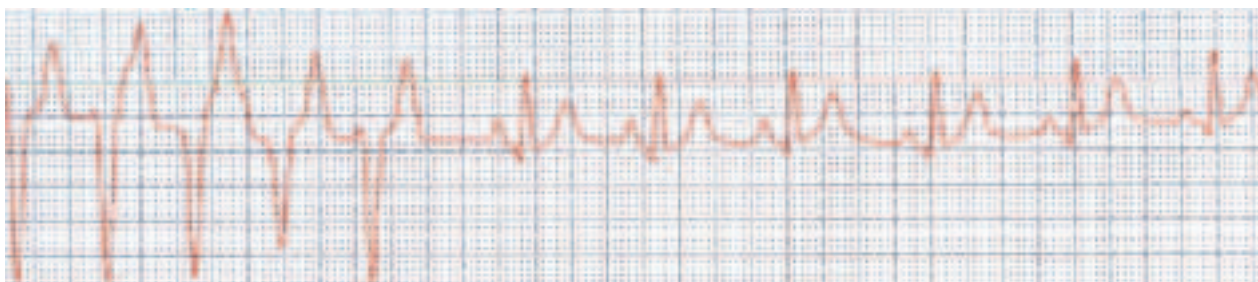


Figure 1: Electrocardiogram (D_{II} , 50 mm/s, 1cm = 1mV) from one of the animals included in the study during the infusion of dobutamine at 20 $\mu\text{g}/\text{kg}/\text{minute}$, showing sustained ventricular tachycardia, which developed suddenly. Shortly after immediate termination of dobutamine infusion sinus rhythm was restored without further interventions.

minute and was ascribed to beta-1 receptor stimulation (Vatner and Baig, 1979; Crawford, 1999). Dobutamine has been shown to increase heart rate in a dose-related fashion in animals and humans (Tisdale et al., 1995). Our findings are in agreement with McEntee et al. (1999), who reported a significant increase in heart rate when administering similar high doses of dobutamine to conscious healthy dogs. In healthy horses, Frye et al. (2003) has also reported a significant increase in heart rate when infusing dobutamine up to 50 $\mu\text{g}/\text{kg}/\text{minute}$. Likewise, Minors and O'Grady (1998) did not observe changes in heart rate when dogs were given dobutamine at 5 $\mu\text{g}/\text{kg}/\text{minute}$.

Although dobutamine is known to affect myocardial oxygen balance and myocardial perfusion (Stump et al., 2000), our findings corroborate other studies that have demonstrated an absence of abnormalities in ST segment in human patients with no coronary artery disease (Martinez-Martinez et al., 2004) and in

healthy dogs undergoing dobutamine stress testing (McEntee et al., 1998). The infusion of higher doses of dobutamine is well tolerated in healthy dogs. Up to an infusion rate of 20 $\mu\text{g}/\text{kg}/\text{minute}$, no changes are observed in electrocardiographic parameters. At higher rates, however, dobutamine exerts chronotropic and dromotropic effects and shortens total electrical systole time. The occurrence of ventricular tachycardia in one out of five healthy dogs is worrisome, and the true proarrhythmic effects of dobutamine in dogs with baseline arrhythmia and/or evidence of myocardial disease are yet to be determined.

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Modification des paramètres électrocardiographiques chez le chien lors d'examen de stress à la dobutamine

On a examiné les conséquences électrocardiographiques d'un examen de stress à la dobutamine (10 à 40 $\mu\text{g}/\text{kg}/\text{min}$.) sur 5 chiens en bonne santé et non tranquillisés. Les modifications de la durée/amplitude de l'onde P, de l'intervalle PR, du complexe QRS, de l'onde R, de l'intervalle QT ainsi que de la fréquence cardiaque ont été examinées. En outre, on a relevé l'éventuelle apparition d'arythmies ou de modifications du segment ST. Il a été constaté que la dobutamine perfusée rapidement influence de façon significative la transmission dans le nœud atrio-ventriculaire et la durée de la systole électrique totale. Chez un chien, on a observé un épisode de tachycardie ventriculaire persistante qui s'est toutefois convertie en un rythme sinusale après l'arrêt de la perfusion de dobutamine. Il n'a pas été observé de modification du segment ST. Sur la base de ces observations on peut conclure que des modifications électrocardiographiques se produisent lors d'un stress à la dobutamine.

Modificazioni dei parametri elettrocardiografici nei cani sani durante un test sotto sforzo con dobutamina

Su cinque cani sani non sedati è stato studiato con l'ECG l'effetto della dobutamina durante un test sotto sforzo (da 10 a 40 $\mu\text{g}/\text{kg}/\text{min}$). Si sono esaminate le variazioni del rapporto tempo/ampiezza dell'onda P, dell'intervalle PR, del complesso QRS, dell'onda R, dell'intervalle QT e della frequenza cardiaca. Inoltre si è fatto attenzione all'insorgere di aritmie e di variazioni del segmento ST. È stato appurato che la dobutamina in casi di alte dosi di infusione ha influenzato significativamente la conduzione nel nodo AV della durata della sistole elettrica totale. In un cane si è osservato un episodio di tachicardia ventricolare persistente, convertita immediatamente in un ritmo sinusale, dopo che l'infusione di dobutamine sia stata interrotta. Non sono state constatate variazioni del segmento ST. Da queste osservazioni si può concludere che durante un test sotto sforzo con dobutamina a alte dosi possono sorgere variazioni dell'ECG.

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