

Short-term Effects of Carvedilol at Clinical Dose Levels on Heart Rate and Exercise Tolerance in Dogs with Heart Failure

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KEY WORDS: heart rate, exercise intolerance, carvedilol, heart failure, dose dependence

ABSTRACT

Objective: To assess the dose-dependent short-term effects of carvedilol on heart rate and exercise tolerance in conscious dogs with experimentally induced heart failure.

Materials and Methods: Five dogs with pacing-induced heart failure (250 beats/min for 3 weeks) were administered carvedilol for 5 days (first day: 0.4 mg/kg SID and second to fifth days: 1.0 mg/kg SID). An exercise test with a treadmill system was performed 3 weeks after pacing (placebo) and on the first (car0.4), second (car1.0), and fifth (car1.0 5days) days of carvedilol administration, and before and 3 hours after administration at each day. Exercise intolerance was defined if the dog refused to run. Heart rate was measured during running for 5 minutes at each speed until the exercise test was discontinued and for 5 minutes at

30 minutes after discontinuation of the pacing as resting heart rate.

Results: Number of dogs showing exercise intolerance increased in the car1.0 and car1.0 5days groups compared with the placebo and car0.4 groups at low speed setting. Heart rate (resting and running) showed dose-dependent reduction after carvedilol administration.

Conclusion: Carvedilol showed a dose-dependent chronotropic effect and increasing prevalence of exercise intolerance at mild exercise in dogs with heart failure. Further clinical investigation into the effects of carvedilol treatment in dogs with heart failure is needed.

INTRODUCTION

Carvedilol is a nonselective β -blocker with vasodilatory properties due to α -blocking effects (McTavish et al 1993). Chronic carvedilol treatment improves left ventricular function (Gilbert et al 1996, Kukin et al 1999) and has also been reported to reduce

cardiac-related mortality in human patients with chronic heart failure (Packer et al 1996, Packer et al 2001). Although the survival benefits of carvedilol are dose-dependent (Bristow et al 1996, Hori et al 2004), severe side effects in some patients preclude treatment with β -blockers at the initiation or up-titration periods (Bristow 2000).

In dogs, the negative inotropic and chronotropic effects of β -blockers have been reported to have several beneficial effects including reduction in myocardial oxygen consumption and improvement in left ventricular function (Guth et al 1987, Nagatsu et al 2000, Colin et al 2003, Colin et al 2004). Short-term carvedilol treatment has been shown to improve left ventricular performance in dogs with experimentally induced dilated cardiomyopathy (Nikolaidis et al 2006), but the beneficial effects of carvedilol in dogs with dilated cardiomyopathy remain controversial (Nikolaidis et al 2006, Oyama et al 2007). The clinical benefits of carvedilol at dosages of 0.3 mg/kg q12h and 1.1 mg/kg q12h in dogs with myxomatous mitral valve degeneration have been evaluated (Oyama et al 2007, Marcondes-Santos et al 2007, Gordon et al 2012), and significant improvement in quality of life score and a significant decrease in systolic blood pressure were revealed in client-owned dogs at a dosage of 0.3 mg/kg q12h dose for 3 months. To date, no significant changes have been noted in echocardiographic parameters in any studies, and relationships between dose-dependent anti-adrenergic effects and prevalences of side effects of carvedilol at clinically relevant doses have not been assessed in dogs with heart failure.

The aim of this study was to assess the dose-dependent chronotropic effects and exercise tolerance of short-term carvedilol administration in dogs with heart failure.

MATERIALS AND METHODS

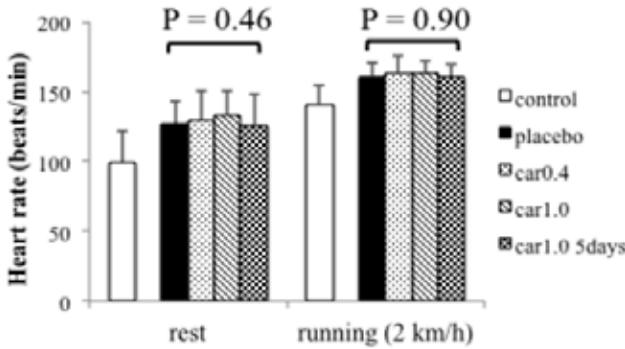
Animals. Five female beagle dogs (age range, 1–3 years; weight range, 8–11 kg) underwent surgical implantation of a pacing wire^a on the right ventricle (Shannon et al 1993). The dogs were premedicated with

atropine^b (0.025 mg/kg s.c.), midazolam^c (0.2 mg/kg i.v.), butorphanol^d (0.2 mg/kg i.v.), and meloxicam^e (0.2 mg/kg s.c.). Anesthesia was induced with propofol^f (4 mg/kg i.v.) and maintained with isoflurane^g (2%). Cefazolin^h (20 mg/kg i.v.) was used as prophylactic antibiotic treatment. The dogs were allowed to recover from the surgical procedure for at least 1 week; during this time they were exposed to treadmill exercise to become accustomed to the exercise protocol and handling. The study was approved by the Animal Care and Use Committee of the College of Bioresource Science, Nihon University, and performed by the Department of Veterinary Medicine, College of Bioresource Science of Nihon University, Japan.

Experimental protocol. A programmable pacemakerⁱ was used to induce heart failure in each dog by rapid right ventricular pacing at 250 beats/min for 3 weeks. After heart failure was confirmed by left ventricular fractional shortening of <15% and left ventricular internal diameter at end-diastole of >35 mm on echocardiography^j, carvedilol^k was administered orally once a day (9:00 AM) for 5 days and rapid pacing was maintained at 240 beats/min. The dose of carvedilol was 0.4 mg/kg on the first day and 1.0 mg/kg on the second to fifth days. The exercise test was performed before pacing (control); 3 weeks after rapid pacing (placebo); and at the first (car0.4), second (car1.0), and fifth (car1.0 5days) days of carvedilol administration.

Exercise test. The exercise test was performed before and 3 hours after carvedilol administration (Uechi et al 2002). The treadmill was set at an initial speed of 2 km/h, and the speed was gradually increased (3, 4.5, and 5.5 km/h). The duration at each speed was 5 minutes. Heart rate was consecutively counted during running at each speed for 5 minutes by using a portable electrocardiograph^m, and the average heart rate during running for 5 minutes was measured as the running heart rate. Resting heart rate was measured 30 minutes after the

Figure 1. Heart rate response to exercise before carvedilol administration in each group. Heart rate did not differ among groups.



cessation of pacing. The exercise test was discontinued when the dog showed exercise intolerance defined as refusal to run, and the heart rate was counted until just before the test was discontinued.

Statistical analysis. All data were presented as the mean \pm SD. We compared changes in heart rate among groups with repeated analysis of variance (ANOVA) followed by post hoc testing (Bonferroni test). We regarded $P < 0.05$ as statistically significant. Prism software version 5ⁿ was used to perform all statistical analyses.

RESULTS

After 3 weeks of pacing, all dogs showed remarkable increases in resting heart rate (99 ± 22 beats/min to 127 ± 16 beats/min) and left ventricular internal diameter at end-diastole (29 ± 2 mm to 36 ± 1 mm) and a significant decline in left ventricular fractional shortening ($35.5\% \pm 1.3\%$ to $10.7\% \pm 0.2\%$).

All dogs (5/5) could complete the exercise test before pacing (control). However, 2/5 dogs showed exercise intolerance at settings of 3.5 to 5.5 km/h at placebo, and

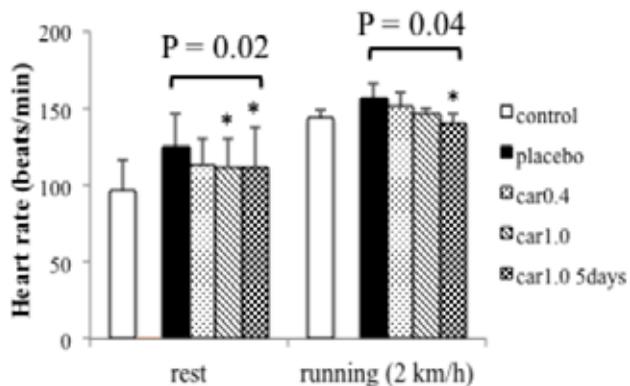
2/5 dogs showed exercise intolerance at settings of 3 to 4.5 km/h at car0.4 and of 2 km/h at car1.0 and car1.0 5days.

Because heart rate data existed until 2 km/h in all groups, resting heart rate and heart rate at 2 km/h were analyzed statistically among groups. Although heart rate did not differ among groups before carvedilol administration (Figure 1), dose-dependent heart rate reduction during resting and running was recognized after administration (Figure 2).

DISCUSSION

In this study, carvedilol showed a dose-dependent negative chronotropic effect at rest and during running in dogs with heart failure. A dose-dependent reduction in heart rate with carvedilol treatment has been shown in patients with heart failure (Bristow et al 1996), and the magnitude of heart rate reduction is associated with the survival benefits (McAlister et al 2009). However, the prevalence of adverse effects such as dizziness and bradycardia due to the dose-dependent negative inotropic and chronotropic effects of carvedilol also increases

Figure 2. Heart rate response to exercise after carvedilol administration in each group. Heart rate reduced in a dose-dependent manner after carvedilol administration. *: $P < 0.05$ vs. placebo.



in a dose-dependent manner (Bristow et al 1996, Ko et al 2002). Thus, some patients cannot tolerate treatment with this agent at the initiation and up-titration periods (Bristow 2000). In dogs with heart failure, high-dose carvedilol therapy has been recommended because of the pharmacokinetics and pharmacodynamics of this agent (Arsenault et al 2005, Gordon et al 2006). However, we determined prevalence of exercise intolerance at mild exercise increased in a dose-dependent manner in dogs treated with carvedilol. Thus, adverse effects such as increased exercise intolerance should be monitored when using high-dose carvedilol in dogs with heart failure.

Decreased exercise capacity is a major symptom in patients with heart failure (Wilson and Mancini 1993). Although the cardiac mechanisms responsible for limited exercise capacity are variable, cardiac index during exercise is associated with maximal exercise capacity as reflected in the peak oxygen consumption (Hummel et al 2012). Decreasing cardiac output response to exercise in heart failure reduces skeletal muscle perfusion and this phenomenon evokes exertional fatigue (Wilson and Mancini 1993, Harrington and Coats 1997). In this study, the dose-dependent negative chronotropic effect of carvedilol during exercise might have further aggravated exercise capacity already reduced by heart failure because of decreased cardiac output. In patients with chronic heart failure, concomitant carvedilol and pimobendan therapy has beneficial survival effects (Murai et al 2013). Pimobendan, an oral inotropic agent via phosphodiesterase III inhibition and Ca²⁺-sensitization, improved exercise capacity in patients with heart failure (Lubsen et al 1996); thus, concomitant therapy may be beneficial to maintain exercise capacity in dogs with heart failure.

This study had several limitations. First, there was no washout period between the 0.4 mg/kg and 1.0 mg/kg administrations. Carvedilol has a half-life of 92 minutes in dogs; thus, there might have been residual

effects at the next exercise test (Arsenault et al 2005). However, we confirmed that heart rate before medication had returned to the value before the medication of the previous day. Second, this study did not perform gradual β -blockade with an up-titration period (Dickstein et al 2008). Thus, the initial administration of maintenance dose might have resulted in abrupt β -blockade effects, and the effect on exercise capacity might have been overestimated. Third, we did not assess blood carvedilol concentration. Thus, we could not evaluate pharmacokinetics of carvedilol in dogs with heart failure.

In conclusion, carvedilol showed a dose-dependent negative chronotropic effect and increasing prevalence of exercise intolerance at mild exercise.

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FOOT NOTES

- a. Temporary pacing wire BM604A, Medical Concepts Europe Inc., Gemert, Netherlands
- b. Atropine, Fuso Pharmaceutical Industries Ltd., Osaka, Japan
- c. Dormicum, Astellas Pharma Inc., Tokyo, Japan
- d. Betorparl, Meiji Seika Pharma Co., Ltd., Tokyo, Japan
- e. Metacam, Kyoritsu Seiyaku Co., Ltd., Tokyo, Japan
- f. Propofol, Mylan Inc., Tokyo, Japan
- g. Isoflurane, Intervet Schering-Plough Animal Health Co., Ltd., Ibaraki, Japan

- h. Cefamezin alfa, Astellas Pharma Inc., Tokyo, Japan
- i. SEP-101, Star Medical Co., Ltd., Tokyo, Japan
- j. APLIO SSA-770A(R), Toshiba Medical Systems Co., Ltd., Tochigi, Japan
- k. Carvedilol, Wako Pure Chemical Industries Ltd., Osaka, Japan
- l. Inu-no-sanpomiti, Sunaga Impulse Co., Ltd., Tochigi, Japan
- m. Read my Heart, Daily Care Biomedical Co., Ltd., Chung-li, Taiwan
- n. Prism version 5, Graphpad software Inc., San Diego, USA