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Effects of treatment with ivabradine and atenolol on reproducibility of echocardiographic indices of left heart size and function in healthy cats[☆]

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Abstract *Objectives:* Data on reproducibility of echocardiographic indices in cats are commonly derived from studies in healthy, non-treated animals. However, medical treatment may alter reproducibility of such data possibly influencing interpretation of results of clinical trials assessing the effects of drugs on cardiovascular function. The objectives were therefore to investigate the effects of ivabradine and atenolol on reproducibility of echocardiographic indices of left heart function. *Animals:* Eight healthy cats.

Methods: Repeated echocardiographic examinations were performed by two observers in mildly sedated cats at baseline and after four weeks of treatment (Group 1, ivabradine 0.3 mg/kg q12 h PO, $n = 4$; Group 2, atenolol 6.25 mg/cat q12 h PO, $n = 4$) in a prospective, double-blind, randomized study. Test reliability was determined by estimating measurement variability, within-day interobserver variability, and between-day intraobserver variability of all echocardiographic indices. Variability was expressed as coefficient of variation (CV) and the absolute value below which the difference between two measurements lay with 95% probability. Effects of treatments on variability were compared using linear mixed effects models ANOVA and Fisher's exact test.

Results: Overall, CVs ranged from 0.5 to 50.6% at baseline, 0.5–45.5% after ivabradine, and 0.5–23.3% after atenolol. Reproducibility of all variables determined did neither improve nor worsen consistently after either treatment although atenolol exhibited a tendency toward higher reliability with none of the CVs exceeding 24% as compared to ivabradine.

[☆] The study was performed at The Ohio State University, College of Veterinary Medicine, Columbus, OH.

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Conclusions: Treatment of healthy cats with either atenolol or ivabradine had only minor effects on reproducibility of echocardiographic data. Whether these findings can be extrapolated to cats with hypertrophic cardiomyopathy deserves further study. © 2012 Elsevier B.V. All rights reserved.

Introduction

Assessment of myocardial function in cats with cardiomyopathy is primarily based on echocardiographic measurements. Echocardiography is also widely used to demonstrate efficacy of cardiac drugs in clinical trials and to monitor effects of treatment in individual cats with cardiac disease.^{1–7} Since both acquisition and quantification of echocardiographic data are operator dependent, variations in imaging and measurement technique may impact interpretation of data. The reproducibility of echocardiographically-derived variables has been studied in healthy cats and in cats with hypertrophic cardiomyopathy (HCM).^{8–13} Although important information regarding inter- and intraobserver variability has been generated, the threshold beyond which echocardiographic indices must change on sequential examinations to demonstrate drug-induced effects – as opposed to methodological variability – has not yet been reported.

Alterations in heart rate (HR) may influence echocardiographic indices of chamber size and function,^{5,12,14} thereby further enhancing the biological variability of such indices. Specifically, high HR and sudden changes of HR, often observed during echocardiographic examinations of cats, may be a relevant cause of measurement variability.¹² Therefore, drugs that control HR might decrease observer variation. To the authors' knowledge, the effects of HR-lowering drugs on reproducibility of echocardiographically-derived variables in cats have not yet been studied.

Accordingly, the objective of this study was to determine the effects of ivabradine, a funny current inhibitor, and atenolol, a selective beta-1 receptor antagonist, on reproducibility of echocardiographic variables used to characterize left ventricle (LV) and left atrium (LA) size and function. We hypothesized that both agents would reduce observer variability and improve reproducibility of echocardiographic data in healthy cats.

Animals, material and methods

Animals

Eight experimental healthy, female-spayed, domestic shorthair cats between 2 and 7 years of

age and weighing 2.8–6.5 kg were studied. All cats were acquired from a commercial vendor.^b The study protocol was reviewed and approved by the Animal Care and Use Committee (2008 A 0154) and the Institutional Review Board of the Department of Veterinary Clinical Sciences, College of Veterinary Medicine, The Ohio State University.

Study design

This was a prospective, double-blind, randomized study of four weeks duration. Four cats each were randomly assigned to a treatment group (Group 1: ivabradine^c 0.3 mg/kg q12 h PO; Group 2: atenolol^d 6.25 mg/cat q12 h PO) by use of a randomization software.^e Prior to randomization, individual doses of both drugs (based on body weight) were prepared for each cat and subsequently filled in opaque capsules^f to assure blinding. The capsules were administered manually twice daily by two of the investigators (SCR and RMC). At baseline (stage 1, days 1–3) and after four weeks of treatment (stage 2, days 31–33) (Fig. 1), each cat underwent repeated echocardiographic^g examinations. Transthoracic echocardiography was performed approximately 3 h after drug administration when the maximum negative chronotropic effect was anticipated.^{h,i,15} All echocardiographic recordings were labeled with random numbers selected by a person uninvolved in the study, allowing subsequent off-line measurements in a blinded manner.

^b Liberty Research Inc., Waverly, NY.

^c Procoralan[®], Les Laboratoires Servier, 22 Rue Garnier, 92200 Neuilly-sur-Seine, France.

^d Atenolol 25 mg[®], Mallincrodt Inc, St Louis, MO.

^e ClinPro[®] software, Clinical Systems, Garden, NY City.

^f Capsules 4 blue, Gallipot Inc, St. Paul, MN.

^g Vivid 7 Vantage, GE Medical Systems, Milwaukee, WI.

^h Riesen SC, Schober KE, Smith DN, Otoni CC, Bonagura JD. Effects of ivabradine on invasive indices of LV function in anesthetized cats with hypertrophic cardiomyopathy (abstract). *J Vet Intern Med* 2010; 24:692-693.

ⁱ Cober RE, Schober KE, Buffington CAT, Riesen SC, Bonagura JD. Effects of ivabradine, a selective I_f channel inhibitor, on heart rate in healthy cats (abstract). *J Vet Intern Med* 2010; 24:695.

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