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Original Article

# Constant rate infusion vs. intermittent bolus administration of IV furosemide in 100 pets with acute left-sided congestive heart failure: A retrospective study

D.G. Ohad[a,*], Y. Segev[b], E. Kelmer[c], I. Aroch[b], T. Bdolah-Abram[b], G. Segev[b], S. Klainbart[c]

[a] Department of Cardiology, Veterinary Teaching Hospital of the Koret School of Veterinary Medicine, Robert H. Smith Faculty of Agriculture, Food, and Environment, Hebrew University of Jerusalem, P.O. Box 12, Rehovot 761001, Israel
[b] Department of Small Animal Internal Medicine, Veterinary Teaching Hospital of the Koret School of Veterinary Medicine, Robert H. Smith Faculty of Agriculture, Food, and Environment, Hebrew University of Jerusalem, P.O. Box 12, Rehovot 761001, Israel
[c] Department of Small Animal Emergency and Critical Care, Veterinary Teaching Hospital of the Koret School of Veterinary Medicine, Robert H. Smith Faculty of Agriculture, Food, and Environment, Hebrew University of Jerusalem, P.O. Box 12, Rehovot 761001, Israel

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ABSTRACT

The aim of this study was to determine whether the addition of constant rate infusion (CRI) to intermittent intravenous bolus (IVB) administration of furosemide resulted in an improvement in medical outcomes in dogs and cats with acute left-sided congestive heart failure (L-CHF). A total of 76 client-owned dogs and 24 client-owned cats admitted with acute L-CHF were retrospectively divided between an IVB group (43 dogs and 16 cats) and a CRI group (33 dogs and 8 cats). The median furosemide dose used in dogs in the CRI group (median 0.99 mg/kg/h; range 0.025–3.73 mg/kg/h) was lower than the dose used in dogs in the IVB group (median 1.19 mg/kg/h; range 0.027–7.14 mg/kg/h; $P = 0.008$). Respiratory rates were lower in the IVB group ($P = 0.005$) and the CRI group ($P = 0.039$) compared to pre-treatment values. The overall short-term mortality was 15%. A trend of longer hospitalisation in the IVB group relative to the CRI group ($P = 0.07$) was shown. Creatinine and total plasma protein concentrations increased more in the CRI group than in the IVB group, suggestive of a higher risk of dehydration and azotaemia. There may be safety profile differences between CRI and IVB, warranting a prospective study using a larger sample size.



## Introduction

Heart disease is a common cause of morbidity in dogs and cats, often leading to congestive heart failure (CHF) (Kittleson, 1998; Goutal et al., 2010). Treatment goals are to minimise oedema and body cavity effusions, while improving cardiac output, perfusion and oxygenation. Much uncertainty remains about the safety and efficacy of various doses and routes of administration of loop diuretics when treating acute left-sided congestive heart failure (L-CHF) (Felker et al., 2009, 2011; Thomson et al., 2010).

The traditional intravenous (IV) route of emergency furosemide therapy entails intermittent intravenous bolus (IVB) administration at 2–8 mg/kg, as needed (DeFrancesco, 2008; Atkins et al., 2009). This might lead to marked intravascular volume fluctuations and intermittently high peak serum drug concentrations, while increasing the risk of both diuretic resistance and toxicity (Lahav et al., 1992; Kittleson, 1998; Salvador et al., 2005; Ellison and Felker, 2017). Alternatively, using constant rate infusion (CRI) administered at a potentially lower cumulative dose of 0.5–1 mg/kg/h might minimise these effects (Copeland et al., 1983; Lahav et al., 1992; Johansson et al., 2003). CRI may also reduce complications by allowing prompt discontinuation of the drug if necessary (Lawson et al., 1978; Lahav et al., 1992; Salvador et al., 2005). Administration of furosemide by CRI in human L-CHF patients resulted in greater natriuresis and diuresis compared to IVB therapy at equal daily cumulative doses, and appeared to be safer compared to IVB schedules (Dormans et al., 1996; Pivac et al., 1998; Salvador et al., 2005). In healthy adult dogs, urine production was higher following CRI compared to IVB administration of furosemide (Adin et al., 2003; Hori et al., 2010). Biochemical parameters of both healthy and sick dogs did not differ between those treated with IVB or with CRI of furosemide (Neshat et al., 2010; Filipejová et al., 2016).

* Corresponding author.
*E-mail address:* dan.ohad@mail.huji.ac.il (D.G. Ohad).

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The aim of this study was to compare the clinical efficacy and safety of furosemide administered by IVB and CRI in client-owned dogs and cats with L-CHF. We investigated whether addition of furosemide by CRI to a loading dose of furosemide by IVB had a measurable beneficial effect on the short-term outcome in such animals. We hypothesised that the addition of furosemide by CRI would lead to lower respiratory rates (RRs) immediately prior to discharge, a shorter length of hospitalisation, and better short-term mortality, without adverse changes in clinical pathology parameters.

## Materials and methods

### *Experimental design, animal selection and furosemide treatment*

This study had a retrospective, cross-sectional, observational design. The database of the Veterinary Teaching Hospital of the Koret School of Veterinary Medicine, Rehovot, Israel, was searched for consecutive admissions of dogs and cats with acute clinical and radiographic evidence of L-CHF to the intensive care unit (ICU) from 2003 to 2010.

Animals were included only if treated with furosemide (Furosemide 5%, Alfasan, Woerden-Holland) by IVB, CRI, or both, and were divided into an IVB group and a CRI group (loading IVB dose along with CRI treatment). Animals suspected to have developed pulmonary thromboembolism based on D-dimer levels were excluded. The study included both newly diagnosed cases with acute L-CHF, and chronically treated animals that presented with acute decompensation. When animals were treated during more than one episode, only the first documented episode was included in the study.

All study animals underwent a complete physical examination and echocardiography (Vivid 3, General Electric) by a board-certified cardiologist. Animals discharged alive from the hospital were defined as short-term survivors, while those that died or were euthanased during hospitalisation were defined as short-term non-survivors.

When administered by CRI, furosemide was diluted to 10 mg/mL using 5% dextrose in water and given at 0.5–1.0 mg/kg/h IV. The overall, cumulative furosemide dose (in mg) administered to each animal was divided by the animal's body weight at admission, and the duration of treatment (h) to calculate the actual dose (mg/kg/h). Furosemide IVB doses and dosing intervals varied, but were generally administered approximately every 2 h.

### *Data collection and laboratory testing*

Data were collected retrospectively from medical records and included age, sex, body weight upon admission, type of underlying heart disease, respiratory rate (RR) at presentation and every 2 h during hospitalisation, length of hospitalisation and short-term outcome (death, euthanasia or discharge).

An averaged respiratory rate for each animal was calculated based on the total documented observations for every 2–3 h long interval, starting at presentation and ending at death or discharge. These data were used to calculate respiratory rate (mean and median) in each group for each of 3–6 h intervals throughout hospitalisation. Mortality (combining both death and euthanasia due to L-CHF) was also recorded.

Samples were collected at presentation and during hospitalisation for a complete blood count (Abacus, Diatron or Advia 120, Bayer; potassium ethylene diamine tetra-acetic acid) and for biochemistry (lithium heparin) and analysed within 30 min. Plasma creatinine concentrations were determined at 37 °C using Cobas-Mira, Cobas-Integra 400 plus or Reflovet Plus analysers (Roche). Electrolyte analysis (sodium, potassium, chloride and ionised calcium concentrations) was performed using ion selective electrode analysers (Nova 8, Nova Biomedical or OmniC, Roche).

### *Statistical analysis*

Quantitative data are presented as mean ± standard deviation (SD) or as median and range. The Shapiro Wilk test was used to assess normality of data set distributions. Quantitative variables between two groups were compared using Student's $t$ test for normally distributed data or the Mann–Whitney $U$ test for non-normally distributed data. Changes in quantitative variables within a group were tested using the paired $t$ test, the non-parametric Friedman test or the non-parametric Wilcoxon signed rank test.

The association between two categorical variables was examined using $\chi^2$ or Fisher's exact tests. Where reference intervals of dogs and cats were identical or nearly identical, i.e. total plasma protein (TPP), sodium and chloride concentrations, laboratory data were pooled from both species and the repeated measures analysis of variance (ANOVA) model was applied for assessing differences between pre-treatment and post-treatment values, differences between treatment groups and the interaction between them. Data available from a sample size of $n < 5$ were excluded from analysis. All tests applied were two tailed and $P < 0.05$ was considered to be statistically significant. The Bonferroni correction of the significance level was applied for multiple comparisons. Analyses were performed using SPSS version 22 (IBM).

## Results

### *Composition of study groups and cardiac diagnoses*

The study included 100 consecutively enrolled animals (76 dogs and 24 cats) with acute L-CHF that were being treated with IV furosemide from 2003 to 2010. The IVB group comprised 59 animals (43 dogs and 16 cats), while the CRI group comprised 41 animals (33 dogs and 8 cats).

The proportions of dogs and cats in each group were not different between groups ($P = 0.24$). Study groups contained more male dogs and cats (dogs: 48/76, 63%; cats: 18/24, 75%) (Table 1). Cats were younger than dogs at the time when the first documented L-CHF event occurred (6.9 ± 4 years vs. 11.3 ± 2.6 years; $P < 0.001$). Study groups did not differ with regards to sex, reproductive status or age. The cardiac diagnoses included mostly chronic degenerative valve disease (CDVD) in dogs (91%), and cardiomyopathy in cats (75%). Study groups did not differ in primary cardiac diagnoses (Table 2).

### *Treatments*

In addition to furosemide, most animals were treated with other cardiac medications (Table 2). The most commonly used additional drugs were enalapril and pimobendan. Pimobendan was administered to more dogs in the CRI group than in the IVB group ($P = 0.007$), but there were no significant differences in the concomitant use of other non-furosemide medications between the two study groups.

All animals in both groups received at least one initial furosemide IVB (1–4 mg/kg). Additional IVBs were administered to animals in both groups, while furosemide at a CRI was administered only to animals in the CRI group. The median number of IVBs administered to animals in the IVB (dogs: median 4.5, range 1–17; cats: median 3, range 1–9) group was higher than the median number given to animals in the CRI group (dogs: median 1, range 1–7, $P < 0.001$; cats: median 1, range 1–4, $P = 0.02$). The cumulative drug dose was documented in 39/41 animals in the CRI group, of which 11 (nine dogs and two cats) received more than one furosemide IVB.

Animals in the IVB group received a higher total dose of furosemide (median dose 1.19 mg/kg/h, minimum dose 0.027 mg/kg/h, maximum dose 7.14 mg/kg/h; $n = 51$) than animals in the CRI

**Table 1**
Signalment of study population in both treatment groups.

| | Males | Females | Mean age | Age range | Total | Males | Females | Mean age | Age range | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| Dogs | 26 | 17 | 11.1 ± 3.0 | 1–17 | 43 | 22 | 11 | 11.5 ± 2.0 | 6–17 | 33 |
| Cats | 16 | 0 | 7.3 ± 4.4 | 1–17 | 16 | 8 | 0 | 6.3 ± 3.2 | 1–10 | 8 |
| Total | 42 | 17 | 10.1 ± 3.8 | 1–17 | 59 | 30 | 11 | 10.5 ± 3.1 | 1–17 | 41 |

SD, standard deviation. When comparing CRI to IVB: Age, $P = 0.59$; Sex, $P = 0.98$.