Survival in dogs with dilated cardiomyopathy and congestive heart failure treated with digoxin, furosemide and propranolol: A retrospective study of 62 dogs

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Abstract  Objectives: To retrospectively evaluate survival and potential adverse effects in dogs with congestive heart failure (CHF) attributable to dilated cardiomyopathy (DCM) treated with propranolol, furosemide and digoxin.

Background: The use of β-blocking agents has been shown to improve survival in human patients with CHF, including patients with DCM.

Animals, materials and methods: Sixty-two dogs with DCM and CHF NYHA class IV were included in the study. All dogs were initially treated with digoxin (mean dose 0.009 mg/kg per day) and furosemide (mean dose 3.6 mg/kg per day). Propranolol (mean dose 2.4 mg/kg per day) was added after signs of CHF had been resolved, approximately one week after initial presentation. Survival analysis was based on the Kaplan–Meier method.

Results: Pulmonary edema was found at initial presentation in 60 dogs, and pleural effusion in 2 dogs. Thirty-one dogs (50%) presented with atrial fibrillation, and ventricular premature complexes were found in 9 dogs. Survival time ranged from 8 to 1335 days (median, 126 days). Nine dogs were censored in the analysis, 8 because euthanasia was performed for reasons unrelated to cardiac disease, and 1 dog was lost on follow-up. Fifty-two dogs were euthanized, 9 dogs died suddenly. Survival rate at 1 year was 34%, and 20% at 2 years.

Conclusions: The present study shows that the median survival time in dogs treated with digoxin, furosemide and propranolol was 126 days, with a survival rate at 1 year of 34%. This treatment regimen was well tolerated.

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The treatment of dogs with congestive heart failure may involve inotropic agents, such as digoxin and phosphodies-
terase inhibitors and calcium sensitzers, diuretics and inhibitors of the renin—angiotensin—aldosterone
system (RAAS) and/or the sympathetic nervous
system.2,3 The effects on survival for some, but not all, of these therapeutic regiments have been inves-
tigated in dogs. Most of these studies have focused on angiotensin converting enzyme inhibitors (ACEIs).
In human patients with congestive heart failure, the
use of ACEIs has been shown to significantly increase
survival.4 In dogs with CHF attributable to chronic
valvular disease two studies were able to show a sta-
tistically significant increase in survival in dogs treated with ACEIs, but in dogs with DCM a statisti-
cally significant difference between the groups was
not reached.5,6 Median survival time in dogs with
DCM and CHF NYHA classes III and IV ranges from
100 to 130 days in different studies.5,6 There is pres-
tently a widespread belief among veterinary cardiol-
ogists that ACEIs are required for successful
treatment of dogs with congestive heart failure.

In addition to alterations in the RAAS, there is
an increased activity of the sympathetic nervous
system in patients with CHF. Activation of the
β-adrenergic receptors will also influence the
RAAS, as stimulation of the β1 receptors in
the kidney will increase renin release.7 Several
studies have provided evidence of long-term expo-
sure of the human failing heart to increased adren-
ergic activity.8,9 In a recent study, concentrations
of catecholamines were reported to be increased
in dogs with DCM and CHF.10 Although the sympa-
thetic stimulation is considered to be beneficial in
the short-time prospective, it is considered to be
detrimental in chronic situations, by inducing elevated heart rate, increase in cardiac afterload,
arrhythmias, cardiac hypertrophy and fibrosis.10,11

A wide variety of β-blocking agents are available, and they may be classified as first, second and third
generation agents. The first generation agents,
such as propranolol and timolol, are non-selective
for β1 or β2 receptors and have no obvious ancillary
cardiovascular effects. Second generation β-
blockers include β1-selective agents, such as
metoprolol, atenolol, bisoprolol and betaxolol. Third
generation agents, including those with vasodilator
properties, such as labetalol and carvedilol, are
essentially non-selective for the β-receptor.9 As it
has been shown that in the end-stage failing human
heart, 40% of the β-adrenergic receptors are the β2
type (as opposed to 10–20% in the normal myocardium), non-selective β-adrenergic agents may pro-
vide greater clinical benefits in the treatment of
CHF compared to β1-selective agents.13

Propranolol is a non-selective agent which has
been extensively used in dogs, hitherto mainly for
the treatment of arrhythmias. Propranolol has a
large volume of distribution and is extensively
metabolized in the liver. Oral bioavailability is low.
The recommended oral dose is 2–4 mg/kg divided
in 2–3 daily doses. Hemodynamic effects include
a decrease in heart rate and contractility, de-
creased arterial blood pressure, and a decrease in
myocardial oxygen consumption.14 The effects of
β-receptor blockade may depend on the functional
status of the myocardium, the prevailing sympa-
thetic tone and numbers of β-adrenergceptors.

The use of β-adrenergic receptor blocking
agents in human patients with DCM and CHF has
been advocated by many authors since 1975, when
Waagstein et al. reported improved ventricular function in patients with dilated cardiomyopathy
with congestive heart failure showed a statistically significant reduction in mortality.15,19 In dogs with naturally
occurring heart disease, however, the number of
studies reporting the use of β-blocking agents is
limited. The hitherto largest study investigated
retrospectively the use of metoprolol in dogs
with DCM or chronic valvular disease.16 Many smaller prospective studies concerning the use of
the non-selective β-blocker carvedilol have been
reported only in abstract form to date.17

The use of β-adrenergic blocking agents in dogs
with congestive heart failure remains a controver-
sial issue, as the potential side effects and poor
tolerance in these patients are of concern. The
purpose of the present study was therefore to
retrospectively evaluate survival and potential adverse effects in dogs with congestive heart failure attributable to DCM, treated with furose-
mide, digoxin and propranolol.

### References

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3. Amberger C. Effects of carvedilol in prevention of congestive heart failure in Cavalier King Charles spaniels with Isachc II mi-
Materials and methods

Dogs

Medical records of dogs, diagnosed as having congestive heart failure caused by DCM and treated according to a protocol used by the author, were analyzed retrospectively. Inclusion criteria were as follows: (1) echocardiographic evidence of left ventricular eccentric hypertrophy (i.e., dilatation), left atrial dilatation and fractional shortening (FS) < 25%, and absence of other significant cardiac lesions; (2) radiographic evidence of left-sided or biventricular cardiac enlargement and heart failure, i.e., pulmonary edema or pleural effusion; and (3) medical treatment consisting of digoxin, furosemide and propranolol, with target dosages of 0.01, 2–4 and 3 mg/kg, respectively.

Echocardiography

M-mode and 2D echocardiographic examinations were performed using a 5 MHz transducer placed on the right precordium with dogs positioned in right lateral recumbency. Echocardiograms were recorded and analyzed according to the recommendations of the American Society of Echocardiography and the Echocardiographic Committee of the Specialty of Cardiology, American College of Veterinary Internal Medicine. Echocardiographic measurements of the left atrial and ventricular dimensions were indexed according to Kittleson and Kienle. Cardiac dimensions were measured in millimeters, and body weight (BW) was measured in kilograms (kg). The following calculations were performed to index the cardiac dimensions: left ventricular end-diastolic diameter (LVEDD) index = LVEDD/BW^{0.32}, left ventricular end-systolic diameter (LVEDS) index = LVEDS/BW^{0.41}, left atrial diameter (LA) index = LA/BW^{0.30}, and aortic root diameter (AO) index = AO/BW^{0.35}. All echocardiographic examinations were analyzed by the author.

Electrocardiography

Standard 6-lead ECG was recorded and analyzed using criteria for dogs. All ECG-recordings were analyzed by the author.

Radiography

Thoracic radiography in two orthogonal views was performed on all dogs. All radiographs were evaluated for heart size, evidence of pulmonary congestion and edema, and pleural effusion. All radiographs were examined by the author.

Post-mortem examinations

All hearts were examined by the same pathologist following the same protocol: specimens were taken from the lower and upper halves of the lateral walls of both ventricles; the proximal, distal and middle portions of the interventricular septum; and the papillary muscles of the left ventricle. Standard histologic techniques were used, including staining with hematoxylin–eosin and Masson’s Trichrome. Three slides of each of the nine specimens were examined.

Statistical methods

All statistical calculations were performed by use of a computerized statistical program. Data are presented as mean and median ± standard deviation. Survival analysis is based on the Kaplan–Meier method. Survival time was counted from the day the dog was presented due to signs of congestive heart failure. Dogs euthanized in severe CHF were considered as cardiac-related deaths. Sudden death was counted as cardiac-related if no other cause of death was obvious. Dogs were censored in the statistical analysis if lost on follow-up, or if the dog died or was euthanized due to reasons unrelated to cardiac disease. A median survival time was determined from the survival curve, as were survival rates at 1 and 2 years after initial diagnosis.

Results

Sixty-two dogs of 21 different large and medium-sized breeds were included in the study, as follows: Newfoundland (16), English Cocker Spaniel (5), Doberman Pinscher (5), Boxer (4), Labrador Retriever (4), Airedale Terrier (4), Flat Coated Retriever (3), Springer Spaniel (3), Briard (2), Old English Sheepdog (2), Saluki (2), Golden Retriever (2), and 1 of each of the following breeds — Bull Terrier, Bouvier de Flandres, German Shepherd, Giant Schnauzer, Great Dane, Leonberger dog, Pyrenean dog, Swedish hunting dog, Weimaraner and 1 mixed breed dog. Forty-five dogs (73%) were

\[ \text{d} \] Digoxin, AstraZeneca, Södertälje, Sweden.
\[ \text{e} \] Furix, Nycomed, Stockholm, Sweden.
\[ \text{f} \] Inderal, AstraZeneca, Södertälje, Sweden.
\[ \text{g} \] JMP 3.2 SAS Institute Inc., Cary, NC, USA.
male and 17 (27%) were female. Age at initial presentation ranged from 10 months to 12.5 years with a mean age of $7 \pm 2.5$ years. Body weight ranged from 12 to 69 kg with a mean body weight of $36.2 \pm 12.7$ kg. Presenting complaints included labored breathing at rest (62 dogs, 100%), cough (45 dogs, 73%), exercise intolerance (37 dogs, 60%), inappetence (26 dogs, 42%), polydipsia (9 dogs, 15%), weight loss (8 dogs, 13%) and syncope (7 dogs, 11%). Findings on clinical examination included dyspnea at rest in all dogs, a soft systolic murmur (grades II–III/VI) in 35 dogs (56%) and ascites in 4 dogs (6%). Pulmonary edema was present in 60 dogs, and pleural effusion in 2 dogs. Based on clinical and radiographic findings, all 62 dogs were classified as modified NYHA class IV. Heart rate ranged from 140 to 270 beats/min (mean, $186 \pm 38$). Thirty-one dogs (50%) presented with atrial fibrillation, and ventricular premature complexes were present in 9 dogs. Echocardiographic measurements are presented in Table 1.

All dogs were treated with digoxin, daily doses ranging from 0.004 to 0.015 mg/kg with a mean and median daily dose of 0.009 mg/kg. The daily digoxin dose was divided and given twice daily to each dog. This dose was not changed in any dog during the course of the treatment and in no case was intoxication suspected. Digoxin serum concentration was not followed systematically in the 62 dogs. Total daily doses of furosemide ranged from 1.5 to 6.7 mg/kg with a mean daily dose of 3.6 mg/kg (median, 3.5 mg/kg). Furosemide was given twice daily to all dogs, and the dose was increased as needed during the disease course. Renal function or electrolyte changes were not followed systematically in the dogs. Propranolol was added when clinical signs of CHF had been resolved, approximately one week after initial presentation. The dose of propranolol was aimed at 1 mg/kg three times daily, with a starting dose at 50% of the full dose during the first 2–4 days. Total daily doses of propranolol ranged from 1.5 to 3.4 mg/kg with a mean of 2.4 mg/kg (median, 2.7 mg/kg). The total daily dose of propranolol was divided three times daily in each dog, and in no dog was the dosage changed during the disease course. No other antiarrhythmic drug was used. The heart rate and rhythm was not systematically followed during the disease course in the dogs.

Recurrence of severe congestive heart failure developed in 10 dogs (16%) within 1 month of treatment. It was not obvious whether or not this could be attributed to the treatment regimen or to the natural development of the disease. However, in no dog did recurrence of signs of uncompensated CHF coincide with the addition of propranolol to the treatment. Two dogs (3%) developed inappetence without signs concomitant with recurring congestive heart failure. The treatment with digoxin, furosemide and propranolol was not discontinued or altered in any of the remaining dogs for the entire duration of therapy, except for an increase of the furosemide dose to effect.

Additional treatment consisted of levothyroxine in 15 dogs, of which 7 dogs diagnosed with hypothyroidism were treated before the onset of CHF. The diagnosis of hypothyroidism was based on serum concentrations of total thyroxine and thyroid stimulating hormone. Eight euthyroid dogs were treated with levothyroxine as an adjunct to the treatment of heart failure. The dose of levothyroxine was 0.002 mg/kg once or twice daily. Spironolactone was added in 4 dogs (1, 10, 20 and 24 days before death) and enalapril in 2 dogs (7 and 20 days before death).

Survival times ranged from 8 to 1335 days with a median of 126 days (Fig. 1). Fifty-two dogs were euthanized and 9 dogs died suddenly. One dog was lost on follow-up. Forty-four dogs were euthanized due to advancing congestive heart failure. Nine dogs were censored in the statistical analysis, 8 of them because euthanasia was performed for reasons unrelated to congestive heart failure, such as diabetes mellitus that the owner elected not to treat (2 dogs), syncopal episodes (2 dogs) pemymota that the owner decided not to treat, metastasizing Sertoli cells tumor, severe pain from arthritis, and 1 dog with extensive myiasis. Survival rate at 1 year after initial diagnosis was 34%, and at 2 years 20%.

### Table 1  Echocardiography measurements in 62 dogs with DCM

<table>
<thead>
<tr>
<th></th>
<th>LVEDD index</th>
<th>LVEDS index</th>
<th>LA index</th>
<th>AO index</th>
<th>LA/AO</th>
<th>FS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>$15.5–31.2$</td>
<td>$9.7–20.5$</td>
<td>$5.6–28.5$</td>
<td>$2.5–9.1$</td>
<td>$1.5–3.4$</td>
<td>$4–22$</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>$21.4 ± 3.3$</td>
<td>$13.7 ± 2.5$</td>
<td>$15.8 ± 3.7$</td>
<td>$6.9 ± 1.3$</td>
<td>$2.0 ± 0.4$</td>
<td>$12 ± 4$</td>
</tr>
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Left ventricular end-diastolic diameter (LVEDD) index = LVEDD/BW$^{0.32}$, left ventricular end-systolic diameter (LVEDS) index = LVEDS/BW$^{0.41}$, left atrial diameter (LA) index = LA/BW$^{0.30}$, and aortic root diameter (AO) index = AO/BW$^{0.35}$. FS% = fractional shortening.
Post-mortem examination was performed in 33 dogs. The attenuated wavy fiber form of DCM, i.e. myofibers that are thinner than normal (<6 μm) with a wavy appearance, was found in 32 dogs. The fatty infiltration-degenerative form of DCM, i.e. myocyte degeneration and replacement fibrosis with fatty infiltration, was found in 1 Boxer.

Discussion

The gold standards for evaluation of different treatment strategies in any disease are prospective placebo-controlled, randomized and double-blind studies. Retrospective studies of treatment strategies can, however, provide valuable information if, as in the present study, the treatment is standardized, inclusion criteria closely defined and all data thoroughly documented. Survival is the most important outcome of any study concerning treatment strategies.

Presently, the majority of treatment protocols of congestive heart failure in dogs include ACEIs or other vasodilating agents. An interesting finding of the present study is that the median survival time was 126 days and survival rate at 1 year was 34% in dogs with congestive heart failure caused by DCM and treated with a combination of furosemide, digoxin and propranolol, excluding ACEIs in all but 2 dogs where enalapril was added 7 and 20 days, respectively, before death. It should, however, be noted that the use of β-receptor blocking agents most likely also decreases the effects of the RAAS, as β1 receptor blocking agents would be expected to decrease renin release. The rationale behind the treatment protocol using a β-blocking agent in combination with conventional therapy in the present study was the reported beneficial effects in human patients with DCM and congestive heart failure reported by Waagstein et al. and others. Although the pharmacokinetics and rapid metabolism of propranolol make this β-blocker less than ideal, it was chosen as it is a non-selective agent that has been extensively used in dogs.

Few studies concerning survival of dogs with DCM and CHF treated with β-blocking agents have been reported to date. In a recent retrospective

![Figure 1](image-url) Survival curve for 62 dogs with dilated cardiomyopathy and congestive heart failure treated with digoxin, furosemide and propranolol.
study, median survival time in 57 dogs with DCM treated with metoprolol was reported to be 359 days. However, as concomitant treatment (supposedly including ACEIs) in these dogs was not declared, and the majority of dogs were presented in a less severe degree of congestive heart failure (NYHA classes I–II), the results are difficult to compare with the current study. The effects of carvedilol, a third generation, largely non-selective β-blocking agent with vasodilator activity, in dogs with naturally occurring heart disease have been reported, but results are inconclusive. The combination of ACEI and β-blocker therapy has been shown to provide a greater increase in survival time in humans with CHF, compared to either treatment alone. This treatment modality has not been reported in dogs with CHF.

Although the rationale for the use of β-blocking agents is their positive effect in decreasing sympathetic tone, concern about their negative inotropic effect has been expressed, especially when used in patients with DCM. Metoprolol therapy was reported to be well tolerated in a study of 87 dogs with acquired heart disease, although treatment was discontinued in 22 of those due to side effects. In the present study, treatment with propranolol in dogs with DCM and CHF appears to be well tolerated, as the medication was not discontinued or altered in any of the dogs in the study, and no obvious side effects were observed, other than inappetence in 2 dogs. Advancing heart failure despite increased doses of furosemide was considered to be part of the natural disease process, rather than caused by the use of propranolol.

Medication other than those pertaining to the treatment protocol may influence survival, depending on type and dose of medication, the number of dogs it involves, and the length of time during which the medication was given. In the present study, concomitant therapy was not considered to significantly influence results, as the addition of levothyroxine (given to 15 dogs) has been shown not to influence survival in dogs with DCM and CHF treated with digoxin, furosemide and propranolol, and spironolactone and enalapril were only given to 4 and 2 dogs, respectively, and only for a limited time of the treatment period.

Other factors presumed to influence survival in dogs with congestive heart failure and DCM are age at onset of clinical signs, sex and breed. Age at the time of diagnosis of DCM has been shown to influence survival time, as young age at presentation was the most significant risk factor identified in a previous study of dogs with DCM and CHF. Mean age of dogs in the present study was comparable to that of previous studies. Longevity for male dogs with DCM has been proposed to be shorter than for female dogs, but no correlation between sex and survival time was found in a previous study. In the present study, approximately 75% of the dogs were male. Breed is considered to influence survival, as survival rate at 1 year was reported to be exceptionally low (3%) in a study of Dobermans as opposed to 20–40% in other breeds. However, as Dobermans are more prone to have the fatty infiltration-degenerative type of DCM rather than the attenuated wavy fiber type of DCM, it may indicate that the difference in prognosis is due to histologic type of DCM rather than breed. No correlation between breed and survival was, however, found in a large study of 189 dogs of 38 breeds with the attenuated wavy fiber form of DCM.

Euthanasia as an end-point of the study of survival times raises potential objections, as owners and veterinarians may have different views on when an animal is close to death. The retrospective design of the study, however, diminishes bias regarding euthanasia.

The role of β-blocking therapy in preventing development of congestive heart failure has been investigated, and the molecular basis for the beneficial effects has been sought. Propranolol has been reported to prevent development of congestive heart failure in dogs with tachycardia-induced heart disease by inhibiting calcium leak through ryanodine receptors in the sarco(plasmatic) reticulum of the cardiac myocyte. The potential benefit of early intervention with β-blocking agents in dogs with preclinical DCM remains to be investigated.

Conclusion

The present study shows that median survival time was 126 days and that survival rate at 1 year was 34% in 62 dogs with DCM and CHF treated with digoxin, furosemide and propranolol, essentially without the use of ACEIs, albeit not necessarily without inhibition of the RAAS per se, as β1-blocking agents would be expected to decrease renin release. Whether or not a combination of β-blocking therapy and ACE inhibition would prove beneficial is presently unknown.

References