Evaluation of the Efficacy of *Crataegus oxyacantha* in Dogs with Early-Stage Heart Failure

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Homeopathy

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Abstract

Background Myxomatous mitral valve disease (MMVD) is the most common cardiopathy in middle-aged dogs. When the dog is asymptomatic and has an enlarged left atrium, treatment is beneficial; however, some allopathic drugs are very costly and may produce side effects. To extend the duration of this asymptomatic phase, complementary therapies such as herbal medicine and homeopathy are available. Although herbal therapy with extract of *Crataegus oxyacantha* is beneficial, there is a risk of adverse reactions—unlike with homeopathy, where the risk is minimized with the administration of ultra-diluted doses.

Objective This study evaluated the efficacy of *Crataegus oxyacantha*, as mother tincture (MT) and in 6 cH homeopathic formulation, in treating the initial phase of heart failure due to MMVD in a veterinary clinic setting.

Methods A total of 30 dogs with MMVD, 7 years or older and weighing up to 10 kg, were randomized into three groups as follows: *Crataegus* 6 cH, *Crataegus* MT, and hydroalcoholic solution (placebo). Animals were evaluated through echocardiography parameters, laboratory blood tests, and systolic blood pressure (SBP) measurements at 30, 60, 90, and 120 days after initiation of therapy, for statistical analysis and monitoring of the blinded study.

Results Patients who received *Crataegus* 6 cH showed a reduction in SBP 60 days after treatment, while those receiving *Crataegus* MT exhibited a reduction 90 days after the therapy was initiated. There was a significant linear regression when evaluating the effect of treatment with *Crataegus* 6 cH on SBP measurements over the evaluation intervals (linear equation: SBP = 176.57 mm Hg – 0.21*x*, where *x* represents days of treatment). There was an increase in both fractional shortening and isovolumetric relaxation time for those patients receiving the homeopathic formulation.

Conclusions Therapy with *Crataegus* was beneficial for hypertensive and cardiopathic dogs with MMVD, extending the duration of the asymptomatic phase. The reduction in SBP occurred more swiftly in the 6 cH group than in the MT-treated dogs.

Keywords

- myxomatous mitral valve disease
- cardiopathy
- dog
- homeopathy
- *Crataegus oxyacantha*

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Introduction

Heart failure occurs when the heart cannot adequately maintain its function of pumping blood. Myxomatous mitral valve disease (MMVD) is the most common and affects mainly older dogs and small breeds,[1] but larger dogs can also develop MMVD and it is suspected that the progression is even faster when compared with small dogs.[2,3]

The most often affected is the mitral valve, being responsible for over 70% of all cases.[4,5] The most common clinical signs are coughing, exercise intolerance and dyspnea which, in severe cases, can lead to death.[6]

The American College of Veterinary Internal Medicine (ACVIM) describes MMVD in stages:[7]

- Stage A refers to dogs at high risk for developing heart disease but that currently have no identifiable structural disorder of the heart.
- Stage B1 refers to asymptomatic dogs that have no radiographic or echocardiographic evidence of cardiac remodeling in response to their MMVD.
- Stage B2 refers to asymptomatic dogs that have more advanced mitral valve regurgitation, which is hemodynamically severe and long-standing enough to have caused radiographic and echocardiographic findings of left atrial and ventricular enlargement, which in turn meet clinical trial criteria used for dogs that clearly should benefit from initiating pharmacological treatment to delay the onset of heart failure (echocardiographic LA: Ao ratio in the right-sided short-axis view in early diastole $\geq$1.6; left ventricular internal diameter in diastole, normalized for body weight, $\geq$1.7 cm).
- Stage C denotes dogs with either current or past clinical signs of heart failure caused by MMVD.
- Stage D denotes dogs with end-stage MMVD, in which clinical signs of heart failure are refractory to standard treatment.

Systolic arterial blood pressure (SBP) is influenced by vascular resistance at the moment when blood is ejected from the aorta during cardiac systole: with higher vascular resistance, the left ventricle needs to exert more force to eject the appropriate blood volume for irrigation and oxygenation of body tissues. Chronic hypertension may cause concentric hypertrophy of the left septum and ventricle wall, reduction of the ventricular chamber, aortic dilatation, and aneurysms.[8,9] The systolic pressure considered normal in dogs is a value lower than 150 mm Hg.[10]

To avoid the high cost of allopathic drugs and their side effects, herbal and homeopathy medicines are available.[11] In the *Rosacea* family, there are over 200 species of *Crataegus*, resulting from hybridization, with their leaves, flowers, and berries providing the medicines. The most studied species is *Crataegus oxyacantha*, also known as hawthorn.[12] It has been indicated for cardiovascular diseases such as hypertension, arrhythmia, and congestive heart failure, as well as for its antioxidant, antithrombosis, and anti-inflammatory activities.[13–15]

Crataegus has cardioprotective effects, which are attributed to the cardiotonic properties of its flavonoid content and to oligomeric procyanidins, whose antioxidant effect can reduce myocardial oxidative stress after reperfusion and inhibit myocardial cell apoptosis.[13] The administration of this drug dilates peripheral vessels and relaxes coronary arteries, improves blood flow to the heart, and increases relaxation time, aiding heart disease and alleviating symptoms in early heart failure.[16] An angiotensin-converting enzyme inhibitor effect has also been reported, promoting vasodilatation and with a diuretic action to reduce preload and afterload that improves cardiac function.[17]

The objective of this veterinary study was to evaluate the efficacy of hypotensive treatment using *Crataegus oxyacantha,* at a potency of 6 cH and mother tincture (MT), in dogs in Stage B2 MMVD that had evidence of heart enlargement but had never suffered from signs or symptoms attributable to congestive heart failure, according to the ACVIM classification. The evaluations, over 120 days per patient to examine the asymptomatic phase of treatment, included echocardiographic parameters, SBP measurement, and observing adverse reactions related to the toxicity of the therapy, through laboratory testing.

Methods

The dogs were recruited in veterinary clinics in the city of the Taubaté, São Paulo, Brazil. Asymptomatic dogs with auscultation murmur during the veterinary examination were referred for research. These dogs then underwent screening assessment with physical examination, echocardiogram, SBP, and blood examination (routine hematology and blood biochemistry: creatinine, urea, alkaline phosphatase, and alanine aminotransferase). A second echocardiogram was performed 30 days after the screening assessment to assure that there was no evolution in the heart disease stage.

The blood was collected by venipuncture of either the jugular or the cephalic vein and was sent to the laboratory. An echocardiogram was performed with the M-Turbo ultrasound device from SonoSite (Bothell, USA) with the 8 to 4 MHz P-10x transducer (►**Fig. 1**), where it was ascertained whether the patient was fit to participate in the study. The following parameters were observed: heart rate, fractional shortening (FS), ejection fraction (Teicholz method) and isovolumetric relaxation time (IVRT). SBP was measured using the Doppler method, with cuffs from sizes 1 to 3, and five consecutive measurements were taken to determine the mean blood pressure values, using the veterinary vascular Doppler Medmega, model DV610V.

Inclusion criteria for this study were as follows: dogs at 7 years of age or older, weighing up to 10 kg, in stage B2 of heart failure according to the ACVIM classification; asymptomatic and presenting remodeling of the left atrium ($\geq$ 1.6 in terms of aortic size, in echocardiogram B-mode).[8] Exclusion criteria were as follows: dogs with pulmonary edema, those undergoing treatment for any disease during screening, or other concomitant heart disease and alteration in stage of heart failure in the second echocardiogram.

A total of 30 dogs of both genders (18 females, 12 males) were selected, weighing between 1.6 and 9.9 kg (mean = 5.40 kg; standard deviation [SD] = 2.32), and aged between 7 and 17

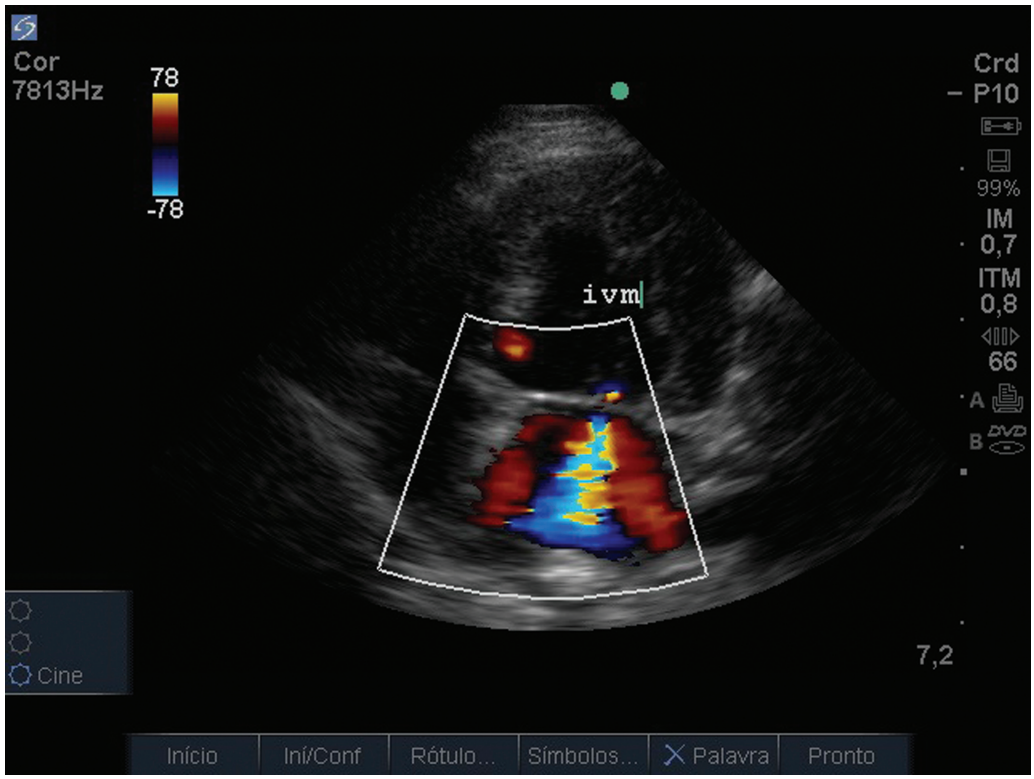

Fig. 1 Echocardiographic image of mitral valve insufficiency of a dog in the study, demonstrating color Doppler flow of valve regurgitation in blue.

years (mean = 11.4 years; SD = 2.46). The selected dogs consisted of the following breeds: Shih Tzu (7), Dachshund (6), Yorkshire Terrier (5), Poodle (4), Maltese (2), Pinscher (2), Mongrel (2), Lhasa Apso (1), and Miniature Schnauzer (1).

Ethical Approval

This study was approved by the Committee on Animal Research and Ethics at the University of Santo Amaro (Protocol Number: 40/2017), whose processes and standards adhere to those of the Brazilian National Council for the Control of Animal Experimentation (**Supplementary File S1** [online only]), including veterinary research. A formal consent form was signed by the informed owner of each dog.

Clinical Trial Design

The dogs were randomly divided into three groups of 10, receiving either[1] *Crataegus* 6 cH in 20% alcohol, according to Hahnemann's centesimal dilution[2]; *Crataegus* MT; or[3] hydroalcoholic solution (placebo). The medications and placebo were orally administered with five drops, three times a day, given by the owner. Each owner received an amber glass bottle with the same label design. The owners and the researcher did not have access to information about the research grouping of the dogs. The treatment blinding process was performed by a pharmacy assistant who was not involved further in the study.

Follow-up measurement was performed at 30, 60, 90, and 120 days after initiation of therapy, with echocardiographic monitoring of the parameters as well as blood pressure measurement. At the end of the period (120 days), the final evaluation was performed by physical examination, echocardiography examination, and blood pressure measurement; a fresh blood sample was also collected. The details of the treatment groups were disclosed after the end of the study, after performing the statistical analysis.

Statistical Analysis

Results were analyzed using the Statistical Analysis System (SAS Institute Inc., 2001) computer program. Normality of the data distribution was determined by the Shapiro–Wilk test (Proc Univariate), and the homogeneity of the variances compared by the chi-squared test (SPEC Command of PROC GLM). The data were submitted to repeated measures analysis of variance (PROC GLM), where the effect of treatment at different times on SBP, heart rate, FS, ejection fraction, IVRT, and hematological and biochemical tests (hematocrit, hemoglobin, platelets, GPT, creatinine, alkaline phosphatase, urea) was verified. Then the Tukey means-comparison test was used. Data were individualized by treatment and then subjected to regression analysis (PROC REG) to assess the effect of time within each treatment and then obtaining a prediction equation. A p-value of < 0.05 was considered statistically significant for all analyses.

Results

None of the dogs exhibited adverse effects from the therapy and no patients presented alterations in the hematological and biochemical examinations.

At time 0, the *Crataegus* 6 cH group had a mean SBP value higher than the other groups. At time 30, 60, 90 and 120 days, there were no differences between the groups, each with a

Table 1 Systolic arterial blood pressure of treatment groups

Time (days)	Treatment	Mean (mm Hg)	SD	CV	SEM
0	*Crat* 6 cH	178.0[A]	20.63	11.59	4.61
	Crat MT	166.3[B]	15.68	9.43	3.51
	Hydroalc. sol.	166.9[A,B]	24.06	14.01	5.38
30	*Crat* 6 cH	166.8[A,B]	14.46	8.67	4.57
	Crat MT	156.4[B,C]	18.03	11.53	5.70
	Hydroalc. sol.	160.0[B,C]	24.89	15.56	7.87
60	*Crat* 6 cH	164.6[B,C]	19.53	11.86	6.17
	Crat MT	153.0[B,C]	16.53	10.80	5.22
	Hydroalc. sol.	154.4[B,C]	20.37	13.19	6.44
90	*Crat* 6 cH	155.4[B,C]	21.12	13.59	6.68
	Crat MT	149.8[C]	14.62	9.76	4.62
	Hydroalc. sol.	154.2[B,C]	20.19	13.09	6.38
120	*Crat* 6 cH	153.6[B,C]	17.96	11.69	5.69
	Crat MT	150.4[C]	16.13	10.73	5.10
	Hydroalc. sol.	157.0[B,C]	17.72	11.28	5.60
	p-Value	0.004			

Abbreviations: *Crat*, *Crataegus*; CV, coefficient of variation; Hydroalc. sol., hydro-alcoholic solution; MT, mother tincture; SD, standard deviation; SEM, standard error of mean.
Note: Means with different letters in the same column presented a significant statistical difference between and within groups (Tukey's test, $p < 0.05$). Means followed by the same letters did not differ from each other. The *p*-value refers to the time versus treatment interaction on the mean systolic arterial blood pressure; it was found using the LSMeans method, which compares all means.

similar mean. However, in within-group analysis, the patients who received *Crataegus* 6 cH showed a reduction in SBP 60 days after treatment, while those receiving *Crataegus* MT exhibited a reduction 90 days after initiating therapy. In the hydroalcoholic solution group, no such effect was witnessed over the course of the 120 days of treatment (►**Table 1**).

There was a significant linear regression when evaluating the effect of treatment with *Crataegus* 6 cH on SBP measurements over the evaluation intervals. SBP = 176.57 mm Hg – 0.21*x* ($p < 0.001$), where *x* is the number of treatment days. The *Crataegus* MT data attained a significant result according to the equation SBP = 164.06 mm Hg – 0.14*x* ($p < 0.01$). In the placebo group, SBP = 164.85 mm Hg – 0.10*x* ($p = 0.12$), there was no statistically significant effect, when compared at the beginning and end of the study period (►**Fig. 2A–C**).

There was no change in the heart rate or ejection fraction within the 120-day period of treatment, in any group.

The FS, which represents ventricular performance, presented a significant increase in the group that received homeopathic therapy: FS = 44.35% + 0.03*x* ($p = 0.05$). In other groups, there was a small reduction in this parameter: *Crataegus* MT, FS = 47.08% – 0.02*x* ($p = 0.21$); placebo, FS = 44.20% – 0.01*x* ($p = 0.30$) (►**Fig. 3A–C**).

The IVRT also showed a statistically significant increase in the *Crataegus* 6 cH group, according to the linear regression equation: IVRT = 68.37 milliseconds + 0.03*x* ($p = 0.05$); whereas the other groups did not present any alteration in the study period (*Crataegus* MT, IVRT = 74.17 milliseconds – 0.03*x*, $p = 0.14$; placebo, IVRT = 71.43 milliseconds – 0.01*x*, $p = 0.75$).

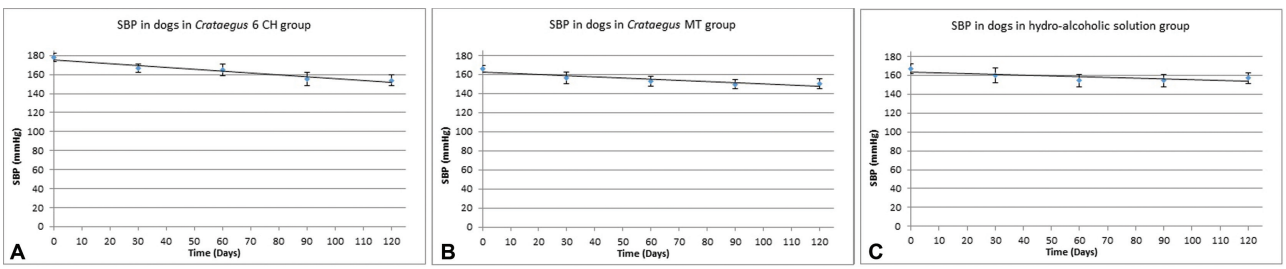

Fig. 2 Systolic arterial blood pressure by days of intervention in (**A**) the *Crataegus* 6 cH group, (**B**) the *Crataegus* MT group, (**C**) the hydroalcoholic solution group. MT, mother tincture; SBP, systolic blood pressure.

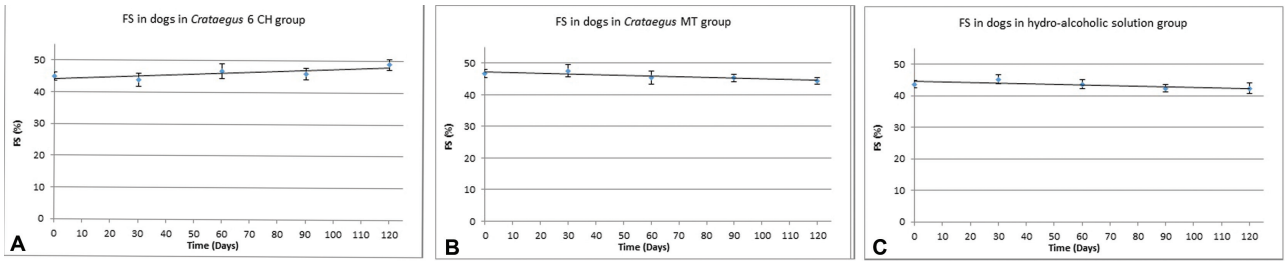

Fig. 3 Fractional shortening by days of intervention in (**A**) the *Crataegus* 6 cH group, (**B**) the *Crataegus* MT group, (**C**) the hydroalcoholic solution group. FS, fractional shortening; MT, mother tincture.

Discussion

The mean age of the dogs in this study (11.4 years) aligns with that of a previous study in which the average age was 11.6 years.[4] However, the gender prevalence in the present study differed from the others, as there were more females than males, while several authors have reported a ratio of 1.5:1.0 males to females.[18]

The use of plant extract in rats attenuated the development of renovascular hypertension in 1 month and there was a reduction in oxidative stress,[19] complementing another study that reported its use increased nitric oxide production in the endothelium of rat aortas, contributing to vasodilatation.[20] SBP reduced by 37% with the use of injectable *Crataegus* aqueous extract in rats,[21] agreeing with a study that also observed a reduction in the mean blood pressure of the same species.[22]

Some dogs in the study were hypertensive, with an SBP of 210 mm Hg, which indicates immediate therapeutic treatment, as it is known that systemic hypertension has the potential to cause serious and irreversible damage, especially in the kidneys heart, brain and eyes.[23–25] There was a reduction in SBP in dogs that received the homeopathic and MT medicine compared with the placebo group. However, in the *Crataegus* 6 cH group this reduction was more evident and rapid in onset, demonstrating superiority of this homeopathic therapy: this was the test group with the higher baseline mean SBP and after 120 days of treatment had a similar mean to the rest of the animals. None of the dogs had been diagnosed with hypertension before the study.

In dogs with MMVD in stage B2, pimobendan, a phosphodiesterase inhibitor with positive inotropic and vasodilator effects, is the recommended treatment; however, the drug is expensive and can produce adverse effects. In a double-blind study, pimobendan and amlodipine, a calcium channel blocker, showed no statistically significant changes in SBP in dogs after 60 days of therapy,[26] corroborating the study where administration of pimobendan did not reduce SBP during 512 days of treatment.[27]

Crataegus has been shown to have a positive inotropic effect due to an increase in the resting potential,[28] corroborated by this study, in which FS increased with a statistically significant outcome in the homeopathy group, compared with the other groups, confirming the improvement in ventricular function. The *Crataegus* 6 cH group showed a slight increase in FS in the regression analysis, which was demonstrated by the change in the graphs (►**Fig. 3A**). The present study can be a reference point for other research, in which the study time should be extended beyond the 120 days of the present investigation.

In vitro studies reported an increase in the heart rate,[29] while in vivo a reduction was ascertained.[22] In the current study, there was no statistically significant outcome from our measurements of heart rate.

Adverse effects from *Crataegus* therapy are rare, being associated with vertigo, gastrointestinal abnormalities and headaches,[30] though there is a report of a 68-year-old man who presented with multi-system hypersensitivity and acute renal failure after consuming *Crataegus orientalis*.[31] With the administration of homeopathic formulations, the risk is low due to drug dilution.

The study sample size is admittedly small, only 10 in each group. Though all animals were asymptomatic, an observational questionnaire was not included at the beginning or during medication, and this might have brought more relevant clinical data regarding the animals. MMVD advances slowly, a fact that would necessitate more research time to confirm significant improvement in relation to echocardiographic parameters, even given the improvement observed in the homeopathy group of the present study.

Published studies on *Crataegus oxyacantha* for the treatment of dogs with MMVD remain scarce. The findings from this study contribute to knowledge in the use of such therapies in dogs with heart disease.

Conclusion

From the results obtained in the present work, it may be concluded that therapy with *Crataegus* was beneficial for hypertensive and cardiopathic dogs. None of the dogs exhibited adverse effects to the medicine. The dogs that received medication had reduction in SBP. For *Crataegus* MT the reduction was 90 days after therapy, with 10% decrease at the end of study; for the *Crataegus* 6 cH group, this hypotensive effect was faster in onset, reducing in 60 days and reaching 15% decrease in SBP after 120 days of therapy. *Crataegus* 6 cH also showed increased fractional shortening and myocardial relaxation time.

Highlights

- The study is the first to use *Crataegus* (6cH and mother tincture) in dogs with myxomatous mitral valve disease (MMVD).
- The study design was randomized, blinded, and placebo-controlled to evaluate efficacy.
- Data analysis included comparison between effects of treatment using homeopathy and mother tincture.
- The results suggest that homeopathic *Crataegus* is beneficial for hypertensive and cardiopathic dogs with MMVD.

Supplementary File

Supplementary File S1 Animal Research Committee approval letter.

Conflict of Interest

None declared.

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