

Using a Complementary Herbal Therapy in Heart Failure

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Abstract

Context: Many patients with congestive heart failure (CHF) experience impaired quality of life (QOL) and would be willing to take an additional safe medication to gain QOL improvement. QOL scores provide meaningful patient-based outcomes for CHF patients. Poorer QOL scores predict an increased number of hospitalizations and a higher rate of mortality.

Objective: This pilot study measures QOL and exercise endurance in CHF patients taking Cardiodoron, a plant-derived extract shown to increase heart rate variability. Medical practitioners prescribe the extract for palpitations, cardiac insufficiency, and orthostatic symptoms.

Design: The research team designed an 18-week, randomized, placebo-controlled, double-blind pilot study.

Setting: The study took place at the Veterans Administration Medical Center, Charleston, South Carolina.

Participants: Eight CHF patients at the center participated in this study.

Intervention: Four participants received the herbal extract

Cardiodoron for 18 weeks, and four received placebo. Both groups received standard therapy as well.

Outcome Measures: The Minnesota Living With Heart Failure Questionnaire and the 6-minute Walk Test were the primary endpoints measured at baseline and end of study.

Results: Participants taking Cardiodoron experienced no side effects. Mean and median QOL scores improved 15 and 12 points, respectively, in the Cardiodoron group, with three of the four participants taking Cardiodoron reporting QOL improvement by 7 or more points. One participant taking Cardiodoron reported a decrease in QOL. Results in this small pilot study were not statistically significant, but they may have clinical relevance to the participants in the study.

Conclusion: CHF patients can safely take the described herbal extract with standard therapy. A future study may determine whether the extract can enable them to benefit from the more favorable prognosis that accompanies a better QOL in heart failure.

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Many patients with congestive heart failure (CHF) experience severe impairment to their quality of life (QOL).¹ Measuring QOL can provide meaningful prognostic information among patients with CHF.^{2,3} Poor QOL predicts an increased likelihood of hospitalization and a higher rate of mortality.⁴ Medical practitioners can appreciate the importance of QOL to heart failure patients by studying the results of a 1995 survey, in which 49% of the CHF patients interviewed would select therapy that improved QOL even if the treatment shortened

life.⁵ Seventy-two percent of these patients would take a medication that improved QOL by 5 points on the Minnesota Living With Heart Failure Questionnaire (MLWHFQ), provided that the medication did not cause significant side effects or increase costs.⁵ Clearly, a role exists for safe therapies that improve QOL for patients with CHF.

CardiodoronTM (Weleda Pharmacy, Schwaebisch-Gmuend, Germany) is a plant-derived extract prescribed by physicians in Europe and North America for at least the past 50 years, as a complementary treatment for cardiac insufficiency, arrhythmias, palpitations, and orthostatic symptoms.^{6,7} Cardiodoron increases heart rate variability (HRV) in normal individuals.⁸ CHF decreases HRV as sympathetic autonomic hyperactivity directly stimulates and predominates the failing myocardium, and the parasympathetic influence withdraws.⁹ Other studies have found that increased HRV may contribute to improved survival in CHF patients.^{10,11}

Cardiodoron is a homeopathically prepared combination of 3 plants. This preparation includes combined extracts of (1) *Primula veris*, the European cowslip blossom, in a 1:10 part dilution with alcohol; (2) similarly prepared extract of flower of *Onopordon acanthium*, the scotch thistle; and (3) a 1:100 part dilution of the flowering plant *Hyocyamus niger* or henbane. Patients take 20 drops of Cardiodoron in 1 oz of water 4 times a day. The Weleda Pharmacy in Schwaebisch-Gmuend, Germany, organically grows the plants, extracts and combines the plants' parts, and standardizes the product. Cardiodoron is registered with the US Federal

Drug Administration and Kommission C, the regulating agency in Germany. During the half-century of its use, neither agency has received any reports of adverse effects in taking Cardiodoron.

Researchers have analyzed some of the constituents of the plants used in Cardiodoron to define their biochemical activities. *Primula veris* contains triterpenoid saponins.^{6,12} Saponins act like a surfactant, increasing air/fluid interface surfaces. They possess a range of biological activities, with antiinflammatory, platelet-aggregation inhibiting, and immune-stimulating properties.¹³ Inflammation has an important role in the development of many chronic diseases, including atherosclerosis, and often precedes and promotes cardiovascular disease and heart failure. Multiple animal studies have shown that the triterpenoid saponins of the plant *Panax notoginseng* have a therapeutic effect on atherosclerosis through an antiinflammatory effect and through regulation of blood lipids.¹⁴ Some saponins are associated with hemolysis, but researchers have not known this activity to occur with the saponins in the primula plant.

Flavonoids are the primary isolates extracted from the onopordon plant family.¹⁵ Flavonoids also possess antiinflammatory effects. They act as antioxidants and free radical scavengers and may regulate inflammatory mediator production.¹⁶

Hyocymus niger is a member of the *Solanaceae* plant family. Plants of this group contain alkaloids like hyosine, hyocymamine, and scopolamine, which are used medically for their activity in the autonomic nervous system. Researchers have shown that very low doses of the alkaloid substance scopolamine improve HRV and exercise performance in patients with heart failure.^{10,11} *Hyocymus niger* has shown vasodilator, blood-pressure lowering, and heart-rate lowering effects in animal experiments.¹⁷ The alkaloid content of *Hyocymus* may be responsible for increased HRV observed in the Cardiodoron study published in 2000.⁸

In this exploratory pilot study, the research team wanted to investigate whether patients with systolic CHF can safely take Cardiodoron and whether these patients would experience improved QOL, improved ambulation, or both of these clinical benefits.

DESIGN AND METHODS

The research team asked nine patients with CHF who attended outpatient clinics at the Veterans Administration (VA) Hospital in Charleston, South Carolina, to participate in this 18-week, prospective, randomized, placebo-controlled, double-blind pilot study. The Medical University of South Carolina's Investigator Review Board (IRB) and the VA's Research and Design (R&D) Committee approved the study's protocol, consent process, and all forms.

Inclusion criteria comprised (1) enrollment in the VA's health care system; (2) a clinical diagnosis consistent with systolic congestive heart failure (CHF), defined as a primary diagnosis of heart failure within the last 2 years; placement in the New York Heart Association's (NYHA's) functional classes II or III; and a history of objective findings on invasive or noninvasive test of left ventricular ejection fraction (LVEF) 45% or less; (3) receipt of standard treatment for CHF, if tolerated, to include at least an angiotensin converting-enzyme (ACE) inhibitor or angiotensin receptor blocker, an aspirin (unless taking warfarin), and a statin; (4) medically stable condition; and (5) the ability to walk 6 minutes. Six participants were taking aspirin, and the three participants not taking aspirin were taking warfarin. To detect any potential interaction of warfarin with the saponins in Cardiodoron, the research team added a coagulation profile to the laboratory testing.

Exclusion criteria included (1) hemodynamically significant aortic or mitral valvular disease; (2) severe lumbar stenosis, symptomatic peripheral vascular disease, or any other condition that would preclude ambulation; (3) a history of multiple drug allergies, active alcohol abuse, or any medical illnesses limiting life expectancy to less than 6 months; and (4) significant lab abnormalities: hematocrit <25%; white blood cell count >13 000; platelet count <70 000; serum creatinine >4; aspartate transaminase or alanine transaminase 3 times the upper normal limit; bilirubin >2.5; albumin <2; and uncontrolled hyper- or hypothyroidism.

Table 1 lists the characteristics of the enrolled participants. The research team asked participants to complete the MLWHFQ at

Table 1. Demographics of Participants in Cardiodoron Pilot Study

Age	Race	Gender	NYHA	EF%	ICM vs NICM	BMI	COPD/Other Lung Disease	Joint or LBP	A fib	DM	PVD
62	W	M	III	25	ICM	35	Restrictive Lung Disease	Chronic Knee Pain			
63	AA	M	II	28	NICM	22			+	+	
75	AA	M	II	38	ICM	25					+
55	W	M	III	28	ICM	31		Chronic LBP			
67	W	M	II	28	ICM	30				+	+
56	W	M	II	30	ICM	25					
71	W	M	II	43	ICM	35			+	+	
67	W	M	II	30	NICM	36.7		LBP	+		
77	W	M	II	28	ICM	32			+	+	

Abbreviations: A fib, atrial fibrillation; AA, African American; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; EF%, left ventricular ejection fraction; ICM, ischemic cardiomyopathy; LBP, low back pain; M, male; NICM, nonischemic cardiomyopathy; NYHA, New York Heart Association functional class; PVD, peripheral vascular disease; W, white.

baseline and at the 18-week endpoint of the study. The MLWHFQ focuses on impairments that patients frequently attribute to their heart failure and that may be amenable to interventions.^{17,18} This QOL instrument is reproducible and specifically relates QOL to heart failure.

The research team measured exercise capacity at baseline and the end of the study using the 6-minute Walk Test (6MWT). The strongest indication for using the 6MWT is to measure the response to medical interventions in patients with moderate-to-severe heart or lung disease.¹⁹

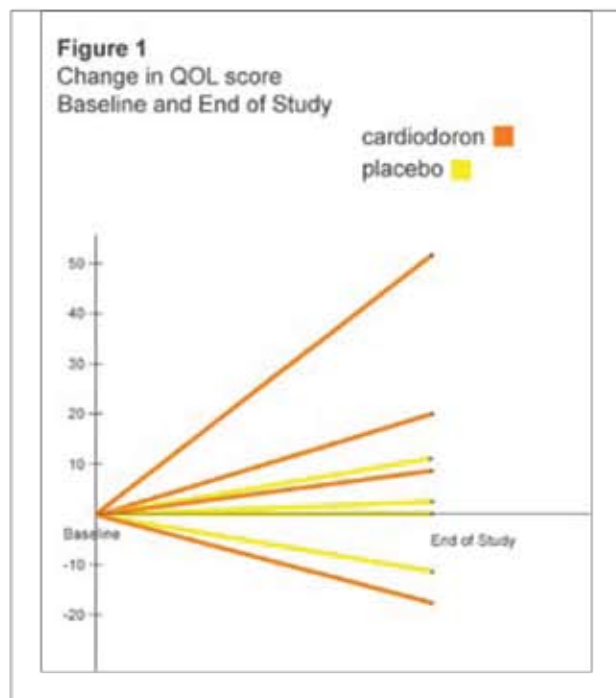
All participants also received a baseline physical exam, electrocardiogram (EKG), and laboratory work. The research team reviewed Cardiodoron administration and repeated an abbreviated physical exam, EKG, and laboratory work at 6, 12, and 18 weeks. The team also phoned participants at weeks 9, 15, and 21 to assess their progress and elicit any new symptoms. The team accomplished safety monitoring by inquiring about side effects, reviewing lab results, and appointing a safety board for reporting adverse events.

The research team assigned participants to a Cardiodoron or a placebo group. The liquid placebo consisted of maple syrup to simulate Cardiodoron’s amber color, the same amount of alcohol contained in the Cardiodoron preparation, and water. Weleda Pharmacy sent 50-mL bottles of Cardiodoron or placebo labeled “volunteer 1, volunteer 2” etc (volunteer=participant) to the VA research pharmacist with an enclosed, sealed identification code. The research pharmacist distributed the bottles in numerical order without the pharmacist or research personnel’s knowledge of the contents. Participants requested refills by volunteer number and self-administered Cardiodoron according to instructions during their scheduled study visits.

RESULTS

Nine heart-failure patients agreed to participate in this study, and 8 completed the study’s protocol. One participant withdrew from the study 2 days after the baseline evaluation due to dizziness, which he reported as a chronic condition but felt had intensified after joining the study. His physical exam was unchanged from baseline, and in follow-up calls, he denied further problems. The research team did not consider his symptoms to be a serious adverse event. At the end of the study, the research team found that the participant had received the placebo. Participants reported no other side effects, and the research team recorded no serious adverse events.

The Figure graphs the change in scores from baseline to the end of the study for the MLWHFQ. For participants receiving the placebo, the mean change in MLWHFQ score was 0.25, and the median change was 1.00 with a 95% confidence interval (CI) (13.6, 14.1). For participants receiving Cardiodoron, the mean change in MLWHFQ score was 15.0, and the median change was 12.0 with a 95% CI (61.9, 31.9). For the MLWHFQ, a lower score denotes fewer symptoms and greater improvement. The Wilcoxon rank-sum *P*-value was .4857. Taken individually, three of the four participants in the Cardiodoron group experienced increased QOL, each reporting improvement equal to or greater than 7 points. The remaining one participant taking Cardiodoron



reported a decrease in QOL.

Table 2 summarizes the number of meters each participant walked at baseline and at 18 weeks for the 6MWT. The mean change in 6MWT distance for the participants receiving placebo was 124.74 m with a 95% CI (10.3, 239.2), and the mean change for the participants receiving Cardiodoron was 59.95 m with a 95% CI (42, 162). The Wilcoxon rank-sum *P*-value was .4857.

Laboratory values for hematocrit, platelets, renal function, electrolytes, and liver function were unchanged for all participants from baseline to the end of the study. Coagulation profiles in the patients taking warfarin varied in the therapeutic and subtherapeutic range. This finding is a typical one that warfarin use alone explains. No instances of supratherapeutic levels occurred.

Table 2. 6-minute Walk Test (6MWT), Results at Baseline and End of Study^a

	Received	Baseline 6MWT, m	End of Study 6MWT, m
Participant #1	Cardiodoron	306.3	372.1
#2	Placebo	149.9	378.9
#3	Cardiodoron	423.3	491.9
#4	Cardiodoron	470.6	445.3
#5	Placebo	327.96	438.9
#6	Placebo	451.1	544.3
#7	Cardiodoron	325.5	456.2
#8	Placebo	303.3	–
#9	Placebo	344.1	409.9

^a The mean change in the 6-minute Walk Test distance for the participants receiving placebo was 124.74 m with a 95% confidence interval ([CI] 10.3, 239.2), and the mean change for participants receiving Cardiodoron was 59.95 m with a 95% CI (–42, 162). The Wilcoxon rank-sum *P*-value was .4857.

DISCUSSION

The results of this exploratory study were not statistically significant. The lack of significance may mean that Cardiodoron is ineffective in heart failure treatment or that this pilot study was too small or that the participants were too heterogeneous for conclusions about effectiveness. For the individuals taking Cardiodoron in this study, the results may have clinical relevance. From baseline to the end of the study, the mean and median QOL scores improved 15 and 12 points, respectively, in the Cardiodoron group, compared with a 0.25 and 1 point worsening, respectively, in the placebo group. Taken individually, 3 of the 4 participants group experienced increased QOL, each reporting improvement equal to or greater than 7 points. As a reference, Rector et al reported a 5-point mean QOL improvement for heart failure patients when taking an ACE inhibitor.²⁰ In the 1995 study cited previously, a QOL score improvement of 5 was sufficient reason for 72% of the CHF participants to take a new medicine with no side effects and acceptable cost.⁵ The research team reported no side effects among the 8 participants who completed the current study, and their laboratory values showed no adverse changes to blood coagulation or to bone marrow, kidney, and liver functions, which medications can impact. Improved QOL of 7 or more points for participants in this pilot study suggests that Cardiodoron provided clinically meaningful benefits to these participants, who might be willing to continue taking Cardiodoron.

One participant taking Cardiodoron reported a decrease in QOL. In addition, mean and median exercise tolerance on the 6MWT improved in the Cardiodoron group, but the placebo group did better. Table 1 summarizes the characteristics of participants that the research team speculates may be possible reasons for the Cardiodoron group's poorer exercise endurance and for the worse QOL experienced by one participant. Two of the study's participants had worse heart failure symptoms at baseline than the others, with functional levels documented as NYHA Class III at the time of enrollment, and medical practitioners would expect them to experience heart failure symptoms with minimal exertion. The same 2 participants were also the only participants with documented histories of chronic back or lower extremity pain. Both of these participants were in the Cardiodoron group. One reported poorer QOL, and both had poor or no improvement in exercise endurance as measured in the 6MWT. In a future study, the research team would match participants' characteristics more closely for CHF symptom severity and would ask participants with chronic low back or lower extremity problems more specifically whether these problems affect their ambulation.

CONCLUSION

Improved QOL predicts increased survival in heart failure patients. In this pilot study, the majority of participants taking Cardiodoron in combination with standard therapy for CHF reported QOL improvement. This result was not statistically significant. All participants tolerated Cardiodoron without side effects and without development of blood-test abnormalities. Participants could safely take Cardiodoron in a future larger study to determine whether QOL improvement consistently occurs. CHF patients may feel better using Cardiodoron than with stan-

dard therapy alone and may benefit from an improved prognosis for their chronic illness.

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