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Letter to the Editor

Probiotic therapy with *Saccharomyces boulardii* for heart failure patients: A randomized, double-blind, placebo-controlled pilot trial

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On the last decade, there has been a progressive increase in a number of publications on microbiota and therapeutic potential of probiotics. Recent studies have been suggesting that consuming probiotics may have benefits on cardiovascular system, as the improvement on blood pressure control by a modest degree [1]. Heart failure (HF) patients present low grade inflammation that participates on the progression of cardiac remodeling [2]. Moreover, when the heart is failing, myocytes show enhanced expression of inflammatory mediators, as adhesion molecules, tumor necrosis factor (TNF)-a, interleukin-6 and others [2]. Chronic HF patients usually manifest disturbance in intestinal motility and villi absorption, with impairment of tissue perfusion and edema [3,4]. These intestinal alterations promote proliferation of enteropathogenic flora and increase in bacterial (endotoxin) translocation [5]. Under this cardio-intestinal interaction, inflammatory cytokines and chemokines appear to be elevated in direct proportion to worsening of symptoms and cardiac function, as estimated by left ventricular ejection fraction (LVEF) [2]. Therefore, we have investigated the impact of a 3-month daily therapy with *Saccharomyces boulardii* for chronic systolic HF outpatients.

Patients admitted to the HF outpatient clinic at the Antonio Pedro University Hospital were recruited through a clinical screening. Twenty HF patients NYHA class II or III, with LVEF <50%, were randomized to probiotic preparation with *S. boulardii* (1000 mg per day) or placebo, for 3-month oral daily therapy. For all patients, HF drug therapy was not modified in the previous 4 weeks of inclusion. Eligible patients provided a consent form after receiving verbal and written details regarding the procedures adopted in the study, which was approved by the Ethics Committee of our Institution (UFF/Huap #0038.0.258.000-08). This trial is registered in ClinicalTrials.gov (NCT01500343). Patients were excluded if there was current or recent (last 4 weeks) use of corticosteroids, non-steroid anti-inflammatory, probiotics or antibiotics; clinical signs or symptoms of infection, independent of location; severe life threatening illness, inflammatory or autoimmune diseases, cancer, renal disease, intestinal surgery, artificial heart valve, history of rheumatic heart disease or infective endocarditis; lactose intolerance or intolerance to dairy products. Patients, physicians and staff, including echocardiographists, were blinded for all steps of the study. Clinical research unit staffs were responsible for delivering treatment supply (probiotic or placebo), according to a randomized numbered list. Four patients were excluded because of therapy discontinuity. For data

Table 1
Comparison of laboratorial and echocardiographic parameters before and after 3-months of probiotic or placebo therapy.

Group	Baseline		After treatment		P value
	Mean	±SD	Mean	±SD	
S. boulardii					
Glycemia	100.67	±13.1	94.7	±3.9	0.803
Total cholesterol	**150.83**	**±27.3**	**143.2**	**±39.7**	**0.010**
Leukocyte count	5885.0	±1563	5783.3	±1616	0.916*
Creatinine	1.12	±0.4	0.9	±0.2	0.051*
Uric acid	**6.15**	**±1.3**	**5.1**	**±1.3**	**0.014**
hsCRP (mg/dL)	0.498	±0.5	0.27	±0.3	0.116*
LVEF (%)	**39.0**	**±6.5**	**45.6**	**±7.6**	**0.005**
Left atrial diameter	**4.49**	**±0.8**	**4.2**	**±0.9**	**0.044**
Placebo					
Glycemia	96.89	±17.6	105.1	±23.2	0.087
Total cholesterol	174.22	±31.3	172.2	±36.8	0.603
Leukocyte count	6723.3	±689.9	7264.4	±1174	0.214*
Creatinine	0.97	±0.1	0.96	±0.1	0.905*
Uric acid	5.6	±1.2	5.59	±0.9	0.930
hsCRP (mg/dL)	**0.22**	**±0.3**	**0.65**	**±0.6**	**0.011***
LVEF (%)	38.9	±9.6	43.3	±10.2	0.173
Left atrial diameter	4.3	±0.9	4.5	±0.7	0.079

hsCRP = high-sensitivity C reactive protein; LVEF = left ventricular ejection fraction. Bold-emphasis means that the variable has reached statistical significance, as defined by p value <0.05.
* Obtained with Wilcoxon signed-rank test.

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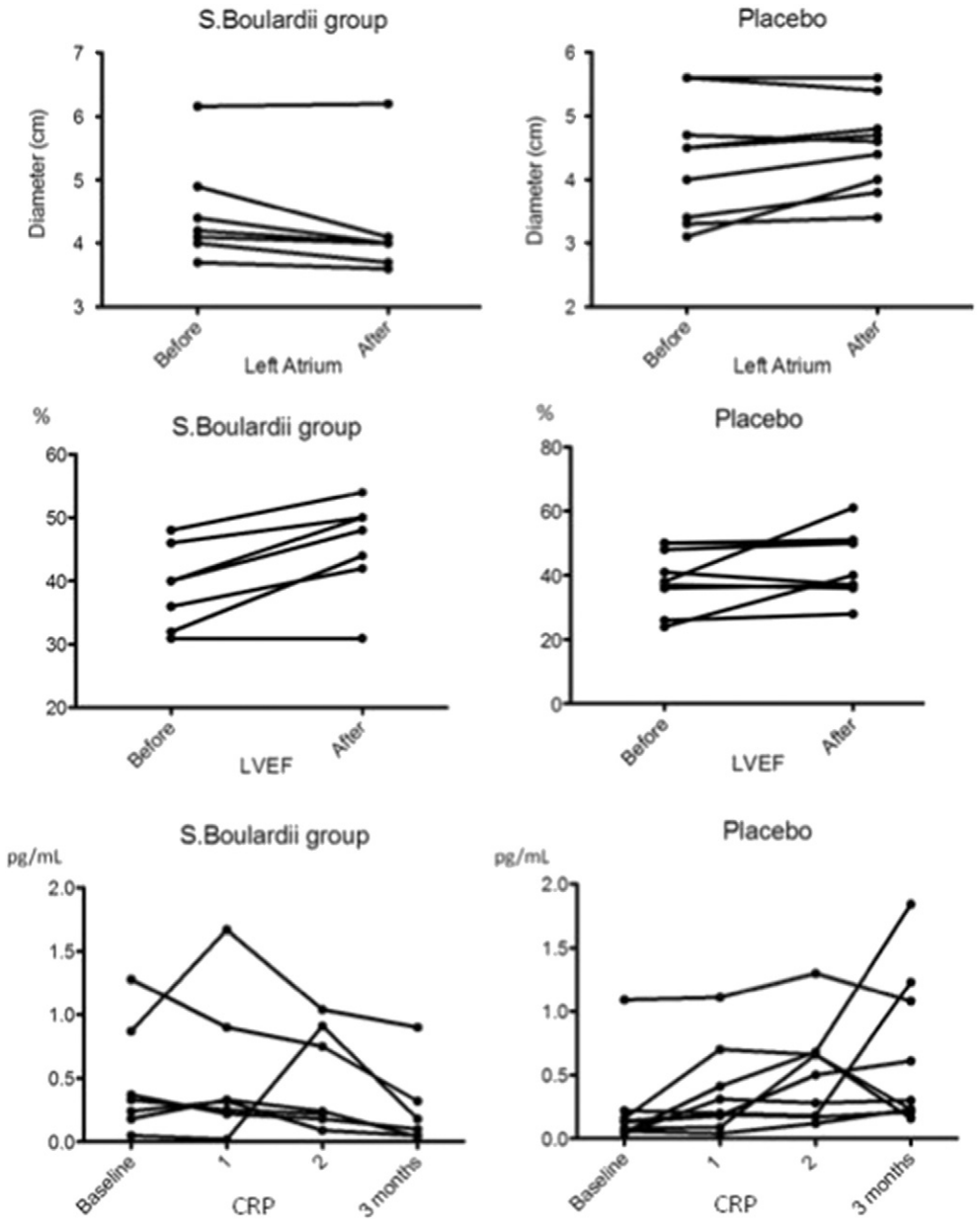

Fig. 1. Dot-plot of atrial diameter (upper), LVEF (middle) and hsCRP (bottom), before and after 3 months of probiotic or placebo therapy.

analysis, SPSS statistical 17.0 was used. The variables with normal distribution were estimated with the Shapiro–Wilk test. Non-parametric variables were leukocyte count, creatinine and hsCRP. Differences for normally distributed variables were analyzed with T test and paired Student's T test. Non-normally distributed variables (hsCRP, leukocyte count and creatinine) were analyzed with the Mann–Whitney test and Wilcoxon signed-rank test. The adopted statistical significance was <0.05.

At baseline, both groups were similar and did not present differences among demographic, laboratorial parameters and echocardiogram. The group treated with probiotic presented a reduction in total cholesterol levels ($p = 0.010$), uric acid levels ($p = 0.014$), left atrial diameter ($p = 0.044$), and an improvement in LVEF ($p = 0.005$), seen in Table 1. Placebo group showed an increase in hsCRP levels, after 3-months ($p = 0.011$), seen in Fig. 1. Comparison of parameter variations (delta) before and after therapy showed that the group treated with probiotic had a significant reduction in left atrial diameter (probiotic: −0.27 vs. placebo: +0.22; $p = 0.007$), uric acid (probiotic: −1.08 vs. placebo: +0.02; $p = 0.009$), hsCRP (probiotic: −0.23 vs. placebo: +0.44; $p = 0.031$), and creatinine levels (probiotic: −0.22 vs. placebo: −0.01; $p = 0.047$). The proposed treatment with this probiotic was safe and well tolerated, as there were no reports on side effects or adverse events according to the study patients.

A recently published study has evaluated the effect of probiotic administration (*Lactobacillus rhamnosus*) in a rat model after inducing a myocardial infarction through an occlusion of sustained coronary artery for 6 weeks, comparing with placebo. This study showed that rats under probiotic regimen have presented a significant attenuation of left ventricular hypertrophy, as showed by tissue weight and gene expression of atrial natriuretic peptide, and an improvement on LVEF [6]. Additionally, another animal study has showed that treating spontaneously hypertensive rats with probiotic-fermented purple sweet potato yogurt is beneficial, as suggested by reduced cardiomyocyte apoptosis and improvement in myocardial and interstitial remodeling [7]. Our study has showed that patients with chronic systolic HF submitted to a short-term probiotic therapy present an improvement in LVEF ($p = 0.005$) and a reduction on left atrial diameter ($p = 0.044$), seen in Fig. 1.

Several other authors also have been tried to modulate intestinal microbiota as therapy for cardiovascular diseases. An interesting pilot study used antibiotic regimen to eradicate Gram-negative intestinal flora in chronic stable severe HF patients [8]. In spite of not being randomized or placebo-controlled, it has showed that selective decontamination of intestinal tract was able to reduce monocyte CD14 expression, intracellular cytokine production and to improve peripheral endothelial function. In another study [9], the antibiotic vancomycin, which also reduces effectively intestinal microbiota, was used to treat rats before myocardial infarction. Same study [9] also tested a probiotic preparation with *Lactobacillus plantarum*. Interestingly, rats treated with vancomycin presented a reduction of 27% in myocardial infarct size with improvement of 35% in mechanical function on post-ischemic recovery, compared with untreated controls. Similarly, rats treated with probiotic showed a reduction of 29% in myocardial infarct size with improvement of 23% in mechanical function on post-ischemic recovery [9]. Our pilot study has demonstrate that chronic systolic HF patients treated with *S. boulardii* for 3-months presented a reduction on biochemical and inflammatory biomarkers (creatinine, uric acid, hsCRP), and also an improvement on cardiovascular functioning (left atrial diameter, LVEF), compared with placebo group.

The probiotic preparation containing *S. boulardii* was donated by the pharmaceutical company EMS, which had no role in the design, conduction of the study, data collection, patient management, data analysis; or in the preparation, review, or approval of the manuscript.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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