Probiotic Administration Attenuates Myocardial Hypertrophy and Heart Failure After Myocardial Infarction in the Rat

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There is strong evidence that the nature of the microbiome plays an important role in the regulation of health and disease.1 For example, there is evidence that cardiovascular disease can be modulated by changes in the gut microbiota, possibly because of alterations in the production of gut-derived hormones, which exert cardiovascular effects and based on this, producing changes in the gut microbiota has been suggested as a possible approach for the treatment of heart disease.2 Probiotics, defined as live microorganisms, which when administered in adequate amounts confer a health benefit on the host, exert numerous health benefits likely because of changes in the gut microbiota.2,5 However, there is a paucity of data with respect to the potential benefit of probiotics on cardiovascular health. Recently, Lam et al6 provided the first evidence that probiotics may be cardioprotective by showing that administration of a commercially available beverage containing the probiotic Lactobacillus plantarum 299v 24 hours before subjecting rats to 30 minutes ischemia and 2 hours reperfusion produced a 27% reduction in infarct size and improved postischemic left ventricular (LV) function after reperfusion by 35%. A major consequence of myocardial infarction, particularly in the absence of timely tissue salvage by reperfusion, is the development of cardiac hypertrophy and heart failure, which occurs through chronic complex persistent remodeling subsequent to the initial insult.7 Although advances in therapy have improved survival rates from the

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Background—Probiotics are extensively used to promote gastrointestinal health, and emerging evidence suggests that their beneficial properties can extend beyond the local environment of the gut. Here, we determined whether oral probiotic administration can alter the progression of postinfarction heart failure.

Methods and Results—Rats were subjected to 6 weeks of sustained coronary artery occlusion and administered the probiotic Lactobacillus rhamnosus GR-1 or placebo in the drinking water ad libitum. Culture and 16s rRNA sequencing showed no evidence of GR-1 colonization or a significant shift in the composition of the cecal microbiome. However, animals administered GR-1 exhibited a significant attenuation of left ventricular hypertrophy based on tissue weight assessment and gene expression of atrial natriuretic peptide. Moreover, these animals demonstrated improved hemodynamic parameters reflecting both improved systolic and diastolic left ventricular function. Serial echocardiography revealed significantly improved left ventricular parameters throughout the 6-week follow-up period including a marked preservation of left ventricular ejection fraction and fractional shortening. Beneficial effects of GR-1 were still evident in those animals in which GR-1 was withdrawn at 4 weeks, suggesting persistence of the GR-1 effects after cessation of therapy. Investigation of mechanisms showed a significant increase in the leptin:adiponectin plasma concentration ratio in rats subjected to coronary ligation, which was abrogated by GR-1. Metabonomic analysis showed differences between sham control and coronary artery ligated hearts particularly with respect to preservation of myocardial taurine levels.

Conclusions—The study suggests that probiotics offer promise as a potential therapy for the attenuation of heart failure.

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Key Words: cardiomegaly ■ heart failure ■ microbiota ■ probiotics

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initial myocardial infarction, mortality rates from heart failure remain high and are expected to rise.\(^6\) We hypothesized that probiotic treatment can alter the course of heart failure development after infarction, independently of myocardial salvage by reperfusion.

### Methods

#### Animals
Male Sprague–Dawley rats weighing \(\approx 250\) g were randomly assigned to 1 of 6 treatment groups as outlined in the following section. The protocol was approved by the Animal Use Subcommittee of the University of Western Ontario and procedures adhered to the guidelines of the Canadian Council on Animal Care (Ottawa, Ontario, Canada).

#### Induction of Heart Failure
Heart failure was induced as described previously.\(^9\) Briefly, rats were anesthetized with pentobarbital sodium (50 mg/kg body weight [bw], IP), intubated, and artificially ventilated using a rodent respirator (model 683, Harvard Apparatus). A left thoracotomy was performed and the heart was gently exposed. To induce myocardial infarction, the left main coronary artery was ligated \(\approx 3\) mm from its origin using a firmly tied silk suture. For sham operation, the ligature was placed in an identical fashion but not tied. Buprenorphine (0.03 mg/kg bw, IP) was immediately administered to all animals after surgery for pain management. All animals were housed singly per cage after surgery. The studies were completed after a total of 6 weeks of sustained coronary artery ligation (CAL) or sham surgery at which time animals were subjected to final echocardiography and catheter-based hemodynamic assessment before euthanasia.\(^9\)

#### Echocardiography
Echocardiography and body weight determinations were performed on each animal immediately before surgery and every 2 weeks thereafter until euthanization. Rats were anesthetized with 2% isoflurane and echocardiography was performed as previously described\(^9\) using a Vevo 770 high-resolution in vivo microimaging system equipped with a real-time microvisualization scan head of 17.5 MHz (VisualSonics, Toronto, Ontario, Canada). M-mode 2-dimensional (2D) echocardiography images were obtained from the parasternal short axis. Images were analyzed using the Vevo 770 Protocol-Based Measurements software and calculations for the dimensions of the LV diameter. Doppler measurements were taken to determine peak early diastolic filling velocity (E wave), peak late diastolic filling velocity (A wave), and E/A ratios.

#### Hemodynamic Measurements
Hemodynamic measurements were taken 6 weeks after surgery. Animals were anesthetized with pentobarbital sodium (50 mg/kg bw). An anterior thoracotomy was performed and the LV was catheterized retrogradely via the right carotid artery using a 2.0F P-V Mikro-Tip catheter (Millar Instruments, Houston, TX) as previously described.\(^9\) Left ventricular pressure–volume relationships (P–V loops) were obtained by increasing afterload by a gradual occlusion of the coronary arteries and using a P-V recorder (model 683, Harvard Apparatus). A left thoracotomy was placed in an identical fashion but not tied. Buprenorphine (0.03 mg/kg bw, IP) was immediately administered to all animals after surgery for pain management. All animals were housed singly per cage after surgery. The studies were completed after a total of 6 weeks of sustained coronary artery ligation (CAL) or sham surgery at which time animals were subjected to final echocardiography and catheter-based hemodynamic assessment before euthanasia.\(^9\)

#### Probiotic Culture and Dosing Regimen
Resuscitation and subsequent propagation of *L. rhamnosus* GR-1 was conducted in MRS broth (18 hours, 37°C under anaerobic conditions, GasPak BD). The organisms were then streaked onto MRS agar (Difco BD, Franklin Lakes, NJ). Single colonies were selected and used to inoculate 3 mL of MRS broth (incubated as above) and in turn were used to inoculate 500 mL MRS broth. The cells were centrifuged (1600g for 20 minutes) and the pellet was resuspended in 25 mL of water ad libitum immediately after completion of surgery to provide an approximate daily dose of 1x10^9 CFUs based on water consumption of \(\approx 50\) mL/d. For most studies, treatments were performed for the entire 6-week follow-up period, although an additional study entailed the probiotic being withdrawn after 4 weeks and replaced with control drinking water for the remaining 2 weeks. Each of the 6 treatment groups had a sample size of 10.

#### Plasma Analyses of Leptin and Adiponectin
Immediately after hemodynamic measurements and before euthanization, blood was collected directly from the heart and kept on ice. Plasma samples were brought to room temperature and assayed for leptin and adiponectin using commercially available ELISA kits (Enzo Life Sciences, Plymouth Meeting, PA).

#### Heart Weight Measurement and Tissue Processing
Hearts were removed after hemodynamic measurements and weighed. A total of 50 to 100 mg of tissue from the LV (nonischemic region) were collected and stored at \(-80°C\) for later determination of atrial natriuretic peptide expression as an index of hypertrophy and metabolic analysis.

#### Cecum Digesta Sample Collection and Analyses
After euthanization, the cecum was removed immediately. Cecum digesta (0.3 g each) was resuspended in 1 mL of sterile 1x phosphate buffered saline. Serial dilutions (10^3–10^8) were made and 10 μL of each dilution was drop-plated on MRS agar (Difco, BD) containing 32-μg/mL fusidic acid (Sigma-Aldrich, Oakville, Ontario, Canada) sterilized using a 0.2-μm filter. Plates were incubated at 37°C anaerobically (GasPak, BD) for 48 hours. GR-1 colonies were identified and enumerated.

The hypervariable V6 region of the 16S rRNA gene from each DNA sample was amplified using left forward 5′ primers each tagged with a unique barcode sequence as previously described.\(^9\) Polymerase chain reaction was performed as described\(^6\) and amplification products were quantified using Qubit to determine DNA concentration, and equal molar quantities were mixed and sequenced using the Ion Torrent platform (Life Technologies, Carlsbad, CA). Raw sequence data were filtered, processed, and analyzed as previously described.\(^11\) Taxonomic assignments were made using Seqmatch from the Ribosomal Database Project,\(^12\) which were verified using the Greengenes database.\(^13\) Taxonomic assignments were arranged and presented using QiIME for 16S rRNA analysis.\(^14\) Communities from each sample were compared using weighted UniFrac β-diversity analysis.\(^15\)

#### ^1H NMR Spectroscopic Analysis of Heart Tissue
Tissue extractions were performed as previously described.\(^16\) Briefly, 30 mg of heart tissue was dissected from the LV and homogenized in 300 μL of chloroform:methanol (2:1). The homogenate was combined with 300 μL of water, vortexed and centrifuged (13,000g for 10 minutes) to separate the aqueous and organic phases. Water was removed from the aqueous phase using a vacuum concentrator (SpeedVac) and then reconstituted in 550 μL of phosphate buffer (pH 7.4) containing 1 mmol/L of the internal standard, 3-(trimethylsilyl)-[2,2,3,3,-2H4]-propionic acid. For each sample, a standard 1D NMR spectrum was acquired with water peak suppression using a standard pulse sequence (recycle delay-90°-t-90°-t-90°-acquire free induction decay). Recycle delay was set as 2 s, the 90° pulse length was 7.7 μs, and the mixing time (t) was 10 ms. For each spectrum, 8 dummy scans were followed by 128 scans with an acquisition time per scan of 2.91 s and collected in 64K data points with a spectral width of 40 ppm.

\(^{1}H\) NMR spectra were manually corrected for phase and baseline distortions and then digitized using an in-house MATLAB (version...
Spectra were aligned as described previously to adjust for subtle shifts in peak position, and each spectrum was normalized using a probabilistic quotient approach. Principal components analysis was performed with Pareto scaling in MATLAB using scripts (Korrigan Sciences Ltd, Maidenhead, United Kingdom). Orthogonal projection to latent structure-discriminant analysis (OPLS-DA) models were constructed using unit variance scaling to aid the interpretation of the model and elucidate metabolic variation between groups. Here, $^1$H NMR spectroscopic data served as the descriptor matrix and class information (sham and CAL treatments) as the response variable. The contribution of each metabolite to sample classification was visualized by back-scaling transformation, generating a correlation coefficient plot. These coefficient plots are colored according to the significance of correlation to treatment with red indicating high significance and blue indicating low significance. For all models, a one orthogonal component...
was used to remove systematic variation unrelated to class. Predictive performance was assessed using a 7-fold cross-validation approach and the Q2Y (goodness of prediction) values are provided.

Statistical Analysis
Data reported are means±SE. Data were analyzed using a 1-way ANOVA followed by a post hoc Tukey test to determine the effect of CAL and potential influence of GR-1. Echocardiographic data were analyzed using 2-way ANOVA with repeated measures and a post hoc Tukey test. All variables analyzed were assumed to be approximately normally distributed. Differences were considered significant when \( P<0.05 \).

Results
Effect of Treatments on Body Weight Gain
None of the treatments exerted any effect on body weight growth throughout the 6-week postsurgery period with identical body weights observed throughout the 6-week postsurgery period, irrespective of treatment (not shown).

Effect of Probiotic Administration on Intestinal Microbial Composition
A total of 242 distinct organizational taxonomic units groupings were identified. *Lactobacillus rhamnosus* was not detected in any of the 60 individual samples (Figure 1A). Overall, there was no distinct grouping of community compositions in any of the 60 samples with respect to probiotic administration nor was there distinct grouping of communities in cecum digesta samples of rats that received CAL surgery versus sham surgery (Figure 1B and IC), suggesting no changes in the microbial composition of the gut. *Lactobacillus rhamnosus* GR-1 was readily cultivated from fresh cecum digesta samples on semi-selective MRS agar containing fusidic acid. Presumptive colonies were identified based on size and morphology and enumerated (Table 1). Colonies with GR-1–like morphology were not detected in samples of rats on the control vehicle treatment (containing only water or skim milk). Thus, when taken together the data in Table 1 and Figure 2 demonstrate that GR-1 was present and alive in the cecum (Table 1), yet did not colonize or change the existing composition of the cecum microbiota (Figure 1).

Table 1. Cultivation of *Lactobacillus rhamnosus* GR-1 From Cecum Digesta With Different Treatment Groups 6 Weeks After Surgery

<table>
<thead>
<tr>
<th>Treatment Group (n=10)</th>
<th>CFU/mL GR-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham surgery/water</td>
<td>Not detected</td>
</tr>
<tr>
<td>Sham surgery/GR-1</td>
<td>8.71×10^7</td>
</tr>
<tr>
<td>Coronary artery ligation/water</td>
<td>Not detected</td>
</tr>
<tr>
<td>Coronary artery ligation/GR-1</td>
<td>6.73×10^7</td>
</tr>
<tr>
<td>Coronary artery ligation/skim milk</td>
<td>Not detected</td>
</tr>
<tr>
<td>Coronary artery ligation/4 wk GR-1+2 wk skim milk</td>
<td>7.56×10^7</td>
</tr>
</tbody>
</table>

Probiotic Supplementation Attenuates Cardiac Hypertrophy
CAL significantly increased LV weight and produced a marked increase in gene expression of atrial natriuretic peptide, thus indicating a robust hypertrophic response at the end of the 6-week follow-up period (Figure 2). However, animals treated with GR-1 showed near-normalized LV:body weight ratio and significantly reduced atrial natriuretic peptide expression.

Probiotic Supplementation Attenuates LV Dysfunction After Coronary Artery Ligation
E/A ratios, indicative of transmural valve blood flow properties, were increased in rats subjected to CAL although this was significantly attenuated by GR-1 (Figure 3A and 3B). In addition, LV internal diameters during systole and diastole were significantly increased during the 6-week CAL period although these were significantly blunted by GR-1 treatment (Figure 3C–3E). CAL induced a significant reduction in both ejection fraction and fractional shortening of ≈25% and 30%, respectively, at the end of the 6-week postinfarction period although these effects were significantly attenuated by GR-1 treatment (Figure 3F and 3G).

Hemodynamic analyses indicate significant systolic and diastolic dysfunctions in animals subjected to 6 weeks of CAL (Figure 4). These effects were significantly but not completely reduced by probiotic treatment with respect to all parameters measured.

Pressure–volume loops for these experiments are shown in Figure 5A to 5D. The end-systolic pressure volume relationship was substantially less steep in animals subjected to 6-week CAL, whereas the end-diastolic pressure volume relationship was increased indicating a reduction in contractile function and increased diastolic stiffness, respectively. However, these changes were significantly attenuated by GR-1 treatment. As shown in Figure 5E and 5F, preload-recruitable stroke work, an index of LV contractility, was significantly depressed in control infarcted animals, whereas the isovolumetric relaxation time (\( \tau \)) was increased, although these responses were significantly attenuated by probiotic administration.

Probiotic Supplementation Prevents the Increased Leptin to Adiponectin Plasma Concentration Ratio
Figure 6 shows that CAL significantly increased plasma leptin concentrations in the control group but not the GR-1 group, whereas adiponectin levels were unaffected.

**Figure 2.** Reduction of hypertrophy by *Lactobacillus rhamnosus* GR-1. Top. The left ventricle to body weight ratios (LV/BW) in animals subjected to 6 weeks of coronary artery ligation or to sham procedure. Corresponding values for LV gene expression of the hypertrophic marker atrial natriuretic peptide (ANP) as a ratio to 18S expression are provided at the bottom. Data are presented as means±SEM (n=10). *P<0.05 vs sham group. #P<0.05 vs coronary artery ligation (CAL) control group.
Probiotic Supplementation Improves Cardiac Metabolic Profile

Based on principal components analysis, differences were observed between the cardiac metabolic profiles of sham-operated and CAL animals treated with water (Figure 7). This metabolic distinction was weakened when CAL animals received milk (Figure 8B) and the probiotic GR-1 (Figure 7C). Pair-wise orthogonal projection to latent structure-discriminant analysis models reinforce this observation. A model with good predictive strength was returned comparing the water sham and water CAL animals (Figure 7D; $Q^2=0.498; P<0.001$). Here, sustained CAL increased the amount of creatinine in the heart tissue and decreased the amount of glutamine, alanine, taurine, scyllo-inositol, inosine, and total creatine. Models with weaker predictive ability were obtained when comparing water sham with milk CAL animals ($Q^2=0.2112; P=0.07$) and water sham with probiotic CAL animals ($Q^2=0.2298; P=0.09$), indicating both milk and GR-1 dampened the metabolic consequences of CAL.

Maintenance of Antiremodeling Effect After Probiotic Withdrawal

We also conducted experiments in which the probiotic GR-1 was administered for only a 4-week period and then withdrawn for the remaining 2 weeks. These results are summarized in Table 2 and show that the reduction in hypertrophy and the associated improvement in LV function are evident 2 weeks after GR-1 withdrawal. Indeed, the improvement in many parameters was similar to that seen in animals treated with GR-1 for the entire 6-week post-CAL period.

Discussion

In this report, we show that administration of a probiotic attenuates postinfarction remodeling and heart failure in rats subjected to sustained CAL. L rhamnosus GR-1 was selected because of its immune-modulatory activity via the gut and our extensive experience with this probiotic strain. A preliminary echocardiography-based study performed in our laboratory but not reported here demonstrated identical benefit of GR-1 and the probiotic L. plantarum 299v in rats subjected to...
particular attention in terms of the gut–brain axis in which prohypertrophic factors. This distant site concept has received possibly secondary to reductions in gastrointestinal-derived pressure in either sham or coronary artery ligated animals, thus precluding a potential benefit of afterload reduction. The benefit of taurine is the most abundant amino acid in the heart, its physiological role is far from clear. However, taurine likely plays an important role in heart failure especially as taurine deficiency results in LV dysfunction, an effect reversed by dietary taurine supplementation. Taurine can directly inhibit hypertrophy produced by angiotensin II in ventricular myocytes and taurine administration improves LV function in the postinfarcted myocardium revealed from metabonomic analysis. The other potential benefit of probiotic administration in the postinfarcted myocardium is the preservation of myocardial taurine content. Although taurine is the most abundant amino acid in the heart, its physiological role is far from clear. However, taurine likely plays an important role in heart failure especially as taurine deficiency results in LV dysfunction, an effect reversed by dietary taurine supplementation. Taurine can directly inhibit hypertrophy produced by angiotensin II in ventricular myocytes and taurine administration improves LV function in patients with heart failure. Overall, however, the precise role of taurine in postinfarction remodeling requires further investigation particularly as it pertains to taurine preservation with probiotic administration in the postinfarcted myocardium. Emerging evidence suggests that adipokines, including leptin and adiponectin, play important roles in cardiovascular regulation and modulate the progression of cardiovascular disease. Of particular relevance to our study, a significant reduction in plasma concentrations of the prosatiety adipokine leptin in rats provided with a probiotic beverage was recently reported suggesting that this mediated the cardioprotective effect of probiotic administration on infarct size reduction, a finding reinforced by reversal of cardioprotection
with exogenously administered leptin. With respect to heart failure, various studies have shown that leptin exerts hypertrophic effects under different experimental conditions. Furthermore, clinical studies have shown that heart failure is associated with hyperleptinemia, and elevated leptin has been proposed as a risk factor for heart failure. A recent report implicated leptin to the development of heart failure in obese men with no history of pre-existing coronary heart disease, suggesting that leptin directly contributes to the development of heart failure in obese individuals. Our study showed a significant increase in plasma leptin concentrations in rats subjected to CAL, which was prevented by GR-1 with no effect on adiponectin concentrations. At the same time, it was surprising to observe that plasma leptin levels tended to increase in sham-operated animals provided GR-1 when compared with their respective control group. As such, it is difficult at the present time to assign a specific role for leptin, or indeed other adipokines, to the salutary effect of probiotic administration on heart failure. However, we believe that absolute plasma concentration values of individual adipokines may be of lesser importance than their concentrations relative to each other. Indeed, in this regard, there is now extensive evidence in both animal and clinical studies that the leptin:adiponectin ratio represents a stronger index for several cardiovascular- and metabolic-related morbidities than each component alone. Our results show for the first time, a substantial increase in the leptin:adiponectin ratio in animals subjected to CAL, which was normalized by probiotic administration. Whether this reflects a cause and effect relationship with respect to the ability of GR-1 to ameliorate heart failure cannot be definitively ascertained. Extending our finding to the clinical scenario must be done with caution, but our data suggest a potential mechanism where probiotics may slow the progression of heart failure.

A potential limitation of our study is that we did not use irradiated GR-1 as a control group to demonstrate the necessity for live bacteria or that the effects reported here were not because of an immunologic effect that could take place with dead bacteria. We also did not detect major changes in the gut microbial composition between treatment groups, which suggests that the GR-1 strain did not colonize and that this is not a prerequisite for its beneficial effect. Preliminary unpublished studies by our group suggest that probiotics could directly attenuate the hypertrophic response, possibly via the release of antihypertrophic factors. In this regard, ventricular myocytes cocultured with GR-1 demonstrated improved viability over time, although of more relevance to the present study, these myocytes were completely unresponsive to the hypertrophic effect either of the α1 adrenoceptor agonist phenylephrine or hydrogen peroxide. These studies are currently attempting...
to identify a GR-1–derived factor(s) as a potential anti hypertrophic agent(s).

In summary, the present study is the first to report salutary effects of probiotic administration to rats subjected to prolonged coronary artery occlusion culminating in cardiac hypertrophy, as well as systolic and diastolic LV dysfunction. The underlying mechanisms for these effects are likely complex and multifaceted, but initial evidence suggests improved myocardial metabolic status including tissue taurine preservation as well as a favorable reduction in the leptin:adiponectin plasma concentration ratio. Although hearts were not reperfused in the current study, the possibility cannot be ruled out that infarct size reduction contributed to the salutary effect of GR-1 on LV function. Whether our findings apply to other animal species or human heart failure remains to be determined.

However, the widespread availability of probiotic preparations may facilitate their testing as a treatment for heart failure particularly in combination with existing therapies. The potential benefit of this conjoint approach includes improvement of therapeutic efficacy and the possibility of reduced dosing of existing medications, thus minimizing their potential for adverse effects. These concepts warrant further study.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Probiotics are defined by the World Health Organization as live microorganisms which when administered in adequate amounts confer a health benefit on the host. Probiotics are readily available and widely consumed by the general population either as supplements or as additives in various food preparations. The major and best-known benefit of probiotics is their ability to promote gastrointestinal health, but emerging evidence suggests that probiotics may also confer many other health benefits. With respect to cardiovascular-related benefits, these include lowering plasma cholesterol levels and protecting the myocardium against acute ischemic insult. Here, we show that administration of the probiotic strain *Lactobacillus rhamnosus* GR-1 to rats subjected to chronic coronary artery occlusion attenuates hypertrophy and improves left ventricular function. This likely occurs independently of infarct size reduction because of the absence of reperfusion but rather via a mechanism or mechanisms resulting in reduced postinfarction hypertrophy and remodeling. We think that this study may be of clinical importance as it suggests that probiotics could reduce the severity of heart failure secondary to myocardial infarction. Although not studied here, the possibility exists that probiotics may offer additional benefit when used in combination with standard heart failure medications. Such potential probiotic–drug interactions need to be studied in detail. Many issues still need to be addressed such as firmly identifying the mechanisms underlying these effects. Moreover, as there is a plethora of probiotics currently available to consumers, it is important to confirm whether the salutary effects of probiotics are shared with other strains.
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