

Study Source & Grant Number

**Fecal Microbiota Transplantation for Elderly Patients
with HFpEF: A Randomized Controlled Trial**

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Study Abstract

Study Title	Fecal Microbiota Transplantation for Elderly Patients with HFpEF: A Randomized Controlled Trial
Study Objectives	To explore the effects and underlying mechanisms of fecal microbiota transplantation (FMT) intervention in elderly patients with heart failure with preserved ejection fraction (HFpEF), so as to provide evidence for the prevention and treatment of elderly HFpEF.
Study Design	Prospective, Randomized, Placebo- Controlled Clinical Study
Total Enrollment	Total 50 subjects (25 in the experimental group and 25 in the control group)
Subject Selection	<p>Inclusion criteria:</p> <ol style="list-style-type: none"> 1. Aged ≥ 60 years old; 2. Meeting the diagnostic criteria for HFpEF: <ol style="list-style-type: none"> (1) Consistent with the epidemiological and demographic characteristics of HFpEF patients; (2) Presence of clinical symptoms and/or signs of heart failure; (3) Cardiac imaging examination indicating LVEF $\geq 50\%$; (4) In sinus rhythm: BNP ≥ 35 pg/ml and/or NT-proBNP ≥ 125 pg/ml; In atrial fibrillation: BNP ≥ 105 pg/ml and/or NT-proBNP ≥ 365 pg/ml; (5) Meet at least one of the following conditions: <ol style="list-style-type: none"> a. LVMI ≥ 115 g/m² (male) or ≥ 95 g/m² (female); b. LAVI > 34 ml/m² ; c. Relative wall thickness > 0.42, or left ventricular free wall thickness > 12 mm; d. Septal e' < 7 cm/s, or lateral e' < 10 cm/s, or average E/e' ≥ 14; e. Tricuspid regurgitation velocity > 2.8 m/s, or pulmonary artery systolic pressure > 35 mmHg; 3. NYHA functional class II - III; 4. Complicated with metabolic diseases such as hypertension, diabetes and

obesity;

5. Accompanied by gastrointestinal symptoms;

6. Well-tolerated to current anti-heart failure regimens with stable medication for at least 1 month;

7. Stable heart failure condition without acute exacerbation;

8. Basically normal cognitive function, capable of understanding scale assessment contents;

9. Able to perform daily activities independently;

10. Fully understanding the purpose of this clinical trial, voluntary participation and signing of written informed consent.

Exclusion criteria:

1. Symptoms caused by non-cardiac diseases;

2. Patients with any contraindication to Fecal Microbiota Transplantation (FMT):

(1) Patients with severe intestinal barrier damage induced by various causes, such as sepsis, active massive gastrointestinal bleeding, intestinal perforation;

(2) Patients diagnosed with fulminant colitis or toxic megacolon;

(3) Patients unable to tolerate enteral nutrition meeting 50% of calorie requirements due to severe diarrhea, significant fibrous intestinal stenosis, severe gastrointestinal hemorrhage, high-output intestinal fistula and other conditions;

(4) Patients with congenital or acquired immunodeficiency diseases;

(5) Patients receiving high-risk immunosuppressive or cytotoxic drugs recently, such as rituximab, doxorubicin, or moderate-to-high dose steroids (prednisone \geq 20 mg/d) administered continuously for more than 4 weeks;

(6) Severely immunosuppressed patients with neutrophil count $< 1500/\text{mm}^3$;

3. History of myocardial infarction, coronary artery bypass grafting, or any

	<p>event that may reduce LVEF within 6 months before enrollment (unless LVEF \geq 50% was confirmed);</p> <p>4.Received valve replacement surgery within 6 months before enrollment;</p> <p>5.Poorly controlled blood pressure (SBP \geq 180 mmHg or DBP \geq 100 mmHg);</p> <p>6.Current acute decompensated heart failure requiring intervention;</p> <p>7.Resting heart rate > 120 beats per minute, or complicated with malignant arrhythmia;</p> <p>8.Significant coronary artery disease requiring PCI revascularization;</p> <p>9.Severe renal insufficiency (serum creatinine > 442 μ mol/L) or patients on dialysis;</p> <p>10.Pre-existing gastrointestinal diseases, including ulcerative colitis, Crohn' s disease, irritable bowel syndrome, chronic diarrhea;</p> <p>11.Current malignant tumors requiring anti-tumor treatment;</p> <p>12.Complicated with acute diseases or acute exacerbation of chronic diseases at present;</p> <p>13.Participation in other interventional clinical trials or oral intake of probiotic preparations within the past 3 months.</p>
Treatment Protocol	<p>A randomized, placebo-controlled study design will be adopted. All enrolled patients meeting the inclusion/exclusion criteria will be randomly assigned to the experimental group and control group at a 1:1 ratio. On the basis of standard anti- heart failure medication, patients in the experimental group will receive allogeneic FMT intervention (bowel preparation with polyethylene glycol or lactulose before transplantation; oral capsules taken within 1 hour after breakfast and lunch, 4 capsules each time, for a 6-day course of treatment). Patients in the control group will receive standard anti- heart failure medication plus placebo (bowel preparation with polyethylene glycol or lactulose; oral placebo capsules taken within 1 hour after breakfast and lunch, 4 capsules each time, for a 6-day course of treatment). Follow-up assessments will be performed at baseline, Week 4</p>

	and Week 20 after treatment initiation. The primary endpoint is defined as 20 weeks post-treatment.
Efficacy Assessment	Efficacy assessment will be based on composite endpoint events. A treatment response is defined as achievement of any one of the following criteria with statistically significant between-group differences: ① Primary outcome: ≥ 5 -point increase from baseline in the Kansas City Cardiomyopathy Questionnaire (KCCQ) score; ② Secondary outcomes: ≥ 1 -grade reduction in NYHA functional class, $\geq 20\%$ decrease from baseline in NT-proBNP (or BNP), or $\geq 5\%$ increase from baseline in 6-minute walk test distance. Non-response is defined as failure to meet any of the above criteria.
	Safety Evaluation Indicators: All-cause mortality, cardiovascular mortality, acute cardiovascular events, hospitalization due to acute exacerbation of chronic heart failure, and potential adverse reactions of fecal microbiota transplantation such as diarrhea, abdominal distension and abdominal pain will be monitored throughout the trial. The incidence of adverse events directly related to the study intervention will be recorded.
Statistical Methods	Changes from baseline in primary endpoint and key secondary endpoint indicators will be compared between the two groups. For normally-distributed continuous data, the t-test will be used; for non-normally-distributed continuous data, non-parametric tests will be adopted. The chi-square test will be applied for comparison of categorical data (rates). Efficacy analysis will be performed on the per-protocol set, including subjects with no major protocol violations regarding eligibility criteria, treatment administration and primary outcome measurement, and good treatment compliance. Safety analysis will be conducted on the safety set, covering all patients who received at least one dose of the study intervention.
Study Duration	January 1, 2026 – December 31, 2028

Background

Heart failure with preserved ejection fraction (HFpEF) is a clinical syndrome characterized by left ventricular diastolic dysfunction accompanied by systemic multi-organ involvement, accounting for more than 50% of all heart failure cases, with high prevalence, mortality and economic burden¹. Most patients are elderly individuals, often complicated with chronic inflammation-related diseases such as obesity, diabetes mellitus and hypertension, with complex and incompletely elucidated pathological mechanisms^{2,3}. Current treatment for HFpEF mainly focuses on comorbidity management, with a lack of specific therapeutic drugs. Although agents such as SGLT2 inhibitors and mineralocorticoid receptor antagonists exert certain efficacy, their clinical application is limited by complications including urinary tract infection, aggravated sarcopenia and hyperkalemia⁴⁻⁶. There is an urgent clinical need to develop safe and effective novel therapies. Patients with HFpEF exhibit prominent chronic low-grade systemic inflammation, gut dysbiosis and reduced microbial diversity. Systemic inflammation and gut dysbiosis interact as both cause and effect, jointly exacerbating myocardial remodeling and diastolic dysfunction. Our previous clinical study demonstrated that 12-week administration of triple viable *Clostridium butyricum* combined with standard anti-heart failure therapy significantly improved symptoms and cardiac function, and enhanced physical performance and quality of life in elderly patients with HFpEF, indicating that gut microbiota reconstitution can serve as an effective adjuvant therapeutic strategy for HFpEF. Fecal Microbiota Transplantation (FMT) has shown therapeutic potential in the management of metabolic and cardiovascular diseases such as obesity and hypertension. Animal studies have demonstrated that FMT can restore gut microbiota balance, increase short-chain fatty acids (SCFAs, e.g., butyrate), inhibit the TMAO/TGF- β pathway, alleviate inflammation, suppress myocardial fibrosis, and improve cardiac function⁷⁻⁹. Clinical studies have shown that 4-week FMT intervention significantly improves gut microbiota diversity, insulin resistance, BMI, glycated hemoglobin and blood glucose in patients with type 2 diabetes mellitus¹⁰. In patients with severe obesity and metabolic syndrome, daily supplementation with low-fermentable fiber can enhance insulin sensitivity after FMT by differentially regulating the engraftment of specific gut microbiota and the enteroendocrine axis¹¹. Other studies have found that FMT can improve lipid profiles and liver stiffness in obese patients with type 2 diabetes¹². No FMT-related adverse events were reported in any of the above clinical trials.

This study is the first clinical trial investigating FMT for HFpEF via the “gut-heart axis”. We evaluate the effects of allogeneic FMT added to standard anti-heart failure

therapy on cardiac function, systemic inflammation, quality of life, and physical performance in elderly HFpEF patients, and explore potential mechanisms. The study aims to overcome limitations of current pharmacotherapy, avoid drug-related complications, provide a novel multi-system interaction theory and treatment strategy for HFpEF, and fill critical gaps in clinical practice. It will generate high-level evidence for FMT in heart failure, promote standardization and industrial translation of microbiota transplantation, and advance the clinical adoption of microecological therapies. If FMT reduces HFpEF readmission rates, it will substantially lower healthcare costs and medical burden. The findings will support a paradigm shift in HFpEF management from a “heart-centric” model to a “systemic syndrome” model, providing microbiome-based evidence for targeted gut microbiota therapy.

Study Objectives

To evaluate the effects of fecal microbiota transplantation added to standard anti-heart failure therapy on cardiac functional class, quality of life, cardiac diastolic function, heart failure biomarkers, gut barrier function, and inflammation in elderly HFpEF patients, as well as its impact on physical performance, frailty, sarcopenia, and nutritional status; to explore the effects and mechanisms of FMT in elderly HFpEF.

Study Design, Principles and Procedures

1. Study Design

Design: Prospective, randomized, placebo-controlled clinical trial.

Randomization: Block randomization with a block size of 4, allocated 1:1 to experimental and control groups; randomization codes generated using SPSS 23.

Sample Size Calculation: Based on two-independent-samples t-test. Power ($1-\beta$)=0.90, α =0.05. Assumed post-intervention means: μ_1 =5.5 (experimental), μ_2 =-2.5 (control), δ =8, σ =7.5. PASS software estimated N=40 (20 per group). Accounting for dropout, final sample size N=50 (25 per group).

2. Study Procedures

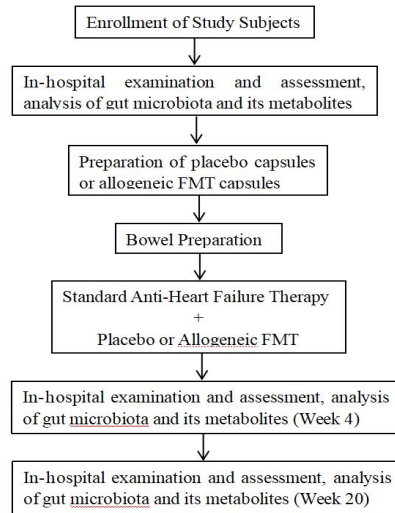


Figure 1 Study Technical Roadmap

Subject Selection

1. Inclusion Criteria

1. Aged ≥ 60 years old;
2. Meeting the diagnostic criteria for HFpEF:
 - (1) Consistent with the epidemiological and demographic characteristics of HFpEF patients;
 - (2) Presence of clinical symptoms and/or signs of heart failure;
 - (3) Cardiac imaging examination indicating LVEF $\geq 50\%$;
 - (4) In sinus rhythm: BNP ≥ 35 pg/ml and/or NT-proBNP ≥ 125 pg/ml;
In atrial fibrillation: BNP ≥ 105 pg/ml and/or NT-proBNP ≥ 365 pg/ml;
 - (5) Meet at least one of the following conditions:
 - a. LVMI ≥ 115 g/m² (male) or ≥ 95 g/m² (female);
 - b. LAVI > 34 ml/m²;
 - c. Relative wall thickness > 0.42 , or left ventricular free wall thickness > 12 mm;
 - d. Septal $e' < 7$ cm/s, or lateral $e' < 10$ cm/s, or average $E/e' \geq 14$;
 - e. Tricuspid regurgitation velocity > 2.8 m/s, or pulmonary artery systolic pressure > 35 mmHg;
3. NYHA functional class II - III;
4. Complicated with metabolic diseases such as hypertension, diabetes and obesity;
5. Accompanied by gastrointestinal symptoms;
6. Well-tolerated to current anti-heart failure regimens with stable medication for at least 1 month;
7. Stable heart failure condition without acute exacerbation;
8. Basically normal cognitive function, capable of understanding scale assessment contents;

9. Able to perform daily activities independently;
10. Fully understanding the purpose of this clinical trial, voluntary participation and signing of written informed consent.

2. Exclusion criteria:

1. Symptoms caused by non-cardiac diseases;
2. Patients with any contraindication to Fecal Microbiota Transplantation (FMT):
 - (1) Patients with severe intestinal barrier damage induced by various causes, such as sepsis, active massive gastrointestinal bleeding, intestinal perforation;
 - (2) Patients diagnosed with fulminant colitis or toxic megacolon;
 - (3) Patients unable to tolerate enteral nutrition meeting 50% of calorie requirements due to severe diarrhea, significant fibrous intestinal stenosis, severe gastrointestinal hemorrhage, high-output intestinal fistula and other conditions;
 - (4) Patients with congenital or acquired immunodeficiency diseases;
 - (5) Patients receiving high-risk immunosuppressive or cytotoxic drugs recently, such as rituximab, doxorubicin, or moderate-to-high dose steroids (prednisone ≥ 20 mg/d) administered continuously for more than 4 weeks;
 - (6) Severely immunosuppressed patients with neutrophil count $< 1500/\text{mm}^3$;
3. History of myocardial infarction, coronary artery bypass grafting, or any event that may reduce LVEF within 6 months before enrollment (unless LVEF $\geq 50\%$ was confirmed);
4. Received valve replacement surgery within 6 months before enrollment;
5. Poorly controlled blood pressure (SBP ≥ 180 mmHg or DBP ≥ 100 mmHg);
6. Current acute decompensated heart failure requiring intervention;
7. Resting heart rate > 120 beats per minute, or complicated with malignant arrhythmia;
8. Significant coronary artery disease requiring PCI revascularization;
9. Severe renal insufficiency (serum creatinine $> 442 \mu\text{mol/L}$) or patients on dialysis;
10. Pre-existing gastrointestinal diseases, including ulcerative colitis, Crohn's disease, irritable bowel syndrome, chronic diarrhea;
11. Current malignant tumors requiring anti-tumor treatment;
12. Complicated with acute diseases or acute exacerbation of chronic diseases at present;
13. Participation in other interventional clinical trials or oral intake of probiotic preparations within the past 3 months.

3. Withdrawal Criteria

1. Incomplete data affecting efficacy/safety assessment.
2. Concomitant medications interfering with study treatment.
3. Interventions/surgery affecting study outcomes during trial.

4. Termination Criteria

- Subject withdraws consent.
- Severe cardiovascular event during follow-up precluding continued participation.
- New severe illness, accident, or mental impairment precluding participation.
- Severe intervention-related adverse event precluding continued participation.

Study Methods and Technical Procedures

1. Study Drug Preparation

FMT capsules manufactured by Qingdao Haier Biomedical Co., Ltd.

(1) **Donor Stool Collection:** Stool from consented donors collected in sterile containers, stored at low temperature, processed within 1 hour.

(2) **Donor Screening:** Bristol Stool Scale type 3–4 only; weight recorded and donor information documented.

(3) **Processing:** 1:5 dilution with normal saline; homogenization, deodorization, filtration via automated processor.

(4) **Capsule Manufacture:** Filtrate centrifuged, pellet mixed 1:1 with lyoprotectant, freeze-dried, milled, and encapsulated under biosafety cabinet.

(5) **Placebo:** Identical capsules containing starch.

2. Treatment Protocol

Elderly HFpEF patients in Xi'an area screened January 2026–December 2028.

Randomized 1:1 to experimental or control group.

•**Experimental group:** Standard anti-heart failure therapy + allogeneic FMT. Bowel preparation with polyethylene glycol or lactulose before FMT. Oral capsules: 4 capsules within 1 hour after breakfast and lunch, daily for 6 days.

•**Control group:** Standard anti-heart failure therapy + placebo. Bowel preparation identical to FMT group; placebo capsules administered identically for 6 days.

Assessments: baseline, Week 4, Week 20. Primary endpoint: Week 20.

3. Concomitant Medications

Standard anti-heart failure therapy maintained during follow-up. Antibiotics discouraged; if required, documented in CRF. All acute-event medications recorded.

Outcomes and Assessment Time Points

Comprehensive assessments at **baseline, Week 4, Week 20:**

1. **Primary outcome:** Kansas City Cardiomyopathy Questionnaire (KCCQ).

2. **Secondary outcomes:** NYHA class, 6-minute walk distance, serum NT-proBNP/BNP.

3. **Other outcomes:** Minnesota Living with Heart Failure Questionnaire; echocardiography (LAVI, LVMI, PASP, E/e'); complete blood count, biochemistry; inflammation (NLRP3, IL-1 β , TNF- α , IL-6, MCP-1, ICAM-1, VCAM-1); gut

microbiome sequencing; microbial metabolites (SCFAs, TMAO, bile acids, indole-3-propionate, indoxyl sulfate); gut barrier function (DAO, D-lactate, endotoxin); endothelial function (NO); body composition; frailty; sarcopenia (SARC-F); nutrition; activities of daily living (BADL).

Efficacy Criteria

Composite endpoint: Response defined as **any one** of the following with statistically significant between-group difference:

1.Primary: ≥ 5 -point increase in KCCQ from baseline.

2.Secondary: ≥ 1 -grade reduction in NYHA class; **or** $\geq 20\%$ decrease in NT-proBNP/BNP; **or** $\geq 5\%$ increase in 6-minute walk distance.

Non-response: Failure to meet any criterion.

Adverse Event Monitoring

1. Definitions

•**Adverse Event (AE):** Any untoward medical event after intervention, not necessarily causal.

•**Serious Adverse Event (SAE):** Death, life-threatening event, permanent/severe disability, hospitalization or prolonged hospitalization.

2. Expected SAEs

Death, severe infection, acute heart failure exacerbation, cardiovascular event requiring hospitalization.

3. Management

Subjects/families instructed to report AEs and seek prompt medical care. All events documented in CRF and causality assessed. SAEs reported to Ethics Committee within **24 hours**; detailed written report submitted after verification.

Quality Control and Assurance

- Pre-trial training for all staff; strict protocol adherence.
- Regular follow-up (phone/WeChat) to minimize loss to follow-up.
- Timely, accurate, legible data recording with signature and date.
- Frequent data accuracy/completeness checks.
- Double data entry for electronic records.

Statistical Analysis

- Sample size: PASS 15.
- Data entry: Excel 2019.
- Analysis: SPSS 23.

Analysis Sets

•**Per- Protocol Set (PPS):** Subjects without major protocol violations and good adherence.

•**Safety Set (SS):** All randomized subjects receiving ≥ 1 intervention dose.

Statistical Methods

- Changes from baseline compared between groups.
- Normally distributed continuous data: t- test.
- Non- normally distributed continuous data: non- parametric tests.
- Categorical data: chi- square test.
- Efficacy analysis: PPS; safety analysis: SS.

Ethics

Conducted in accordance with the Declaration of Helsinki. Protocol approved by the Ethics Committee prior to initiation. Informed consent obtained before enrollment, including purpose, procedures, risks/benefits, and right to withdraw. Confidentiality of personal data maintained.

Timeline

- 2026.01.01–2026.03.30:** Randomization scheme development, pilot trial.
- 2026.04.01–2028.03.31:** Trial implementation, clinical data collection.
- 2028.04.01–2028.06.30:** Data analysis.
- 2028.07.01–2028.12.31:** Final report, manuscript submission, academic dissemination, clinical translation.

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