Gut microbiota in heart failure and related interventions

An-Tian Chen，Jian Zhang*，Yuhui Zhang*
State Key Laboratory of Cardiovascular Disease, Fuwai Hospital,
Chinese Academy of Medical Sciences & Peking Union Medical College/National Center for Cardiovascular Diseases

Chen, An-Tian, Jian Zhang, and Yuhui Zhang. 2023. “Gut Microbiota in Heart Failure and Related Interventions.” ***iMeta*** e125. https://doi.org/10.1002/imt2.125

Highlights

- **Heart failure (HF)** is associated with the **gut microbiota**, while the **gut hypothesis** of HF is less discussed in a thorough manner.
- We reviewed how changes in **metabolites** of the gut microbiota contribute to HF and possible underlying mechanisms.
- We also reviewed potential **interventions** for HF targeting the gut microbiota, including dietary interventions, probiotic therapy, fecal microbiota transplantation, antibiotics, and other approaches.

Introduction—Prevelence and definition of HF

- Worldwide, there are approximately **64.3 million** HF patients, with HF patients accounting for 1% ~ 2% of adults in developed countries.

- The 2022 AHA/ACC/HFSA guideline indicates that “HF is a complex clinical syndrome with symptoms and signs that result from any **structural or functional impairment of ventricular filling or ejection of blood**”, and **asymptomatic stages with either cardiomyopathies or structural heart disease** are considered at-risk for HF or pre-HF.

Introduction—The gut hypothesis

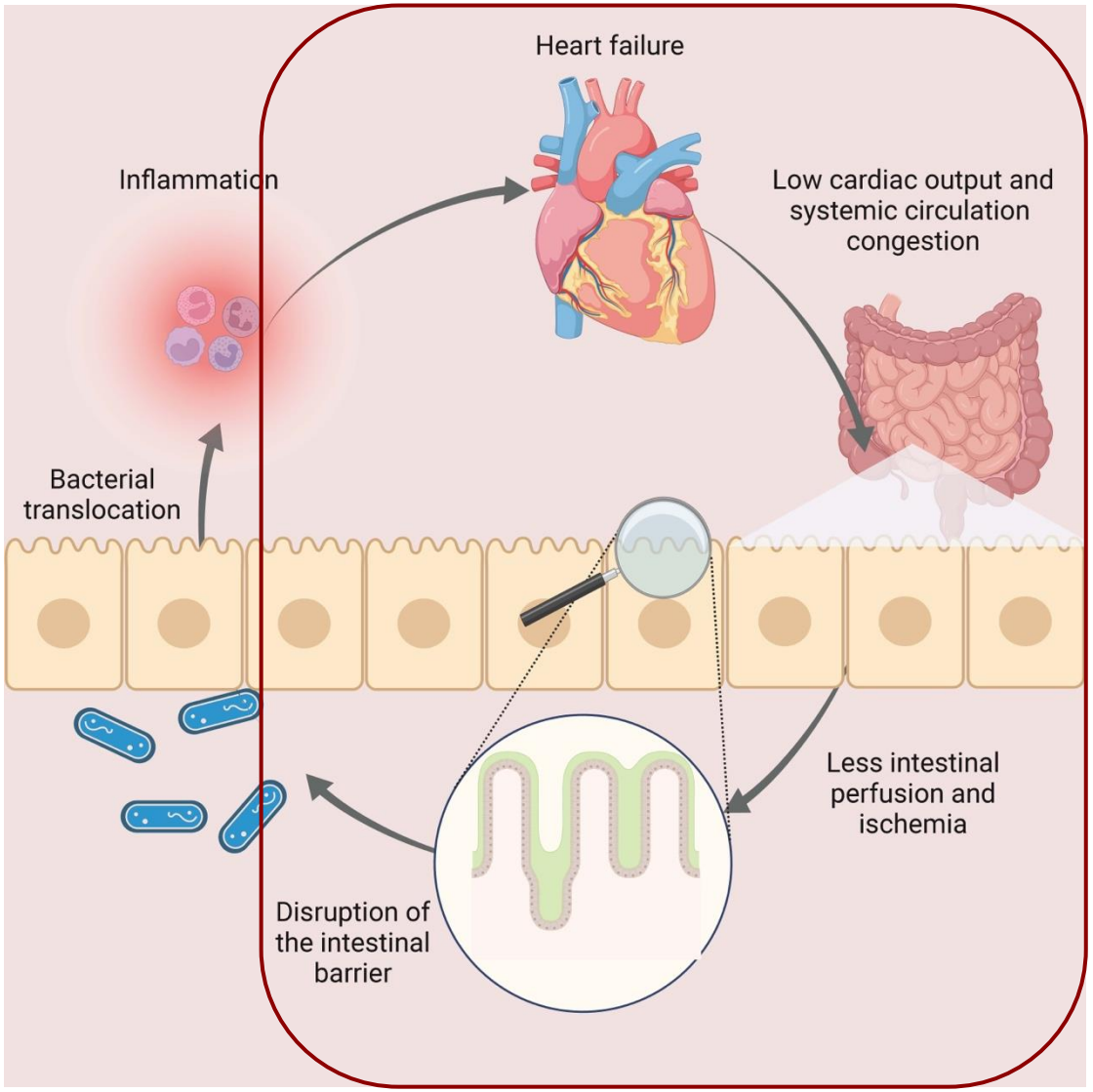
- no later than 1997
- imply the role of CHF in leading to **increased bowel permeability** and consequently **bacterial translocation** and **release of endotoxin**

- Metabolites, mainly **trimethylamine N-oxide (TMAO)** and **short-chain fatty acids (SCFAs)**, play an important role in the interaction with HF.
- Other metabolites like **N, N, N-trimethyl-5-aminovaleric acid (TMAVA), phenylacetylgutamine (PAGln)** are also involved in HF.

- In this review, we aim to briefly introduce **“the gut hypothesis of heart failure”, role of gut microbiota metabolites in HF**, and **related interventions**.

Gut hypothesis of HF and impairment of intestinal barrier

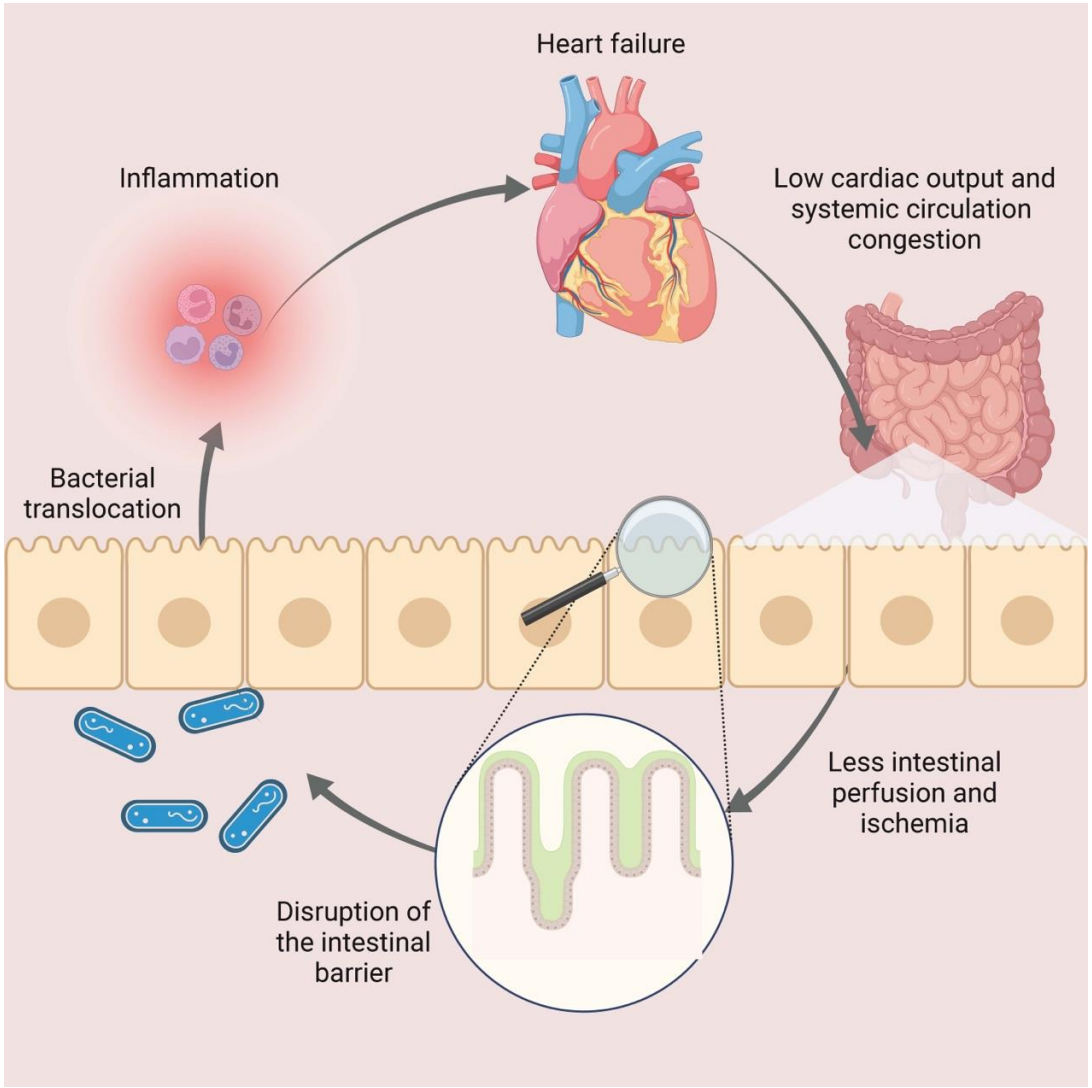
- **Low cardiac output** and **circulation congestion in the system** lead to **reduced intestinal perfusion**, resulting in **ischemia and damage to the intestinal barrier**.
- Ischemia of the intestines would generate a series of **pathological changes**



Gut hypothesis of HF and impairment of intestinal barrier

- 1997: hypothesized that **mesenteric venous congestion** in CHF leads to an **increase in bowel permeability**, thus contributing to **bacterial translocation** and **release of endotoxin** deteriorating inflammation.
- **Proved** in 1999.
- **Metabolites** of the gut microbiota also have an impact on HF.

Refined hypothesis: Congestion in HF would cause **increased bowel permeability**, followed by **bacterial translocation** and **inflammation**, and alterations in the gut microbiota can exacerbate HF through metabolites, mainly TMAO, SFCAs, and resulting in a **vicious cycle**.



Changes in gut microbiota composition

- Multiple studies have revealed that the gut microbiota **composition is different** between HF patients and healthy controls.
- Cbacteria, such as *Bacteroides/Prevotellain*, *Eubacterium rectale*, and *Fusobacterium prausnitzii*, are found to be more frequent in HF patients, while others, such as *Coriobacteriaceae*, *Erysipelotrichaceae*, and *Ruminococcaceae*, are decreased
- The **diversity** of the gut microbiota is **reduced** in HF patients.

	Increase	Decrease
Phylum	—	*Firmicutes*
Family	*Enterococcaceae*	*Lachnospiraceae, Rumminococcaceae*
Genus	*Bacteroides/Prevotellain, Campylobacter, Shigella, Salmonella, Prevotella, Hungatella, Succinclasticum Enterococcus, Synergistete, Lactobacillus*	*Blautia, Collinsella*, uncl. *Erysipelotrichaceae*, uncl. *Ruminococcaceae, Faecalibacterium, Ruminococcaceae UCG-004, Ruminococcaceae UCG-002, Lachnospiraceae FCS020* group, *Butyricicoccus, Sutterella, Lachnospira, Ruminiclostridium*
Species	*Eubacterium rectale*[a], *Fusobacterium prausnitzii, Yersinia enterocolitic*	*Eubacterium rectale*[a], *Dorealongicatena*
Fungi	*Candida, Candida* species	—

Abbreviation: uncl., unclassified.

[a]*Eubacterium rectale* is found to increase in HF patients by Sandek et al., while it is also reported to decrease by Kamo et al.

Changes in gut microbiota composition-Increase

- *Bacteroides/Prevotellain*, *Eubacterium rectale*, *Fusobacterium prausnitzii*, *Campylobacter*, *Candida*, *Salmonella*, *Shigella*, *Yersinia enterocolitica*, and *Candida* species are **more frequently** found in CHF patients.
- *Candida*, *Campylobacter*, *Shigella*, and *Salmonella* were found to be higher in **NYHA III to IV** than in **NYHA I to II** CHF patients, while *Yersinia enterocolitica* was similar between the two groups.

Source	Time	Sample size[a]	Microbiota	Results	Other
Sandek et al. [28]	2007	22 CHF and 22 controls	*Bacteroides/Prevotellain*, *Eubacterium rectale*, and *Fusobacterium prausnitzii*	Increase	Bacteria were adherent to the mucosa more often
Sandek et al. [34]	2014	21 CHF and 17 control	Both anaerobic and aerobic bacteria	Similar	Bacteria were restricted to the juxtamucosal zone more often
Pasini et al. [35]	2016	60 CHF (NYHA I–II 30, III–IV 30) and 20 controls	Pathogenic bacteria and *Candida* such as *Campylobacter*, *Salmonella*, *Shigella*, *Yersinia enterocolitica*, and *Candida* species	Increase	Abundancy was different between two NYHA groups
Luedde et al. [36]	2017	20 HFrEF and 20 controls	*Blautia*, *Collinsella*, uncl. *Erysipelotrichaceae* and uncl. *Ruminococcaceae*.	Decrease	Diversity decreased
Kamo et al. [37]	2017	12 HF and 12 controls (age-matched)	*Eubacterium rectale* and *Dorea longicatena*	Decrease	Older HF patients have less *Bacteroidetes* and more *Proteobacteria*
Kummen et al. [38]	2018	84 stable HFrEF (40 discovery, and 44 validation (NYHA II–IV) and 266 controls	*Genus Prevotella, Hungatella* and *Succinclasticum* *Lachnospiraceae* family,[b] *Rumminococcaceae Faecalibacterium* and *Bifidobactericeae Bifidobacterium*	Increase Decrease	Bacterial richness decreases in HF patients after adjustment
Sun et al. [39]	2021	29 Severe CHF (NYHA III–IV) and 30 controls	*Enterococcus* and *Enterococcaceae* Phylum *Firmicutes*, genera *Ruminococcaceae UCG-002*, *Ruminococcaceae UCG-004*, *Lachnospiraceae FCS020* group	Increase Decrease	Lower bacterial richness in chronic HF patients. Remarkable decrease in bacteria generating SCFAs. Increased production of lactic acid.
Huang et al. [40]	2021	30 HFpEF and 30 controls	Phylum *Synergistetes*, genus *Enterococcus* and *Lactobacillus* Genus *Butyricicoccus*, *Sutterella*, *Lachnospira*, and *Ruminiclostridium*	Increase Decrease	Increase of microbiota linked with inflammation and decrease of microbiota linked with anti-inflammatory effects

Abbreviations: CHF, chronic heart failure; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association.

[a]Only includes samples used to identify microbiota changes.

[b]Includes *Anaerostipes*, *Blautia*, *Coprococcus (3)*, *Fusicatenibacter*, *Lachnospiraceae FCS020*, *NCS2004*, *ND3007*, and *Pseudobutyrivibrio*.

Changes in gut microbiota composition-Decrease

- The abundance of *Coriobacteriaceae*, *Erysipelotrichaceae*, and *Ruminococcaceae families* , *Blautia*, *Collinsella*, *unclassified Erysipelotrichaceae*, *unclassified Ruminococcaceae Eubacterium rectale* is **lower** in HF patients.
- The abundance of *Bacteroidetes* is higher, while *Proteobacteria* is lower in **young** compared with **older** HF patients.
- **Bacteria that generate SCFAs** are also decreased in the HF group.

Source	Time	Sample size[a]	Microbiota	Results	Other
Sandek et al. [28]	2007	22 CHF and 22 controls	*Bacteroides/Prevotellain*, *Eubacterium rectale*, and *Fusobacterium prausnitzii*	Increase	Bacteria were adherent to the mucosa more often
Sandek et al. [34]	2014	21 CHF and 17 control	Both anaerobic and aerobic bacteria	Similar	Bacteria were restricted to the juxtamucosal zone more often
Pasini et al. [35]	2016	60 CHF (NYHA I–II 30, III–IV 30) and 20 controls	Pathogenic bacteria and *Candida* such as *Campylobacter*, *Salmonella*, *Shigella*, *Yersinia enterocolitica*, and *Candida* species	Increase	Abundancy was different between two NYHA groups
Luedde et al. [36]	2017	20 HFrEF and 20 controls	*Blautia*, *Collinsella*, uncl. *Erysipelotrichaceae* and uncl. *Ruminococcaceae*.	Decrease	Diversity decreased
Kamo et al. [37]	2017	12 HF and 12 controls (age-matched)	*Eubacterium rectale* and *Dorea longicatena*	Decrease	Older HF patients have less *Bacteroidetes* and more *Proteobacteria*
Kummen et al. [38]	2018	84 stable HFrEF (40 discovery, and 44 validation (NYHA II–IV) and 266 controls	*Genus Prevotella, Hungatella* and *Succinclasticum* *Lachnospiraceae* family,[b] *Rumminococcaceae Faecalibacterium* and *Bifidobactericeae Bifidobacterium*	Increase Decrease	Bacterial richness decreases in HF patients after adjustment
Sun et al. [39]	2021	29 Severe CHF (NYHA III–IV) and 30 controls	*Enterococcus* and *Enterococcaceae* Phylum *Firmicutes*, genera *Ruminococcaceae UCG-002*, *Ruminococcaceae UCG-004*, *Lachnospiraceae FCS020* group	Increase Decrease	Lower bacterial richness in chronic HF patients. Remarkable decrease in bacteria generating SCFAs. Increased production of lactic acid.
Huang et al. [40]	2021	30 HFpEF and 30 controls	Phylum *Synergistetes*, genus *Enterococcus* and *Lactobacillus* Genus *Butyricicoccus*, *Sutterella*, *Lachnospira*, and *Ruminiclostridium*	Increase Decrease	Increase of microbiota linked with inflammation and decrease of microbiota linked with anti-inflammatory effects

Abbreviations: CHF, chronic heart failure; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association.

[a]Only includes samples used to identify microbiota changes.

[b]Includes *Anaerostipes*, *Blautia*, *Coprococcus (3)*, *Fusicatenibacter*, *Lachnospiraceae FCS020*, *NCS2004*, *ND3007*, and *Pseudobutyrivibrio*.

Changes in metabolites contributing to HF-TMAO

TMAO can contribute to HF development through various and complex interactions.

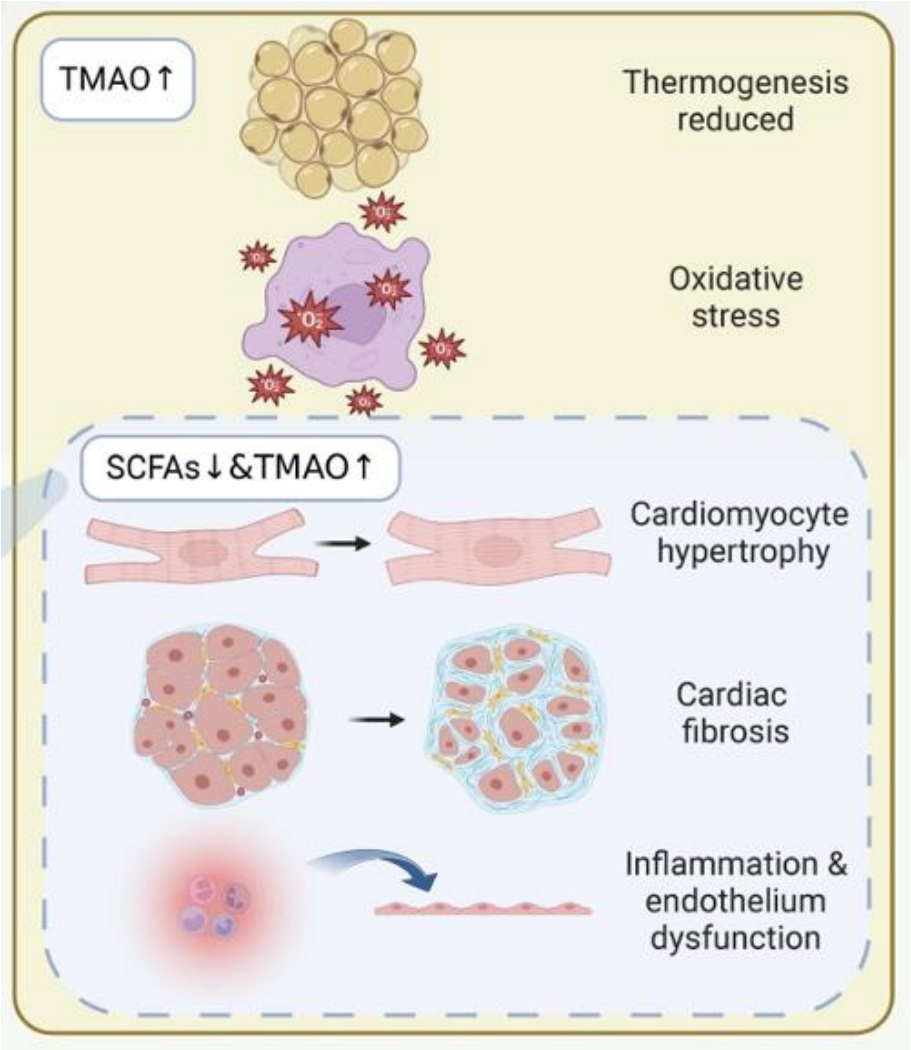
Source	Year	Species	Level	Pathway	Effect
Organ et al. [51]	2016	C57BL6/J mice	Organ/system	—	Leads to pulmonary edema, enlargement of heart, increased BNP, decreased left ventricular ejection fraction and myocardial fibrosis
Seldin et al. [52]	2016	Human endothelial cells, LDLR (−/−) mice	Molecule and gene	NF-κB pathway	Elevated inflammatory gene expression in mice, promotes recruitment of activated leukocytes to endothelial cells
Sun et al. [53]	2016	Human umbilical vein endothelial cells	Molecule	—	Induces inflammation and endothelial dysfunction through ROS-TXNIP-NLRP3 inflammasome activation
Chen et al. [54]	2017	Human umbilical vein endothelial cells, aortas from ApoE −/− mice	Molecule	SIRT3–SOD2–mitochondrial ROS signaling pathway (inhibition)	Boosts vascular inflammation through NLRP3 inflammasome activation
Makrecka-Kuka et al. [55]	2017	ICR mice	Organ/system	—	Impairs β-oxidation in cardiac mitochondria, promotes cardiac energy metabolism disturbances, and decreases pyruvate metabolism by impairing substrate flux
Li et al. [56]	2019	Sprague-Dawley rats	Molecule	Smad3 pathway	Promotes myocardial hypertrophy and fibrosis
Brunt et al. [57]	2020	Human and mice	Organ/system	—	Promotes age-related vascular oxidative stress and endothelial dysfunction
Yoshida et al. [58]	2022	Mice	Molecule	—	Induces decrease of phosphocreatine and ATP levels in heart tissue by suppressing mitochondrial complex IV activity

Abbreviations: ATP, adenosine triphosphate; BNP, brain natriuretic peptide; LVEF, left ventricular ejection fraction.

Changes in metabolites contributing to HF-TMAO

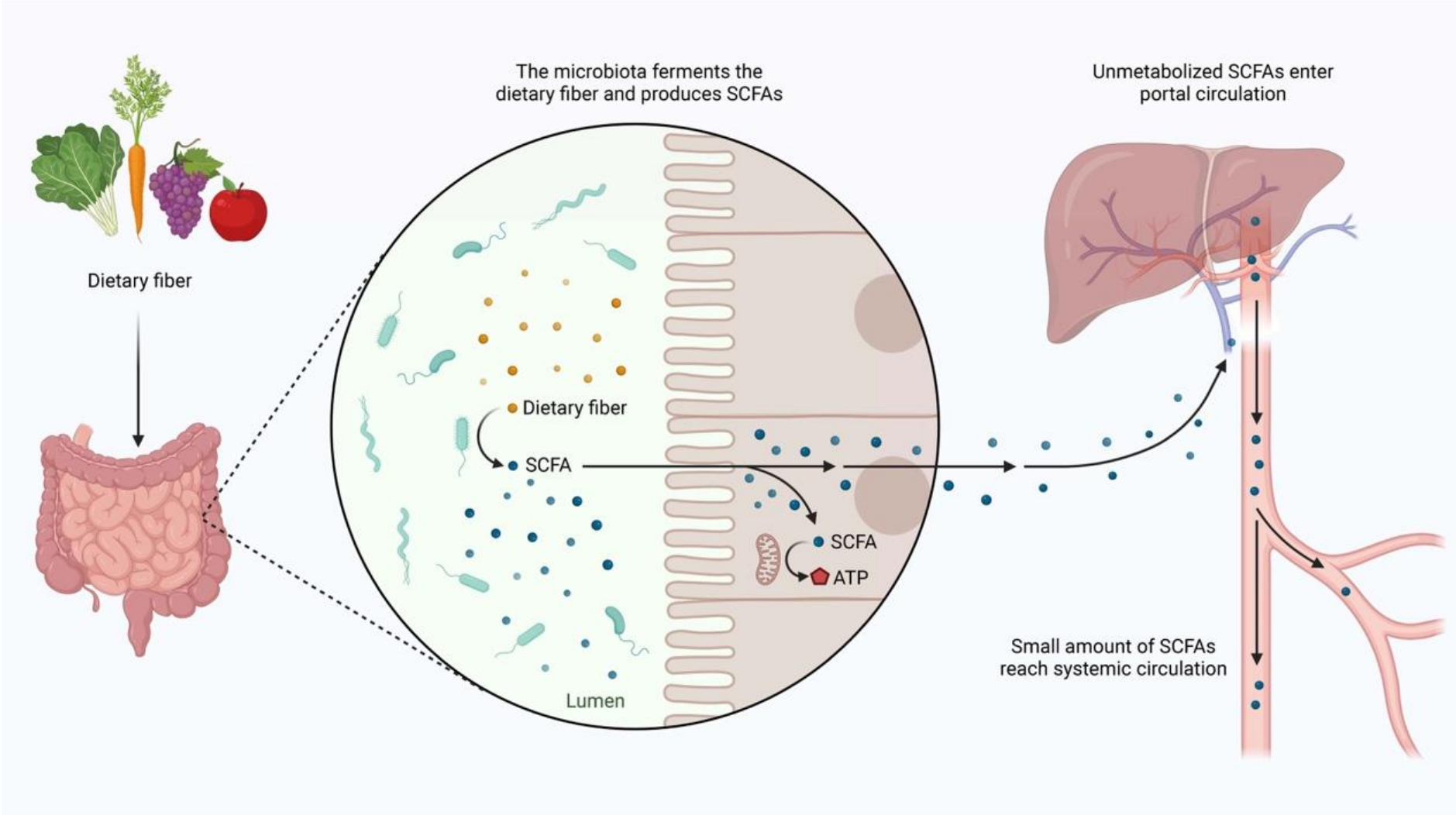
TMAO could

- promote **cardiac fibrosis and hypertrophy**, leading to myocardial damage
- trigger an **inflammatory response** and **endothelial dysfunction**
- alter the **oxidation** process, leading to disturbances in energy metabolism
- affect **thermogenesis**, which in turn may promote HF.



Changes in metabolites contributing to HF-SCFA

SCFAs are mainly produced from **dietary fiber** by the gut microbiota. Unmetabolized SCFAs would enter **portal circulation**, with a small number of SCFAs reaching the **systemic circulation**

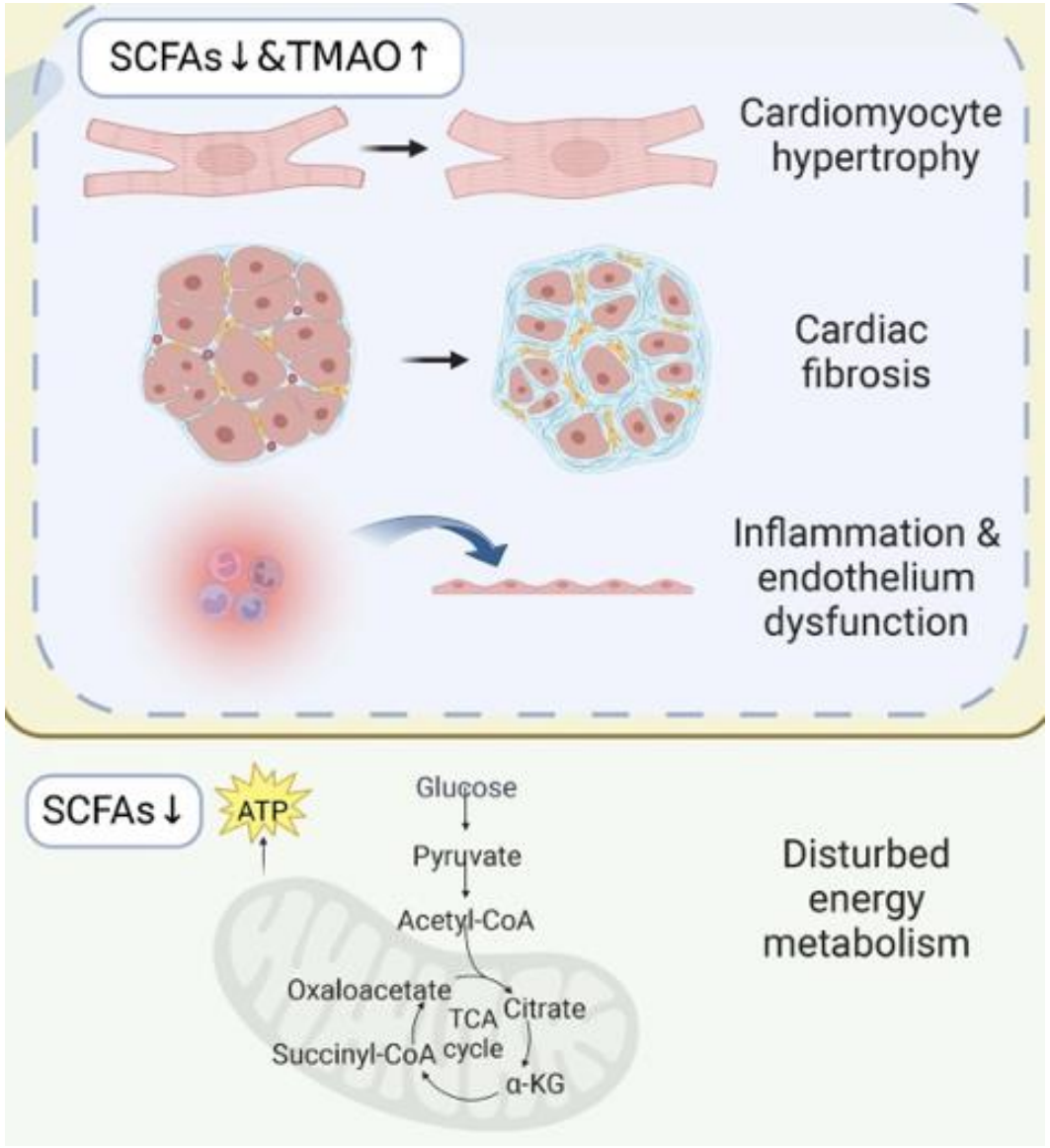


Changes in metabolites contributing to HF-SCFA

Studies have shown a **decrease in SCFAs-producing bacteria** in CHF patients

SCFAs could

- mitigate cardiac **fibrosis, hypertrophy, and vascular dysfunction**
- relieve inflammation: **down-regulate pro**-inflammatory cytokines and **up-regulate anti**-inflammatory cytokines
- **improve vascular endothelial function**
- **support the failing heart** by bypassing palmitoyltransferase 1 (CPT1) and be used as an energy



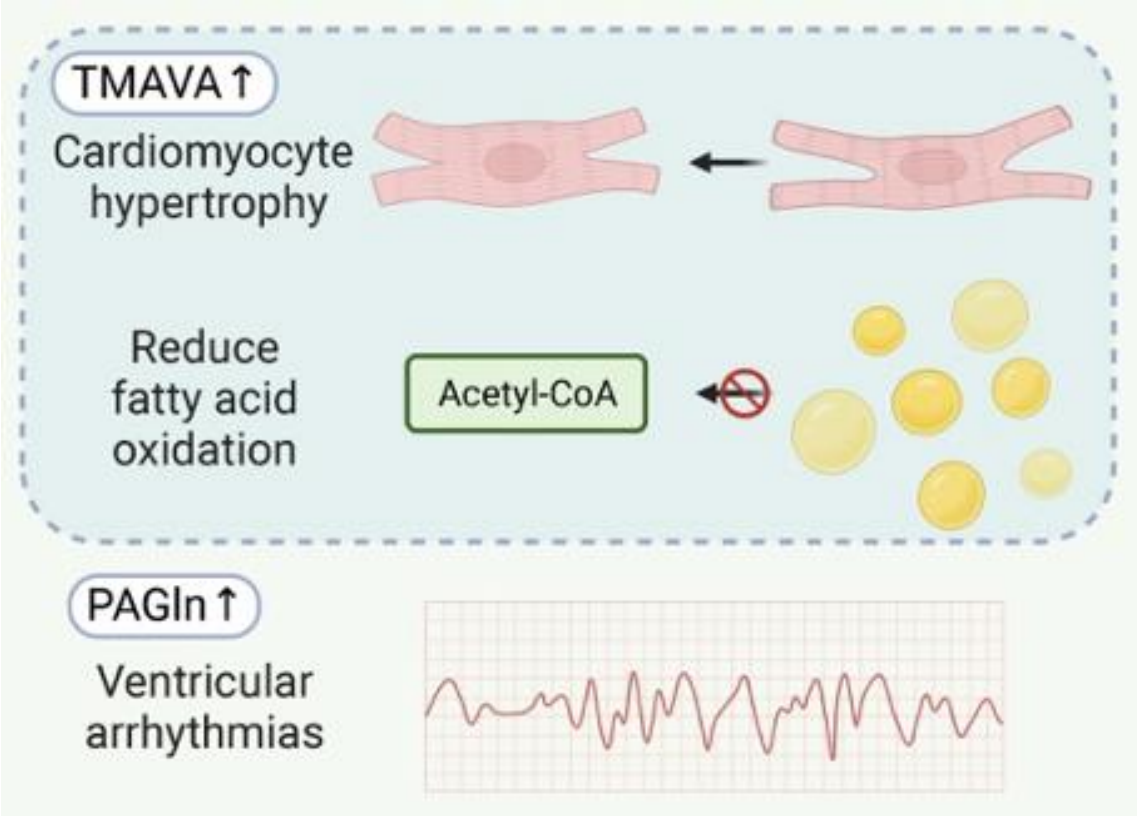
Changes in metabolites contributing to HF-Other agents

TMAVA

- Elevated and associated with an **increased risk of cardiac mortality and transplantation**
- reduce fatty acid oxidation and promote **cardiac hypertrophy** in mouse models

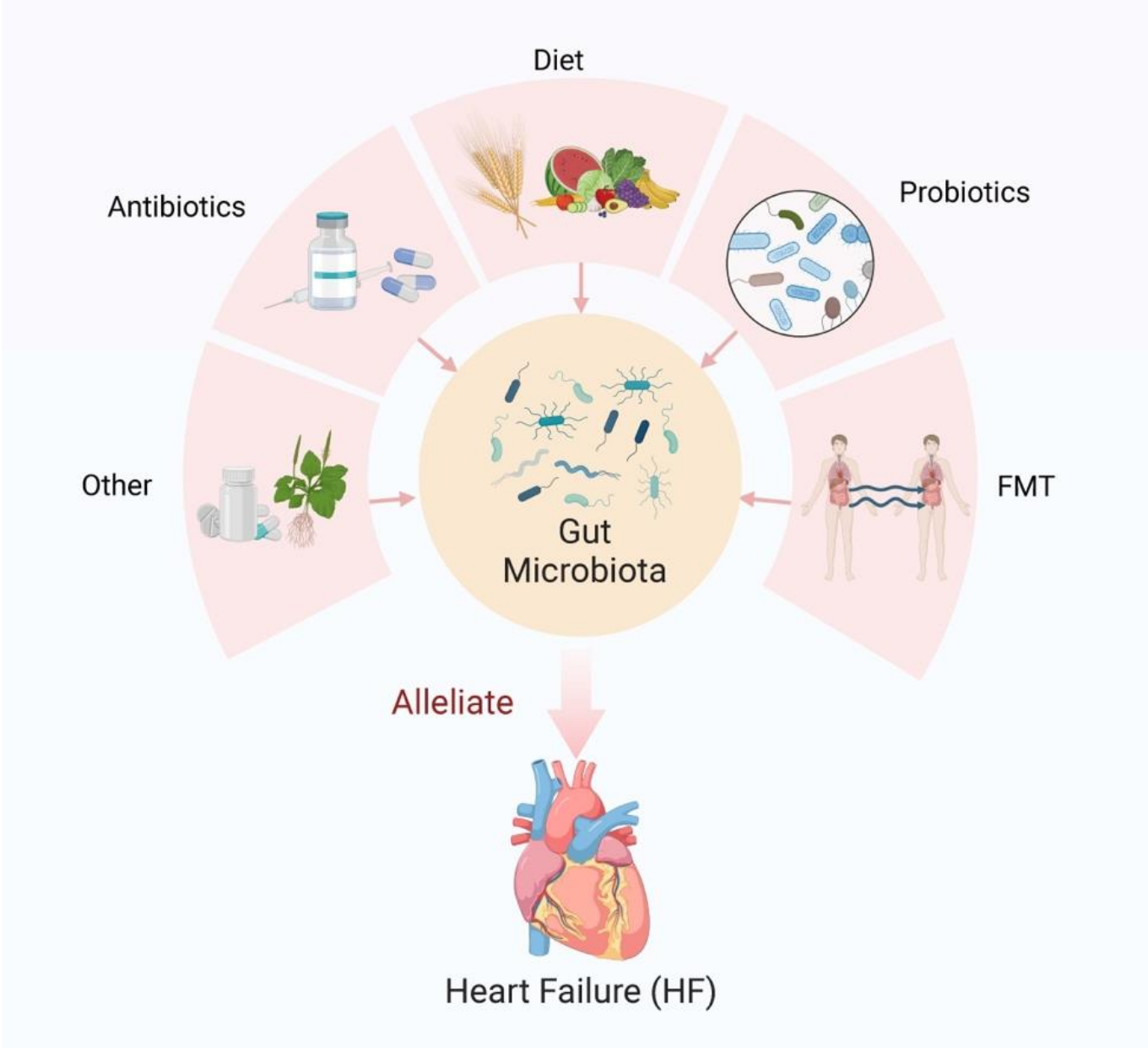
PAGln

- **risk factor** and **prognostic indicator** of HF
- related to the presence and severity of HF
- In an HF mouse model, PAGln increased the chance of **ventricular arrhythmias** by TLR4/AKT/mTOR signaling pathway activation



Gut microbiota and HF interventions/treatments

- Dietary interventions
- Probiotic therapy
- Fecal microbiota transplantation （FMT）
- Antibiotics
- Other interventions



Gut microbiota and HF interventions/treatments-Dietary

Dietary Approaches to Stop Hypertension （DASH）diet

- In **HF** patients, the DASH diet can **improve** 6-minute walking test performance, compliance of artery, exercise capacity, and quality of life scores evaluated after an intervention for 3 months

Mediterranean diet

- linked with lower all-cause mortality in CVD patients, **did not find a significant decrease in HF incidence**

Gut microbiota and HF interventions/treatments-Probiotic

Lactobacillus rhamnosus GR-1

- Attenuate hypertrophy and improve systolic and diastolic function of the left ventricle, preserve LVEF and fractional shortening

Saccharomyces boulardii

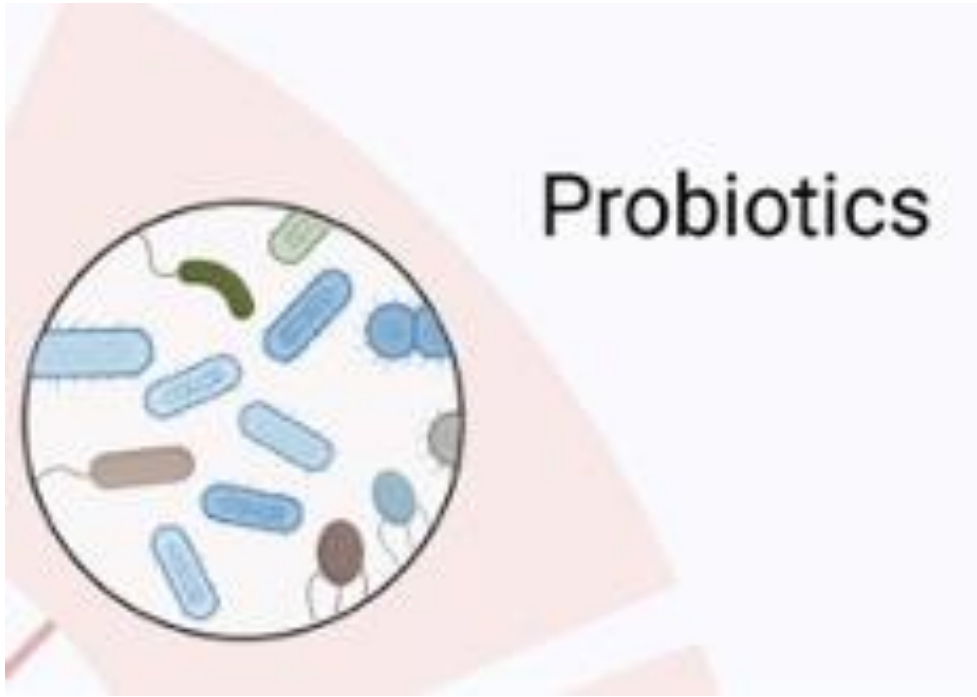
- improve LVEF, shorten left atrial diameter, and lower total cholesterol and uric acid levels

Probiotic yogurt

- Relieve the inflammatory status in CHF patients

GutHeart trail

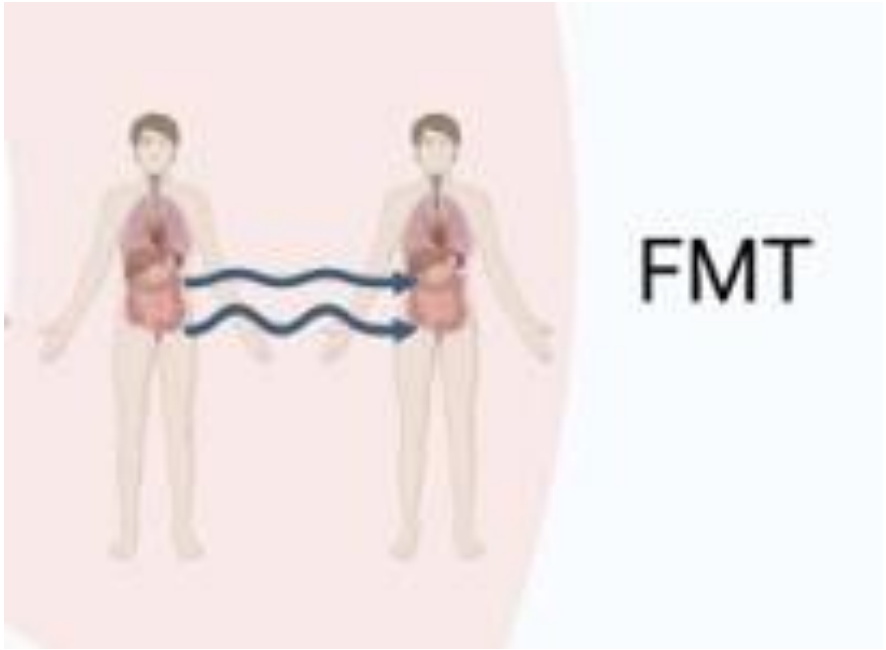
- treatment with *Saccharomyces boulardii* or rifaximin for three month, on top of standard of care, had **no significant effect** on LVEF, diversity of microbiota, or the measured biomarkers in HFrEF patients



Gut microbiota and HF interventions/treatments-FMT

FMT/stool transplantation

- The procedure of transplanting stool from a healthy donor into another patient’ s intestine
- Primarily used to treat recurrent ***Clostridium difficile*** **infection**
- The potential effects of FMT on HF are not well studied , may hold promise as a supplementary treatment for HF.



Gut microbiota and HF interventions/treatments-Antibiotics

microbial translocation

- after an ST-elevation myocardial infarction, microbial translocation can induce inflammation and cardiovascular events, which can be alleviated by antibiotics
- **Rifaximin** is widely used to treat microbiota toxicity and translocation
- The effects of antibiotics on gut microbiota in HF have not been extensively studied.
- Antibiotics are a **double-edged sword**, with potential benefits and risks that need to be carefully weighed.

Gut microbiota and HF interventions/treatments-Other

- **Vitamin D**: High TMAO levels are linked with deficiency in vitamin D, indicating that vitamin D may help reduce TMAO levels in patients
- **B vitamins + vitamin D** can result in lowering of TMAO levels compared to vitamin D alone
- **Berberine**: decrease TMAO production in animal intestines and lower TMA and TMAO levels in both feces and plasma of patients through vitamin-like effects.
- **3,3-dimethyl-1-butanol (DMB)**: raise cardiac function and alleviate cardiac remodeling in HF mice induced by pressure overload by down-regulating plasma TMAO levels.
- **Traditional Chinese medicine**: regulates metabolism and is metabolized by gut microbiota.

Summary

- **The gut hypothesis of HF** highlights the potential of targeting gut microbiota for the interventions or treatments of HF.
- The **composition and diversity of gut microbiota** are altered in HF.
- It produces **more TMAO and fewer SCFAs** compared to healthy individuals.
- **TMAO** promotes HF by **promoting cardiac hypertrophy, fibrosis, inflammation, and endothelial dysfunction**, while **SCFAs** have a protective role by **preventing pathophysiological changes and satisfying energy metabolism**.
- Other microbiota metabolites like **TMAVA** and **PAGln** may also play a role in HF.
- **Dietary interventions** and **probiotic therapy** have shown potential in **attenuating HF and improving cardiac function**. Further research and studies are needed to determine the effectiveness of FMT and antibiotics in HF treatment.
- The gut microbiota represents a **promising avenue** for the development of novel HF treatments.

Chen, An-Tian, Jian Zhang, and Yuhui Zhang. 2023. "Gut Microbiota in Heart Failure and Related Interventions." ***iMeta*** e125. https://doi.org/10.1002/imt2.125

iMeta: Integrated meta-omics to change the understanding of the biology and environment

WILEY

"***iMeta***" is an open-access Wiley partner journal launched by scientists of the Chinese Academy of Sciences. iMeta aims to promote metagenomics, microbiome, and bioinformatics research by publishing original research, methods, or protocols, and reviews. The goal is to publish high-quality papers (Top 10%, IF > 15) targeting a broad audience. Unique features include video submission, reproducible analysis, figure polishing, APC waiver, and promotion by social media with 500,000 followers. Three issues were released in March, June , and September 2022.

Society: http://www.imeta.science
Publisher: https://wileyonlinelibrary.com/journal/imeta
Submission: https://mc.manuscriptcentral.com/imeta

office@imeta.science
iMeta

iMetaScience
iMetaScience