It has been reported that trimethylamine N-oxide (TMAO), a gut microbiome-derived metabolite, promotes upregulation of multiple macrophage scavenger receptors linked to atherosclerosis, suggesting a relationship between gut-flora-dependent metabolism of dietary phosphatidylcholine and the pathogenesis of several cardiovascular diseases (CVDs). Heart failure (HF) is a systemic disease with a devastating prognosis that affects not only the cardiovascular system, but many other organ systems, such as kidney and liver. HF causes liver dysfunction with a combination of reduced arterial perfusion and passive congestion, and is associated with adverse prognosis. Alterations in gastrointestinal function also occur in HF patients as a result of low cardiac output or increased central venous pressure, leading to intestinal epithelial dysfunction, barrier defect, and increased juxtagomucosal gut flora and lipopolysaccharide (Figure). Altered gut flora may be associated with cardiac cachexia or frailty, and delayed prognosis of HF patients. Thus, alterations in gut flora and microbiome-derived metabolites and the prognostic effect may be more clearly associated with pathophysiology in HF patients than in other CVD patients. It has been reported that TMAO can serve as a prognostic biomarker in both chronic and acute HF, independent of traditional risk factors or levels of B-type natriuretic peptide. Differences in gut microbiome from HF patients, relative to healthy or control subjects with different comorbidities, medications, and diet, have been reported.

In this issue of the Journal, Hayashi et al report comprehensive profiles of gut flora and plasma levels of microbiome-related metabolites in HF patients, considering both decompensated and compensated phases, during

Figure. Altered gut flora and microbiome-related metabolites in patients with heart failure. TMAO, trimethylamine N-oxide.
hospitalization. They found that: (1) phylum Actinobacteria was enriched in HF patients compared with control subjects; (2) at the genus level, *Bifidobacterium* was abundant while *Megamonas* was depleted in HF patients; (3) the plasma concentrations of TMAO were increased in HF patients; (4) there were positive correlations between genus *Escherichia/Shigella* and levels of both TMAO and indoxyl sulfate; and (5) that *Escherichia/Shigella* became more abundant in decompensated than in compensated HF in a relatively short period. Their study findings suggest that gut microbiome composition and microbiome-related metabolites are altered in HF patients, and that there are possible correlations between specific bacterial genera and circulating levels of harmful metabolites such as TMAO and indoxyl sulfate. Although there are several study limitations, including changes in gut flora and gut microbiome-derived metabolites in a relatively small sample size over a short period during hospitalization, I believe that their findings add novel insights regarding the gut microbiome of HF patients. Studies of the prognostic effect of gut flora or gut microbiome-derived metabolites on HF patients, and their therapeutic utility in HF patients, are awaited with interest.

References