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Pathogenic Gut Flora Tied to Heart-Failure Severity

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BRESCIA, ITALY — Patients with chronic heart failure (CHF) are likely to have "intestinal overgrowth" of pathogenic gut flora and permeability that is associated with disease severity, new research suggests[1].

A study of 80 total participants showed that the CHF patients had "massive quantities" of pathogenic bacteria and candida vs a group of healthy controls. Specific types of the increased pathogens found in stool samples included *Campylobacter*, *Shigella*, *Salmonella*, *Yersinia enterocolitica*, and *Candida* species. Those with CHF also had significantly increased inflammation, intestinal permeability, and right atrial pressure (RAP), which is a signal of venous blood congestion.

In addition, most associations were stronger in those with moderate-severe HF (NYHA 3-4) vs those with mild HF (NYHA 1-2).

"Our study suggests gut microbiota need to be continually investigated as soon as CHF is diagnosed," note the investigators, led by Dr Evasio Pasini (Salvatore Maugeri Foundation, IRCCS, Medical Center of Lumezzane, Brescia, Italy). They add that using simple, noninvasive, reproducible methods to measure gut-flora development could provide "important clinical information to treat complicated multiorgan syndromes."

The study reaffirms earlier research "in a very nice, single packet," commented Dr Stanley L Hazen (Cleveland Clinic, OH) to **heart*wire*** from Medscape. "It's well-known that with heart failure, you have enhanced intra-abdominal pressure and vasculature that has poor edema and intra-abdominal lymph flow. As a consequence, you get bowel-wall edema, and there's a breakdown in the barrier of the gut," he said.

"This concept of a 'leaky gut' in heart failure has been out there for quite some time." But this study nicely shows, through several different measures, that impairment in intestinal bowel-wall function is associated with severity of HF, said Hazen, who was not involved with this research.

The findings were published online December 9, 2015 in *JACC: Heart Failure*.

Important to Reestablish Gut Microbiota

In the study, 60 "well-nourished and stable" patients with either mild (n=30) or moderate-severe CHF (n=30) were evaluated and then compared with a group of 20 healthy controls. All had a body mass index of less than 30 kg/m^2 and participated in a 12-hour overnight fast, after which blood variables were assessed.

"In all subjects, we measured the presence and development in the feces of bacteria and fungi (candida)," added the investigators. A cellobiose sugar test of urine was used to document intestinal permeability, and RAP was measured by ECG.

Exclusion criteria including renal failure or metabolic disorders and treatment during the previous 3 months with any antibiotics or probiotics.

Interestingly, 100% of the CHF group had increased permeability and 78.3% of them had altered gut flora.

The full CHF group had substantially greater amounts of campylobacter vs the healthy controls group (85.3 vs 1.0 colony-forming units/mL, respectively; P<0.001). They also had larger quantities of shigella (38.9 vs 1.6) and candida (21.3 vs 0.8; both comparisons, P<0.001), as well as of salmonella (31.3 vs 0) and *Yersinia E* (22.9 vs 0; both comparisons, P<0.0001).

In addition, the CHF group had increased RAP (12.6 mm Hg) and systemic inflammation, as measured with C-reactive protein (12.5 mg/dL), and greater intestinal permeability vs the healthy controls (10.2 vs 1.5 mg, P<0.001).

The subgroup of moderate-severe CHF patients had significantly greater development rates of candida, campylobacter, and shigella compared with the subgroup with mild CHF. They also had greater intestinal

permeability.

"Further studies are needed to confirm the link between gut pathogenic bacteria and CHF severity," write the investigators, "If confirmed, this link could suggest additional personalized therapeutic strategies . . . in support of traditional drugs," they write.

However, they note that there are currently "no clinical gut-flora modifiers available," and using probiotics could be potentially dangerous. "At present, reestablishing the gut microbiota may be the only option for patients to reverse intestinal dysbiosis," they write.

Consequence, Not Cause of HF?

The study's main take-home message, according to Hazen, is a reemphasis of the connection between cardiac function and bowel-wall edema, "and the breakdown of the barrier function of the intestines" in HF. In addition, "I think a lot of what was shown in the paper was a consequence of the heart failure and not a cause of the heart failure."

Hazen and other colleagues from Cleveland Clinic have written before about these issues and continue to study the associations. A new preclinical study published in *Cell* earlier today, for which Hazen was the principal investigator, showed that targeting and inhibiting gut microbes may prevent the development of atherosclerosis[2]

For the current study, Hazen said the findings give "another fingerprint showing that there's an abnormal environment going on in the gut of subjects with heart failure and is dose-dependent, depending on the severity of the heart failure."

Preclinical Findings: Natural Gut-Microbe Inhibitor May Prevent Atherosclerosis Development

Findings from a new preclinical study suggest that the gut-microbe–dependent metabolite trimethylamine (TMA), the first step in the production of trimethylamine N-oxide (TMAO), which has been linked to atherosclerosis in animal studies and with CV risks in clinical studies, can be targeted and even inhibited[2].

The choline analog 3.3-dimethyl-1-butanol (DMB), which is found naturally in grape seed and some extra virgin olive oils, nonlethally inhibited TMA formation and reduced the development of atherosclerotic lesions in mice who were fed a high-choline diet.

The findings "may serve as a potentially therapeutic approach for the treatment of cardiometabolic diseases," write the investigators, led by Dr Zeneng Wang (Cleveland Clinic).

Hazen added to **heart*wire*** that if these preliminary findings can be replicated in further studies, it could potentially lead to a treatment that targets this very specific microbial pathway, while letting patients avoid the overuse of antibiotics.

"Our study showed that diet-induced accelerated atherosclerosis can be blocked by giving this drug in animal models. And we went with this drug because it's a natural product that might be linked to the Mediterranean diet," said Hazen.

"It's like 'drugging' the microbe without killing it as a means of having a beneficial effect in the host."

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Pasini and the study authors report no relevant financial relationships. Wang and Hazen report being named as a coinventors on patents held by the Cleveland Clinic. Hazen reports being paid as a consultant for Esperion and Procter & Gamble; receiving research funds or support from AstraZeneca, Pfizer, Procter & Gamble, Roche, and Takeda; and "having the right to receive royalty payments for inventions or discoveries related to cardiovascular diagnostics and/or therapeutics" from the Cleveland Heart Laboratory, Siemens, Esperion, and Frantz Biomarkers. Disclosures for the coauthors are listed in the article.

References

1. Pasini E, Aquilani R, Testa C, et al. Pathogenic gut flora in patients with chronic heart failure. *JACC: Heart Fail.* 2015; DOI:10.1016/j.jchf.2015.10.009. Article

2. Wang Z, Roberts AB, Buffa JA, et al. Non-lethal inhibition of gut microbial trimethylamine production for the treatment of atherosclerosis. *Cell* 2015; DOI:10.1016/j.cell.2015.11.055. Article

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