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Pathogenic Gut Flora in Patients With Chronic Heart Failure

Evasio Pasini, MD,[a] Roberto Aquilani, MD,[b] Cristian Testa, MD,[c] Paola Baiardi, PhD,[d] Stefania Angioletti, MD,[c] Federica Boschi, PhD,[e] Manuela Verri, PhD,[b] Francesco Dioguardi, MD[f]

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CME Objective for This Article: After reading this article, the reader should be able to discuss: 1) the finding of abnormal gut flora in patients with heart failure; 2) the increased intestinal permeability seen in patients with heart failure; and 3) the clinical implications of these findings.

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From the [a]Fondazione "Salvatore Maugeri," IRCCS, Medical Centre of Lumezzane, Brescia, Italy; [b]Department of Biology and Biotechnology "L. Spallanzani," University of Pavia, Pavia, Italy; [c]Laboratory of Clinical Microbiology and Virology Functional Point, Bergamo, Italy; [d]Direzione Scientifica Centrale, Fondazione Salvatore Maugeri, IRCCS, Pavia, Italy; [e]Department of Drug Science, University of Pavia, Pavia, Italy; and the [f]Department of Clinical Science and Community Health, University of Milano, Milan, Italy. The authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Pasini and Aquilani contributed equally to this work.

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Pathogenic Gut Flora in Patients With Chronic Heart Failure

ABSTRACT

OBJECTIVES The goal of this study was to measure the presence of pathogenic gut flora and intestinal permeability (IP) and their correlations with disease severity, venous blood congestion, and inflammation in patients with chronic heart failure (CHF).

BACKGROUND Evidence suggests that translocation of gut flora and/or their toxins from the intestine to the bloodstream is a possible trigger of systemic CHF inflammation. However, the relation between pathogenic gut flora and CHF severity, as well as IP, venous blood congestion as right atrial pressure (RAP), and/or systemic inflammation (C-reactive protein [CRP]), is still unknown.

METHODS This study analyzed 60 well-nourished patients in stable condition with mild CHF (New York Heart Association [NYHA] functional class I to II; n = 30) and moderate to severe CHF (NYHA functional class III to IV; n = 30) and matched healthy control subjects (n = 20). In all subjects, the presence and development in the feces of bacteria and fungi (*Candida* species) were measured; IP according to cellobiose sugar test results was documented. The study data were then correlated with RAP (echocardiography) and systemic inflammation.

RESULTS Compared with normal control subjects, the entire CHF population had massive quantities of pathogenic bacteria and *Candida* such as *Campylobacter* (85.3 ± 3.7 CFU/ml vs. 1.0 ± 0.3 CFU/ml; $p < 0.001$), *Shigella* (38.9 ± 12.3 CFU/ml vs. 1.6 ± 0.2 CFU/ml; $p < 0.001$), *Salmonella* (31.3 ± 9.1 CFU/ml vs 0 CFU/ml; $p < 0.001$), *Yersinia enterocolitica* (22.9 ± 6.3 CFU/ml vs. 0 CFU/ml; $p < 0.0001$), and *Candida* species (21.3 ± 1.6 CFU/ml vs. 0.8 ± 0.4 CFU/ml; $p < 0.001$); altered IP (10.2 ± 1.2 mg vs. 1.5 ± 0.8 mg; $p < 0.001$); and increased RAP (12.6 ± 0.6 mm Hg) and inflammation (12.5 ± 0.6 mg/dl). These variables were more pronounced in patients with moderate to severe NYHA functional classes than in patients with the mild NYHA functional class. Notably, IP, RAP, and CRP were mutually interrelated (IP vs. RAP, $r = 0.55$; $p < 0.0001$; IP vs. CRP, $r = 0.78$; $p < 0.0001$; and RAP vs. CRP, $r = 0.78$; $p < 0.0001$).

CONCLUSIONS This study showed that patients with CHF may have intestinal overgrowth of pathogenic bacteria and *Candida* species and increased IP associated with clinical disease severity, venous blood congestion, and inflammation.
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It is well established that chronic heart failure (CHF) is also a systemic chronic inflammatory disease (1). Morphological, functional, and bacterial flora alterations in the intestine have all been reported as causes of inflammation (2). Indeed, increased wall thickness and permeability of both the small and large intestine, as well as increased bacterial populations (e.g., *Bacteroides, Prevotella, Eubacterium, Fusobacterium*) adherent to the intestinal mucosa, have been found (3). Bacteria and/or translocation of their toxins, from the intestine to the bloodstream, directly correlate with systemic inflammation (4).

The present study considered 2 hypotheses: 1) that the CHF intestine may be colonized by more pathogenic bacteria than have so far been reported; and 2) that this state may be associated with the severity of the CHF deterioration and venous blood congestion. These hypotheses are based on the following suppositions. First, the high prevalence of infection in patients with CHF (12%) (5) affects heart failure (despite optimal treatment) and increases the mortality rate (6). Second, the antibiotics used to treat infection may select the development of gut pathogenic bacteria over saprophytes. Third, the plasma levels of toxin lipopolysaccharide, a component of pathogenic bacteria walls, are higher during edematous heart decompensation (4). This finding would suggest that severe venous blood congestion may be an important factor for both intestinal pathogen overgrowth and increased intestinal permeability (IP) (7).

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The present study was conducted in patients with moderate and severe CHF to determine the intestinal pathogenic bacterial and fungal (*Candida* species) profiles in addition to IP. We also related IP to venous blood congestion as indicated by right atrial pressure (RAP).

ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CHF = chronic heart failure

CRP = C-reactive protein

IP = intestinal permeability

NYHA = New York Heart Association

RAP = right atrial pressure

TNF = tumor necrosis factor

METHODS

POPULATION. A total of 60 patients with mild CHF (New York Heart Association [NYHA] functional class I to II; n = 30) and moderate to severe CHF (NYHA functional class III to IV; n = 30) were studied. Eighty percent of these patients were ambulatory, and 20% had been admitted to our rehabilitation center from other hospitals. The patients' demographic, clinical, and functional characteristics are reported in Table 1. They had been treated with beta-blockers, diuretic agents, and angiotensin-converting enzyme inhibitors for at least the previous 3 months.

None of the selected subjects was obese (all, body mass index [BMI] <30 kg/m^2). They were receiving normal nutrition and adequate calories and protein (30 ± 0.8 kcal/kg; protein >0.80 ± 0.03 g/kg day) because they were on a standardized diet (carbohydrates 55% to 57%, lipids 24% to 26%, saturated fat <7%, protein 15% to 19% of total calories/day) as previously described (8). This diet is part of our rehabilitation program for both outpatients and inpatients.

Exclusion criteria included water retention, infection, renal failure (serum creatinine levels >2 mg/dl), endocrine disorders (e.g., thyroid disease), metabolic disorders (e.g., diabetes being treated with hypoglycemic drugs, insulin resistance according to homeostasis model of assessment values >2.5), and inflammatory or malabsorptive intestinal diseases. In addition, the patients had not undergone any antibiotic, steroid, laxative, antidiarrheal, and/or probiotic treatment over the previous 3 months. These exclusion criteria were specifically restrictive to avoid any confounding effects. The study was approved by our local institutional review board.

STUDY PROTOCOL. The anthropometric variables were measured, and BMI was calculated according to the following formula: weight (kilograms)/height (in meters squared). Blood variables were measured in peripheral venous samples after a 12-h overnight fast. Cardiac evaluation by using Doppler echocardiography was performed according to current guidelines. The images obtained were stored digitally and later analyzed by an experienced cardiologist, proficient in echocardiography, who was unaware of the study protocol.

Gut flora was determined by the development of bacteria and *Candida* species in stools, as previously described (9). Stool samples were collected with strikers and inserted into hermetic vials using a specific medium. Subsequently, the microbiota was measured after 48 h of incubation under proper conditions using a selective agar. Further proof of isolation was performed by using bacterial metabolic tests on isolated organisms through the BBL Crystal Identification System (Becton Dickinson, Franklin Lakes, New Jersey). The results are expressed in colony-forming units per milliliter of stool. The test was performed by Functional Point (Bergamo, Italy), a clinical and virology laboratory that adheres to international quality control standards and is accredited as an official laboratory within the National Health System. The test coefficient of variation was <9%.

TABLE 1 Patient Demographic, Clinical, and Functional Characteristics

	NYHA I to II (n = 30)	NYHA III to IV (n = 30)	p Value
Age, yrs	65 ± 1.3	63 ± 1.5	NS
Men/women	25/5	26/4	NS
Body weight, kg	82 ± 1.2	74.3 ± 1.6	<0.01
BMI, kg/m^2	28 ± 0.3	24 ± 0.5	<0.01
Nutritional intake			
Energy, kcal/kg	25.0 ± 0.57	25.6 ± 0.33	NS
Carbohydrates, g/kg	3.41 ± 0.07	3.58 ± 0.16	NS
Lipids, g/kg	0.86 ± 0.03	0.82 ± 0.03	NS
Proteins, g/kg	0.88 ± 0.02	0.96 ± 0.04	NS
Etiology	Ischemic, 66%	Ischemic, 64%	NS
	Idiopathic, 34%	Idiopathic, 36%	NS
Duration of disease, months	28 ± 2.2	30 ± 1.3	NS
Comorbidities			
Chronic obstructive pulmonary disease			
Frequency, %	33.3	26.6	
FEV_1/FVC, %*	64.5 ± 0.5	49.2 ± 0.8	0.05
Hypertension, %	36.6	30.0	<0.001
Cholelithiasis, %	6.6	10	NS
Gastroesophageal reflux disease, %	10.0	13.3	NS
Hemoglobin, g/dl	14.0 ± 0.1	12.2 ± 0.2	<0.01
Principal medications			
Bisoprolol, % patient treated (dose: mg)	63.4% 5.0 ± 0.5	66.7% 3.8 ± 0.4	NS
Furosemide, % patient treated (dose: mg)	100% 43.3 ± 3.6	100% 133 ± 14.1	<0.01
Ramipril, % patient treated (dose: mg)	100% 5.1 ± 0.4	100% 1.9 ± 0.33	NS
Serum creatinine, mg/dl	0.9 ± 0.001	0.9 ± 0.002	NS
Albumin, g/dl	3.6 ± 0.02	3.3 ± 0.03	<0.01
Sodium/potassium, mmol/l	140 ± 0.8/4.4 ± 0.2	139 ± 0.5/4.3 ± 0.1	NS
Total bilirubin, mg/dl	0.7 ± 0.04	0.8 ± 0.04	NS
AST, IU/l	21.3 ± 0.9	23.1 ± 1.7	NS
ALT, IU/l	21.4 ± 1.2	20.8 ± 1.5	NS
GGT, IU/l	20.8 ± 1.4	29 ± 4.4	NS
Alkaline phosphatase, IU/l	98.4 ± 1.5	103.2 ± 4.0	NS
CRP, mg/dl nv: 0 to 0.5mg/dl	6.0 ± 0.3	12.5 ± 0.6	<0.001
LVEF, %	39 ± 1.4	35.0 ± 1.2	<0.01
RAP, mm Hg	6.3 ± 0.4	12.6 ± 0.6	<0.001
Cardiac index, l/min/m^2	3.0 ± 0.07	2.6 ± 0.07	<0.01
Mitral regurgitation			
Mild: 1+/2+	1.5 ± 0.02		<0.01
Severe: 3+/4+		3.5 ± 0.02	

Values are mean ± SD, n, or %.

BMI = body mass index; GGT = gamma-glutamyltransferase; nv = normal value; NYHA = New York Heart Association; other abbreviations as in Table 1.

TABLE 2 Main Biochemical, Cardiologic, and Respiratory Measurements of Healthy Control Subjects

Hemoglobin, g/dl	15.1 ± 0.08
Serum creatinine, mg/dl	0.95 ± 0.01
Albumin, g/dl	4.2 ± 0.04
AST, IU/L	17.3 ± 0.4
ALT, IU/l	19.0 ± 0.3
CRP, mg/dl	0.15 ± 0.02
LVEF, %	60.2 ± 0.06
RAP, mm Hg	2.1 ± 0.08
Cardiac index, l/min/m^2	2.85 ± 0.04
FEV_1/FVC, %	94.7 ± 0.05

Values are mean ± SD.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRP = C-reactive protein; FEV_1/FVC = forced expired volume in 1 s/forced vital capacity; LVEF = left ventricular ejection fraction; RAP = right atrial pressure.

TABLE 3 Pathogenic Gut Flora in HC and CHF Patients

	Candida	*Campylobacter*	*Shigella*	*Salmonella*	*Yersinia enterocolitica*
% of patients having pathogens in stool					
HC	8	12	16	0	0
Total CHF	33.3	79.1	37.5	38.7	32.8
NYHA I to II	8.9	58.4	33.3	41.2	33.6
NYHA III to IV	92.0	96.3	40.5	36.2	32.0
Colony-forming units/ml ($\times 10^5$) of stool					
HC	0.8 ± 0.4	1.0 ± 0.3	1.6 ± 0.2	0	0
Total CHF	21.3 ± 1.6*	85.3 ± 3.7*	38.9 ± 12.3*	31.3 ± 9.1*	22.9 ± 6.3*
NYHA I to II	2.9 ± 1.1	8.3 ± 1.3†	7.9 ± 1.7†	20.2 ± 4.9*	23.1 ± 5.9*
NYHA III to IV	37.2 ± 4.4*‡	164.0 ± 6.1*‡	70.4 ± 17.2*‡	37.6 ± 13.1*	24.8 ± 7.5*

Values are % or mean +/− SD. *p < 0.001, total patients with chronic heart failure (CHF) versus healthy control subjects (HC) and NYHA functional class I to II versus HC and NYHA functional class III to IV versus HC. †p < 0.01, NYHA functional class I to II versus HC. ‡p < 0.001, NYHA functional class III to IV versus NYHA functional class I to II.

NYHA = New York Heart Association.

IP was evaluated by quantifying the disaccharide cellobiose content in the urine after a sugar drink test. This test is considered to be an index of IP, reflecting damage to the mucosa barrier (10). Cellobiose is not absorbed by healthy mucosa, has no enzymatic degradation, and is limited to the extracellular compartment. The cellobiose sugar test is noninvasive, well tolerated, safe, and easy to perform; in addition, the results are reproducible. Furthermore, cellobiose is not present in the diet or produced endogenously and is completely excreted by the kidneys.

Urine cellobiose levels were determined by using a sugar drink test, as described previously (9). Briefly, 3 hours after the evening meal (consumed between 6:00 PM and 7:00 PM), the subjects emptied their bladder and ingested the sugar test solution. The composition of the sugar test solution comprised 2 g of mannitol, 5 g of cellobiose, and 20 g of sucrose made up to 150 ml of water to provide an osmolality of approximately 1,500 mOsm/l. To avoid any possible interference, patients were forbidden to drink any soft drinks, alcohol, fruit juice, or milk during the tests.

Urine was collected during the subsequent 12-h overnight fast. At 9:00 to 10:00 AM the following day, the urine volume was quantified; an aliquot was used to measure urine cellobiose concentrations by spectrophotometer, as previously described (10). The normal values of the excreted cellobiose were between 0 and 3 mg/24 h. Twenty matched healthy subjects were used as control subjects and were selected for their similar age (62.1 ± 1.4 years), sex distribution (16 men, 4 women), and body weight (BMI 27 ± 0.4 kg/m^2). These subjects underwent evaluations identical to those of the test subjects.

STATISTICAL ANALYSIS. Any differences in variables between control subjects and the entire CHF population were evaluated by using an unpaired Student *t* test. In addition, the same statistical test was used to analyze data from mild (NYHA functional class I to II) and moderate-severe (NYHA III-IV) CHF. A chi-square test was used for dichotomous variables. The relations between variables were assessed by using a simple regression analysis. Statistical significance was set at $p < 0.05$.

RESULTS

Table 1 presents the patients' demographic, nutritional, clinical, and functional characteristics, and Table 2 presents the measured variables of the control subjects. Compared with the population with mild CHF, patients with more severe disease had similar nutritional intakes, lower BMI, fewer circulating proteins (e.g., hemoglobin, albumin), higher diuretic

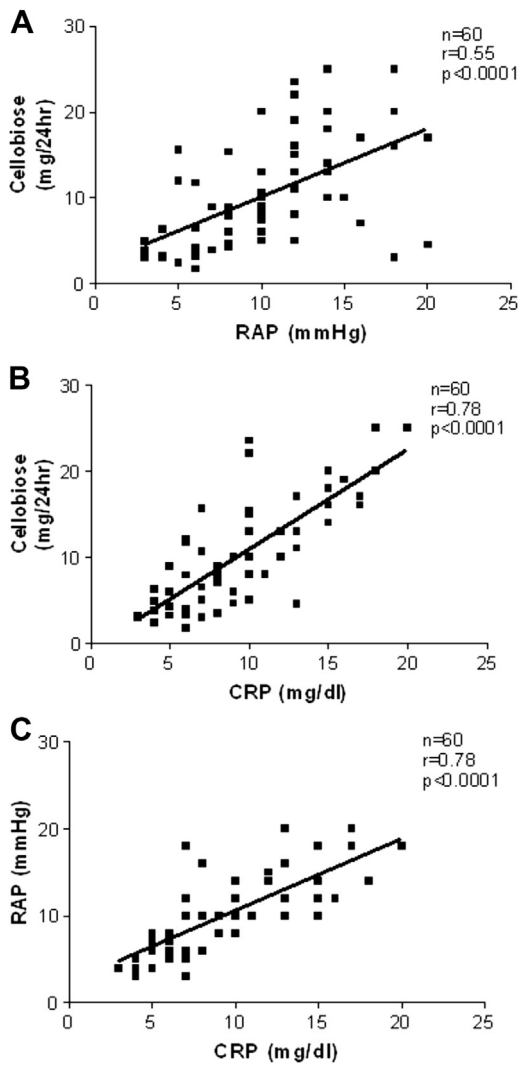
TABLE 4 Urine Excretion of Cellobiose, as a Marker of Intestinal Permeability, in HC and CHF Patients

% of subjects with normal intestinal permeability	
HC (n = 20)	100
Total CHF (n = 60)	21.7
NYHA I to II (n = 30)	43.3
NYHA III to IV (n = 30)	6.7
Intestinal permeability evaluated by urine cellobiose excretion nv = 0 to 3 mg/24h	
HC (n = 10)	1.5 ± 0.8
Total CHF (n = 60)	10.2 ± 1.2*
NYHA I to II (n = 30)	7.3 ± 0.9*
NYHA III to IV (n = 30)	12.4 ± 1.1*

Values are % or mean ± SD. *p < 0.001, total CHF versus HC, NYHA I to II vs HC, NYHA III to IV vs HC, and NYHA I to II versus NYHA III to IV.

Abbreviations as in Tables 1 and 3.

FIGURE 1 Relationship Between Intestinal Permeability, Right Atrial Pressure, and Systemic Inflammation. Correlation Between Right Atrial Pressure and Systemic Inflammation



(A) Relation between right atrial pressure (RAP) and intestinal permeability (cellobiose: 24-h urinary excretion). **(B)** Relation between inflammation (C-reactive protein [CRP]) and intestinal permeability (cellobiose: 24-h urinary excretion). **(C)** Relation between inflammation (CRP) and RAP.

agent dose, more impaired left ventricular cardiac function, and higher rates of RAP and inflammation.

Compared with control subjects, the entire CHF population had significant changes in gut flora and developed more pathogenic bacteria colonies in their stools. Indeed, CHF gut was colonized by species of *Candida, Campylobacter, Shigella*, and *Yersinia* (Table 3). Compared with patients with mild CHF, patients with more severe disease had a significantly increased development rate of *Candida, Campylobacter*, and *Shigella* species in stools. There were no major differences for saprophytic microorganisms and commensal strain, either between control subjects and the CHF population as a whole, or between the 2 groups of patients (data not shown).

The results showed that IP was normal in healthy control subjects but was increased for 78.3% of the CHF population. For the patients with CHF, the intestine was more permeable for those with NYHA functional class III to IV than for those with NYHA functional class I to II (Table 4). IP, RAP, and CRP were mutually interrelated (IP and RAP, $r = 0.55$, $p < 0.0001$; IP and CRP, $r = 0.78$, $p < 0.0001$; and RAP and inflammation, $r = 0.78$, $p < 0.0001$) (Figure 1). Left ventricular function did not significantly correlate either with IP or with CRP (data not shown).

DISCUSSION

This study found that patients with CHF had intestinal overgrowth of pathogenic bacteria and increased IP. Moreover, the results show that IP was associated with inflammation, RAP, and clinical disease severity.

PATHOGENIC GUT FLORA OVERGROWTH. Pathogenic gut flora overgrowth was present in most patients with CHF. This finding may be explained by considering that the intestinal microbial population is highly sensitive to both external and internal environmental alterations; as a result, gut flora may rapidly change its composition. External factors (e.g., antimicrobial use, exposure to other patients, use of other drugs) can also reduce the diversity of intestinal microbiota (11), ensuring intestinal health. In terms of antibiotic use, although the study patients had not been treated in the 3 months before their recruitment, we cannot exclude antibiotic use earlier than this period. Internal factors that may potentially alter gut flora include: acute changes of fluid balance, chronic bowel congestion, bowel ischemia, hypoxia and acid/base disturbance, gastrointestinal dysmotility, nutrient deprivation, and various types of fat intake.

All of these factors, individually or combined, may be present in patients with CHF, especially in those with more severe disease. Acute changes in fluid balance, as in cases of hemodynamic instability and/or use of large diuretic agent doses, might affect gastrointestinal motility and transit time. This effect, in turn, reduces the clearance of luminal content (e.g., bacteria, food remnants), leading to stasis and bacterial overgrowth or translocation (12). Chronic bowel congestion causes edema of the gastrointestinal tract, altering the response to gut hormones

and neurotransmitters, aggravating gastrointestinal dysmotility, and impairing the absorptive function of intestinal mucosa (13).

Hypoxemia (and hypercarbia) may also play a role in altering gut flora and intestinal function. Animal studies have shown that low blood oxygen pressure causes not only gastro-pyloric dysmotility but also gut mucosa acidosis and intestinal barrier disruption, leading to increased permeability (13). Interestingly, the CHF neuroendocrine response of decreasing gastrointestinal motility may further promote alterations in gut flora and function (14). Gastroparesis, for instance, may be relevant for patients with CHF because it is encountered in a large number of conditions, including diabetes, heart or lung transplantation, and chronic liver or renal failure, which are also frequent in CHF (15). Moreover, gastroparesis is present during parenteral nutrition. Antimotility agents and acid-suppressing therapies, particularly important in clinical practice because of their frequent use, may alter normal gut flora, allowing the overgrowth of pathogenic bacteria (16).

Intestinal bacterial overgrowth can exert negative effects on nutritional status, as patients with altered gut flora may experience vitamin B_{12} deficiency and malabsorption of fat and fat-soluble vitamins (17). Nutrient deprivation and fat intake might also play a major role in altering gut flora. Nutrient deprivation, which may occur during CHF hemodynamic instability, can expand microbiota consisting of *Enterobacter, Shigella, Klebsiella*, and *Fusobacterium* overgrowth (14).

The effects of enteral nutrition deprivation on gut microbiota were confirmed in a mouse model of parenteral nutrition (18). In this experiment, microbiota was found to change from a gram-positive *Firmicutes* to gram-negative *Proteobacteria*-dominated population. Relevant to this study, enteral deprivation causes an immunologically gut pro-inflammatory state by both increasing intraepithelial lymphocyte–derived tumor necrosis factor (TNF)-alpha and interferon-gamma and decreasing the anti-inflammatory interleukin-10 level (19). This proinflammatory state leads to the loss of intestinal epithelial barrier function and increases bacteria translocation. Conversely, enteral nutrition diminishes IP (13).

Fat intake per se and the digested fat may change the diversity of the macrobiota (20). In the present study, macrobiotic diversity was probably not due to high fat intake because the subjects ingested fat <30% calories/die with saturated fats <7%. Thus, the interplay of extrinsic and intrinsic factors could explain why we found that 78.3% of CHF patients had altered gut flora, and all of them had increased IP.

INCREASED IP. This study showed that for patients with CHF, increased IP was more accentuated in the moderate to severe stages of the disease than in the mild stages. The pathogenic gut flora is probably a major factor of IP because these microorganisms can cause chronic intestinal wall and systemic inflammation (21–25). The effects of chronic intestinal inflammation contribute to malabsorption caused by increased collagen content (26). Our study expands the results of a previous investigation, documenting mainly the presence of intestinal commensals in gut flora (3).

CORRELATIONS BETWEEN RAP, IP, AND SYSTEMIC INFLAMMATION. To best of our knowledge, this is the first study to report an association between pathogenic gut flora overgrowth, RAP, IP, and CPR. High RAP, by impairing both intestinal microcirculation and trophism and intestinal inflammation by pathogen overgrowth, leads to a dysfunctional and permeable intestine (26). This finding is suggested by the correlation between RAP and IP.

Interestingly, gut edema causes intestinal dismotility and increased bowel thickness (3). This outcome may be further amplified by a concomitant state of hypovolemia and shock leading to splanchnic hypoperfusion and ischemia with subsequent release of catecholamines and other vasoactive peptides. The hyperadrenergic response further aggravates bowel ischemia (13). Notably, post-compensated reperfusion-induced oxidative stress can lead to further IP damage. Subsequently, intestinal bacterial overgrowth may depress myocardial function by increasing circulatory inflammatory cytokines such as TNF-alfa and interleukin-6, as indirectly suggested in this study by the increase in serum CRP levels (27).

CLINICAL IMPLICATIONS. Pathogenic gut flora and increased IP could complicate the clinical course of patients with CHF. For instance, these patients are prone to a higher risk of infection and anastomotic complications when undergoing operations (28), as well as a perpetuating/aggravating inflammatory state. Indeed, *Campylobacter* species, found predominantly in patients with severe CHF, is a potent activator of innate immunity (29).

Pathogenic gut flora might negatively affect patients' nutrition as well as their metabolic efficiency by reducing microbiota diversity, which would decrease the production of beneficial metabolites such as short chain fatty acids (30). These substances are important body mechanisms for retrieving the calories of both nondigested foods such as plant polysaccharides and nonabsorbed proteins. In addition, the overgrowth of pathogenic gut flora may impair metabolic efficiency by reducing intestinal

absorptions of vitamin B_{12}, folic acid, and vitamin K, which are essential for protein metabolism (31).

Diet also influences the composition of intestinal microbiota. Indeed, as discussed earlier, the exposure of patients with CHF to external environmental factors, oral/intestinal nutrient deprivations, and an excess of total and saturated fat intake are all gut alteration modifiable factors. Of clinical importance, patients with CHF during the decompensation phase of the disease should either enterally or orally ingest at least 400/500 kcal to reduce the risk of gut barrier disruption (32). Our study suggests that gut microbiota should be continually investigated as soon as CHF is diagnosed.

STUDY LIMITATIONS. First, we studied a selected population excluding subjects with kidney and/or hepatorenal insufficiency and glucose intolerance or diabetes. This topic deserves further research, as these diseases are very common in CHF. According to our clinical practice, kidney insufficiency is present in 37%, diabetes mellitus in 25%, glucose intolerance in 47%, and hepatorenal syndrome in 17% of patients with CHF (unpublished data from our database 2012 to 2014). Furthermore, future studies should address additional risk factors to evaluate the contributory role of gut microbiota in cardiovascular diseases under other conditions such as obesity and/or the formation of TMA-N-oxide, which is linked to atherosclerosis and cardiovascular disease risk (33).

The moderate to severe mitral regurgitation might explain why, in NYHA functional class III to IV, there is the co-presence of a moderately reduced ejection fraction and a marginally conserved cardiac index. The comorbidity chronic obstructive pulmonary disease could misclassify the level of CHF-related functional decline.

It would also be interesting to document whether a vegetarian diet or meat consumption influences gut dysbiosis and/or the inflammatory state of the patients. Furthermore, the determination of TNF-alfa and interleukin-6 would have strengthened the discussion. Unstated, we used CRP because it is stimulated by interleukin-6, and CRP is the balance between proinflammatory and anti-inflammatory cytokines (34).

The use of a multiple testing correction method to better clarify the statistically significant differences between patients with CHF and control subjects would have increased the robustness of our results. However, due to difficulties in identifying a pathogenic bacterium more involved than others and the large differences found in several bacteria levels between patients and healthy control subjects, we thought it useful for the reader to evaluate the raw results and then draw their own conclusions regarding the clinical impact of our findings. Notwithstanding these limitations, 1 strength of the study was the use of noninvasive, reproducible, and feasible methods to measure gut flora development and IP.

CONCLUSIONS

At present, no clinical gut flora modifiers are available. Indeed, the use of probiotics could possibly be dangerous. At least in intensive care, there have been reported cases of bacteremia in patients taking probiotics (35) or in patients neighboring those who were administered probiotics (36). Moreover, it has been reported that even preventive multistrain probiotics cause bowel ischemia and/or death in patients with severe acute pancreatitis (37). It would be interesting to determine whether the host benefits from the use of prebiotics (38). Currently, re-establishing the gut microbiota may be the only option for patients to reverse intestinal dysbiosis (39).

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REPRINT REQUESTS AND CORRESPONDENCE: Dr. Federica Boschi, Dipartimento di Scienze del Farmaco, Department of Drug Science, Università degli Studi di Pavia, Viale Taramelli, 12-27100 Pavia, Italy. E-mail: federica.boschi@unipv.it.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Gut pathogenic bacteria were associated with inflammation, increased intestinal permeability, high right atrial pressure and clinical disease severity in patients with stable CHF. Gut flora development and intestinal permeability can be measured using noninvasive, reproducible and feasible methods which could provide important clinical information for the treatment of complicated multiorgan syndromes such as CHF.

TRANSLATIONAL OUTLOOK: Further studies are needed to confirm the link between gut pathogenic bacteria and severity of CHF. If confirmed, this link could suggest additional personalized therapeutic strategies for patients with CHF in support of traditional drugs.

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KEY WORDS chronic heart failure, gut flora, inflammation, intestinal permeability

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