Intestinal Blood Flow in Patients With Chronic Heart Failure
A Link With Bacterial Growth, Gastrointestinal Symptoms, and Cachexia

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ABSTRACT

BACKGROUND Blood flow in the intestinal arteries is reduced in patients with stable heart failure (HF) and relates to gastrointestinal (GI) symptoms and cardiac cachexia.

OBJECTIVES The aims of this study were to measure arterial intestinal blood flow and assess its role in juxtamucosal bacterial growth, GI symptoms, and cachexia in patients with HF.

METHODS A total of 65 patients and 25 controls were investigated. Twelve patients were cachectic. Intestinal blood flow and bowel wall thickness were measured using ultrasound. GI symptoms were documented. Bacteria in stool and juxtamucosal bacteria on biopsies taken during sigmoidoscopy were studied in a subgroup by fluorescence in situ hybridization. Serum lipopolysaccharide antibodies were measured.

RESULTS Patients showed 30% to 43% reduced mean systolic blood flow in the superior and inferior mesenteric arteries and celiac trunk (CT) compared with controls (p < 0.007 for all). Cachectic patients had the lowest blood flow (p < 0.002). Lower blood flow in the superior mesenteric artery and CT was correlated with HF severity (p < 0.04 for all). Patients had more feelings of repletion, flatulence, intestinal murmurs, and burping (p < 0.04). Burping and nausea or vomiting were most severe in patients with cachexia (p < 0.05). Patients with lower CT blood flow had more abdominal discomfort and immunoglobulin A antilipopolysaccharide (r = 0.76, p < 0.02). Antilipopolysaccharide response was correlated with increased growth of juxtamucosal but not stool bacteria. Patients with intestinal murmurs had greater bowel wall thickness of the sigmoid and descending colon, suggestive of edema contributing to GI symptoms (p < 0.05). In multivariate regression analysis, lower blood flow in the superior mesenteric artery, CT (p < 0.04), and inferior mesenteric artery (p = 0.056) was correlated with the presence of cardiac cachexia.

CONCLUSIONS Intestinal blood flow is reduced in patients with HF. This may contribute to juxtamucosal bacterial growth and GI symptoms in patients with advanced HF complicated by cachexia. (J Am Coll Cardiol 2014;64:1092-102)

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Chronic heart failure (HF) is a multisystem disease. Along with increased sympathetic tone and chronic low-grade systemic inflammation, there is an anabolic-catabolic imbalance, with cardiac cachexia as a terminal stage of the disease. The occurrence of this unintentional weight loss is a serious complication and predicts poor survival (1). The prevalence of cachexia...
in patients with chronic HF ranges from 16% to 42% (2).

The role of the gut in the pathophysiology of chronic HF has only recently undergone detailed investigations. There is increasing evidence that the gut plays an important pathophysiological role in malnutrition and cachexia in chronic HF. Significant morphological and functional alterations of the intestine in patients with chronic HF have been previously shown (3). Patients display a thickened bowel wall, suggestive of bowel wall edema; intestinal barrier dysfunction; and diminished transcellular transport activity (4). There are increased numbers of bacteria in the mucus layer adjacent to the apical surface of the colonic mucosa, and increased permeability of both the small and large intestines has been demonstrated. Restricted arterial blood flow to the intestine is a major candidate explaining these functional alterations and may create an abnormal environment in the juxtamucosal mucus layer that encourages the increased growth of bacteria. However, arterial blood flow to the intestine and gastrointestinal (GI) symptoms in cachectic and noncachectic patients with HF have not yet been analyzed.

We hypothesized that arterial blood flow in the main intestinal arteries is reduced in patients with stable compensated HF and relates to possible GI symptoms and to the prevalence of cardiac cachexia.

METHODS

We prospectively studied intestinal blood flow in 65 patients with chronic HF and 25 control subjects. Demographic and clinical details are shown in Table 1. The diagnosis of chronic HF was based on symptoms arising during exercise, clinical signs, and documented left ventricular impairment (left ventricular ejection fraction [LVEF] ≤ 40%) according to guidelines (5). Patients were classified as cachectic independent of their absolute body mass indexes if they had experienced nonedematous unintentional weight loss of ≥5% within the previous 6 to 12 months (6). All patients were clinically stable (mean New York Heart Association [NYHA] functional class 2.5 ± 0.5) and received unchanged medications for at least 4 weeks before assessment. Patients were allowed to take aspirin 100 mg once daily but no other nonsteroidal anti-inflammatory drugs, steroid hormones, or antibiotics within at least 4 weeks before study participation. In patients with HF, medications consisted of angiotensin-converting enzyme inhibitors (71%), angiotensin receptor blockers (32%), beta-blockers (88%), aldosterone receptor antagonists (52%), other diuretic agents (72%), glycoseide agents (20%), and statins (80%) in varying combinations. None of the control subjects were taking any cardiovascular medications, except for a calcium channel blocker in 1 subject and angiotensin-converting enzyme inhibitors in 2 subjects for mild arterial hypertension without evidence of left ventricular dysfunction. Subjects with clinical signs of infection, rheumatoid arthritis, renal failure, intestinal diseases, severe chronic obstructive pulmonary disease, significant valvular heart disease, cancer, or histories of autoimmune disorders were excluded. None of the subjects had known immune system disorders, and no subject received immune modulation therapy. The local ethics committee approved the study, and all subjects gave written informed consent.

CLINICAL ASSESSMENTS. Echocardiography was performed according to standard procedures. LVEF was measured using the biplane Simpson’s technique. All subjects underwent symptom-limited treadmill exercise testing (instantaneous breath-by-breath method) using the modified Naughton protocol (Innocor system [Innovision, Odense, Denmark]; HP Cosmos treadmill [HP Cosmos Sports & Medical GmbH, Nussdorf-Traunstein, Germany]). The following variables were measured: peak oxygen consumption, total exercise time, ventilatory response to exercise, anaerobic threshold, peak heart rate, and peak systolic and diastolic blood pressures. Blood flow velocities in the celiac trunk (CT), superior mesenteric artery (SMA), and inferior mesenteric...
beam and the mesenteric artery was previously described (7). The angle between Doppler beam and the artery was <60°. Systolic blood flow in the SMA was assessable in 63 patients and 23 controls. Systolic blood flow in the IMA was assessable in 56 patients and 23 controls, and flow in CT was measured in 53 patients and 25 controls.

Transcutaneous abdominal sonography (12-MHz linear-array transducer, HDI 5000) was used to measure bowel wall thickness in the middle segment of the sigmoid (in subjects #1 to #65), descending, transverse, and ascending colon (subjects #7 to #65). Measurement of the terminal ileum (subjects #7 to #65) was performed 5 cm proximal to the ileocecal valve. Because of obesity, the sigmoid colon was not assessed in 3 subjects, the transverse colon was not assessed in 3 subjects, the ascending colon was not assessed in 1 subject, and the terminal ileum was not assessed in 1 subject. Patients were scanned under identical conditions after overnight fasting.

Measurement of bowel wall thickness was carried out in true cross and longitudinal sections of the relaxed bowel by assessment of the anterior bowel wall. Overall thickness of the bowel wall was measured from the first mucosal interface echo to the first serosal echo. Each measurement was repeated 3 times at different positions of the intestinal wall, and the mean was calculated.

All sonographic recordings were performed in a standardized way, and the same experienced physician, who was blinded to the subjects' study groups, analyzed the readings. The intraobserver coefficient of variation for intestinal ultrasound measurements of bowel wall thickness repeated on consecutive days is 5%. Accuracy of measurement is <0.2 mm for all segments.

Venous occlusion plethysmography was performed to assess peripheral blood flow and vascular capacity using a plethysmograph (EC 6; Hokanson, Inc., Bellevue, Washington) in 55 patients and 17 control subjects, as previously described (8). The subjects rested in a supine position for at least 15 min, and forearm blood flow was determined using a mercury-in-Silastic strain gauge (Hokanson). A cuff around the right upper arm was connected to a rapid inflation pump with an air source and solenoid valves, used to

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**TABLE 1** Baseline Data for Patients With Chronic HF With and Without Cachexia and Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>Controls (n = 25)</th>
<th>All Patients With Chronic HF (n = 65)</th>
<th>Patients With Cachexia Chronic HF (n = 53)</th>
<th>Patients With Cachectic Chronic HF (n = 12)</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>28</td>
<td>15</td>
<td>17</td>
<td>8</td>
<td>0.70</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td>2.5 ± 0.5</td>
<td>2.4 ± 0.5</td>
<td>2.9 ± 0.4</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>Ischemic etiology</td>
<td>74</td>
<td>77</td>
<td>58</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>63 ± 7</td>
<td>30 ± 7†</td>
<td>31 ± 7†</td>
<td>25 ± 7†</td>
<td>0.006</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>62 ± 10</td>
<td>65 ± 10</td>
<td>66 ± 9</td>
<td>64 ± 9</td>
<td>0.50</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26 ± 4</td>
<td>28 ± 5</td>
<td>29 ± 5†</td>
<td>25 ± 5</td>
<td>0.02</td>
</tr>
<tr>
<td>Height, cm</td>
<td>174 ± 8</td>
<td>174 ± 8</td>
<td>175 ± 9</td>
<td>171 ± 8</td>
<td>0.20</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>79 ± 15</td>
<td>86 ± 19</td>
<td>89 ± 19†</td>
<td>74 ± 17</td>
<td>0.01</td>
</tr>
<tr>
<td>Peak VO₂, ml/min/kg</td>
<td>27.4 ± 7.2</td>
<td>15.2 ± 4.6†</td>
<td>15.8 ± 4.6†</td>
<td>12.7 ± 4.1†</td>
<td>0.09</td>
</tr>
<tr>
<td>Hemoglobin, g/dl</td>
<td>13.7 ± 1.5</td>
<td>13.6 ± 1.7</td>
<td>13.9 ± 1.6</td>
<td>12.2 ± 1.5†</td>
<td>0.007</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>40.5 ± 3.0</td>
<td>40.6 ± 4.5</td>
<td>41.2 ± 4.5</td>
<td>37.3 ± 3.6</td>
<td>0.01</td>
</tr>
<tr>
<td>White blood cells, ×10⁹/l</td>
<td>6.4 ± 1.4</td>
<td>7.3 ± 1.7†</td>
<td>7.4 ± 1.9†</td>
<td>7.0 ± 1.0</td>
<td>0.50</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>0.9 ± 0.2</td>
<td>1.2 ± 0.3</td>
<td>1.2 ± 0.3</td>
<td>1.2 ± 0.4</td>
<td>0.60</td>
</tr>
<tr>
<td>ASAT, U/l</td>
<td>27.8 ± 7.6</td>
<td>29.1 ± 8.4</td>
<td>29.2 ± 7.4</td>
<td>23.9 ± 12.4</td>
<td>0.90</td>
</tr>
<tr>
<td>C-reactive Protein, mg/dl</td>
<td>6.3 ± 14.4</td>
<td>25.0 ± 13.1</td>
<td>27.0 ± 13.7</td>
<td>21.5 ± 9.4</td>
<td>0.20</td>
</tr>
<tr>
<td>Midregional pro-ANP, nmol/l</td>
<td>160 (321)</td>
<td>178 (160)†</td>
<td>410 (321)†</td>
<td>1.0 ± 0.6</td>
<td>0.006</td>
</tr>
<tr>
<td>Midregional proadrenomedullin, nmol/l</td>
<td>0.5 ± 0.1</td>
<td>1.0 ± 0.5†</td>
<td>0.9 ± 0.4†</td>
<td>1.4 ± 0.6</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Values are %, mean ± SD, or median (interquartile range). †Cachectic chronic HF versus noncachectic chronic HF. ‡p < 0.05 versus controls. ALAT = alanine aminotransferase; ANP = atrial natriuretic peptide; ASAT = aspartate aminotransferase; HF = heart failure; NYHA = New York Heart Association; VO₂ = oxygen consumption.
inflated and deflated the occlusion cuff rapidly to the required pressure of 40 mm Hg. To measure the peak forearm blood flow, the cuff was inflated to suprasystolic pressure (30 mm Hg above systolic blood pressure) for 3 min. Blood flow was measured after release of the cuff in 10-second intervals for at least 2 min. The highest flow results were considered to represent peak forearm blood flow.

Results for plethysmography are given in milliliters per 100 ml tissue per min. All assessments were performed in a dedicated, quiet room between 9 and 10 AM to prevent data bias from noise and circadian rhythms.

GI symptoms were assessed with the Gastrointestinal Symptom Rating Scale questionnaire, which was completed by 59 patients and 18 control subjects (9). Items include abdominal pain, reflux syndrome, diarrhea syndrome, indigestion syndrome, and constipation syndrome (10) and have good internal consistency, reliability, construct validity, and responsiveness (9).

Mucosal bacterial biofilm was assessed by fluorescence in situ hybridization in biopsies taken during sigmoidoscopy in 22 patients with chronic HF and 20 control subjects, as previously described (3), according to a well-established technique without sedation after a glycerol enema.

Stool samples were available from 21 patients with chronic HF and 17 control subjects. Total bacteria and bacterial groups were studied by fluorescence in situ hybridization and epifluorescence microscopy in blinded fecal samples, as previously described (11). In 13 controls (subjects #10 to #22) and 12 patients (subjects #9 to #20), intestinal blood flow was assessed in that group. Blood immunoglobulin A (IgA)-anti-lipopolysaccharide (LPS) were assessed in these patients and controls by enzyme-linked immunosorbent assay (12,13).

In 27 patients and 18 control subjects, C-reactive protein was measured. Plasma concentrations of midregional proadrenomedullin and midregional pro-atrial natriuretic peptide (ANP) were measured by using a chemiluminescence immunoassay on the Kryptor System (Brahms AG, Hennigsdorf/Berlin, Germany), as previously described in detail (14,15).

**Statistical Analysis.** Statistical analysis was performed using StatView version 5.0 (SAS Institute Inc, Cary, North Carolina). Normality of distribution was assessed using the Kolmogorov-Smirnov test. Results are reported as mean ± SD (indicating a normal distribution of data; statistical comparisons were made using Student unpaired t tests). Analysis of variance, Student unpaired t tests, Fisher exact tests, Pearson simple regression, and logistic regression were used as appropriate. Non-normally distributed data were log10 transformed to achieve a normal distribution where indicated. Parameters that were significantly different between noncachectic and cachectic patients were tested using multivariate regression analysis. Variables of interest were adjusted for age and sex as indicated. A 2-tailed p value ≤0.05 was considered significant in all analyses.

**RESULTS**

There were no significant differences between control subjects and patients with chronic HF in terms of age and sex (Table 1). As expected, patients had lower LVEFs and peak oxygen consumption. Patients with cardiac cachexia had lower body mass indexes and were hemodynamically more severely compromised, as reflected by lower peak oxygen consumption, lower LVEFs, and higher blood levels of pro-ANP.

**TABLE 2** Systolic and Diastolic BF in the 3 Main Intestinal Arteries

<table>
<thead>
<tr>
<th>Intestinal Blood Flow (ml/min)</th>
<th>Controls (n = 25)</th>
<th>All Patients With Chronic HF (n = 65)</th>
<th>Patients With Noncachectic Chronic HF (n = 53)</th>
<th>Patients With Cachectic Chronic HF (n = 12)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean systolic BF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMA</td>
<td>483 (272)</td>
<td>534 (224)†</td>
<td>543 (203)†</td>
<td>205 (148)†</td>
<td>0.001</td>
</tr>
<tr>
<td>IMA</td>
<td>86 (62)</td>
<td>49 (26)†</td>
<td>51 (30)†</td>
<td>39 (23)†</td>
<td>0.05</td>
</tr>
<tr>
<td>CT</td>
<td>542 (373)</td>
<td>377 (246)†</td>
<td>416 (219)†</td>
<td>234 (182)†</td>
<td>0.01</td>
</tr>
<tr>
<td>Peak systolic BF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMA</td>
<td>2,779 (1,641)</td>
<td>1,696 (959)†</td>
<td>1,774 (889)†</td>
<td>1,142 (951)†</td>
<td>0.003</td>
</tr>
<tr>
<td>IMA</td>
<td>411 (315)</td>
<td>260 (165)†</td>
<td>265 (163)†</td>
<td>254 (115)†</td>
<td>0.20</td>
</tr>
<tr>
<td>CT</td>
<td>2,619 (1,462)</td>
<td>1,717 (978)†</td>
<td>1,822 (815)†</td>
<td>1,249 (518)†</td>
<td>0.009</td>
</tr>
<tr>
<td>Mean diastolic BF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMA</td>
<td>291 (161)</td>
<td>211 (159)†</td>
<td>214 (149)†</td>
<td>158 (208)†</td>
<td>0.10</td>
</tr>
<tr>
<td>IMA</td>
<td>43 (30)</td>
<td>30 (22)†</td>
<td>30 (22)†</td>
<td>27 (27)†</td>
<td>0.10</td>
</tr>
<tr>
<td>CT</td>
<td>512 (360)</td>
<td>291 (261)†</td>
<td>308 (246)†</td>
<td>190 (197)†</td>
<td>0.05</td>
</tr>
<tr>
<td>Maximal diastolic BF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMA</td>
<td>555 (312)</td>
<td>449 (341)†</td>
<td>445 (348)†</td>
<td>465 (346)†</td>
<td>0.25</td>
</tr>
<tr>
<td>IMA</td>
<td>78 (50)</td>
<td>54 (47)†</td>
<td>58 (47)</td>
<td>52 (50)</td>
<td>0.75</td>
</tr>
<tr>
<td>CT</td>
<td>750 (760)</td>
<td>548 (390)†</td>
<td>636 (420)†</td>
<td>473 (214)†</td>
<td>0.30</td>
</tr>
<tr>
<td>Minimal diastolic BF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMA</td>
<td>376 (263)</td>
<td>266 (264)†</td>
<td>266 (259)†</td>
<td>272 (268)†</td>
<td>0.70</td>
</tr>
<tr>
<td>IMA</td>
<td>72 (56)</td>
<td>38 (31)†</td>
<td>43 (30)†</td>
<td>33 (20)†</td>
<td>0.50</td>
</tr>
<tr>
<td>CT</td>
<td>526 (279)</td>
<td>346 (242)†</td>
<td>365 (250)†</td>
<td>297 (142)†</td>
<td>0.80</td>
</tr>
<tr>
<td>Arm resting BF, ml/100 ml/min</td>
<td>4.6 ± 2.3</td>
<td>3.1 ± 1.9†</td>
<td>3.1 ± 2.0†</td>
<td>3.0 ± 1.2†</td>
<td>0.90</td>
</tr>
<tr>
<td>Arm peak post-ischemic BF, ml/100 ml/min</td>
<td>21.2 ± 7.7</td>
<td>16.3 ± 6.5†</td>
<td>17.0 ± 6.7†</td>
<td>13.4 ± 5.4†</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Values are median (interquartile range) or mean ± SD. *Cachetic chronic HF versus noncachetic chronic HF. †p < 0.05 versus controls.

BF = blood flow; CT = celiac trunk; HF = heart failure; IMA = inferior mesenteric artery; SMA = superior mesenteric artery.
compared with patients without cachexia (Table 1). Patients with HF had higher blood concentration of white blood cells compared with control subjects (Table 1). Serum concentrations of C-reactive protein were higher in patients compared with controls, with the highest levels in cachectic patients compared with noncachectic patients (Table 1).

**Intestinal Blood Flow.** Patients with chronic HF had lower mean and peak systolic blood flow in the SMA, IMA, and CT compared with control subjects (Table 2). The lowest systolic blood flow in the SMA, IMA, and CT was in patients with cardiac cachexia, with flow reductions of 58%, 55%, and 57%, respectively, compared with control subjects. Lower mean systolic flow in the SMA and CT was correlated with the severity of HF in patients, according to higher blood pro-ANP (Figures 1A and 1B). We did not detect any stenoses of the mesenteric arteries or CT in either patients or controls.

Mean diastolic blood flow was lower in the CT and IMA in patients compared with controls (Table 2). There was a trend toward lower diastolic flow in the CT in patients with more severe HF according to blood pro-ANP ($r = 0.25$, $p = 0.096$). Lower maximal diastolic flow and a trend toward lower minimal diastolic flow in the SMA were correlated with the severity of HF in patients according to higher blood pro-ANP ($r = 0.3$, $p < 0.03$, and $r = 0.25$, $p = 0.077$).

In patients with HF, both resting arterial limb blood flow (arm) and peak post-ischemic flow were reduced, the latter indicating impaired vasodilator capacity due to endothelial dysfunction compared to controls (Table 2). Higher blood midregional pro-adrenomedullin levels in patients underlined impaired endothelial function in our patient group (Table 1). However, there was no correlation of arm blood flow and intestinal blood flow ($p > 0.12$ for all). Arm blood pressure was not correlated with intestinal blood flow either ($p > 0.40$ for all).

**Bowel Wall Thickness.** Patients had increased bowel wall thickness in the terminal ileum, representing the small bowel, ascending colon, transverse colon, descending colon, and sigmoid colon, compared with control subjects ($p < 0.01$ for all; Table 3). However, bowel wall thickness was not correlated with patients’ edema status at lower leg and lower arterial intestinal blood flow.

**GI Symptoms.** Compared with controls, patients more often reported feelings of repletion (34 of 58 vs. 4 of 18, $p = 0.014$), burping (15 of 59 vs. 0 of 18, $p = 0.0016$), flatulence (43 of 59 vs. 8 of 18, $p = 0.03$), and murmurs from the intestine (34 of 59 vs. 5 of 18, $p = 0.027$). In cachectic versus noncachectic patients, burping was more frequent and more severe (5 of 11 vs. 8 of 46, $p < 0.05$, and $1.8 \pm 0.4$ vs. $1.3 \pm 0.3$, $p = 0.01$), and murmurs from the intestine were, as a trend, more severe ($p < 0.08$). Nausea and vomiting, if present, were more severe as well (2.25 $\pm 0.5$ vs. $1.1 \pm 0.1$, $p < 0.02$).

In those patients with abdominal discomfort, we found lower mean systolic blood flow in the CT ($274 \pm 36$ vs. $480 \pm 38$ ml/min, $p = 0.02$). In univariate regression, both high NYHA class and low CT flow were correlated with abdominal discomfort ($p < 0.04$ for all).

Patients with intestinal murmurs had greater bowel wall thickness of the sigmoid and descending colon ($0.23 \pm 0.017$ cm vs. $0.18 \pm 0.01$ cm, $p = 0.03$,...
and 0.20 ± 0.01 cm vs. 0.16 ± 0.01 cm, p = 0.04) and similar bowel wall thickness of the terminal ileum and the ascending colon (p > 0.20 for all).

There was a consistent trend toward increased heartburn, reflux, and constipation in patients with chronic HF compared with controls (21 of 59 vs. 2 of 18, p = 0.075; 21 of 59 vs. 2 of 18, p = 0.075; and 15 of 58 vs. 1 of 18, p = 0.097). However, pain in the upper abdomen (14 of 58 vs. 2 of 18, p = 0.30), defecation frequency (2 of 18 vs. 13 of 56, p = 0.30), and nausea or vomiting (13 of 59 vs. 2 of 18, p = 0.50) were similarly reported in patients and controls.

**STOOL BACTERIA.** Concentrations and proportions of both anaerobic and aerobic bacteria in the stool were similar in patients and controls (Table 4). The number and composition of stool bacteria did not reflect the higher concentration of mostly anaerobic bacteria in the mucosal biofilm of patients or the increased proportion of strictly anaerobic *Eubacterium rectale, Bacteroides/Prevotella,* and *Fusobacterium prausnitzii* in the biofilm of patients (r = 0.4 and r = 0.3, p = 0.12, p > 0.17, p > 0.50, and p > 0.37, respectively). This finding points to an increase in bacteria restricted to the juxtamucosal zone. The concentration of total stool bacteria, aerobes, Gram-negative aerobes, anaerobes, lactobacilli, enterococci, *Bacteroides,* bifidobacteria, or yeast in stool was not associated with lower intestinal blood flow (p > 0.10 for all).

In contrast, a higher proportion of the strictly anaerobic *E. rectale* in the juxtamucosal biofilm of the sigmoid colon in patients was correlated with lower systolic flow in the IMA supplying the sigmoid colon (r = 0.64, p = 0.047).

In 13 of 22 patients with high concentrations of juxtamucosal bacteria of ≥10⁷/mL, there was a strong trend toward an association of increased growth of juxtamucosal bacteria and serum concentrations of IgA-anti-LPS (r = 0.55, p = 0.05) (Figure 2). Luminal stool bacteria was not correlated with serum IgA-LPS antibodies.

Lower blood flow in the CT was correlated with higher serum IgA-LPS antibodies (r = 0.76, p < 0.02) (Figure 3) and with higher serum C-reactive protein (r = 0.61, p = 0.003) (Figure 4). Lower intestinal blood flow in the SMA was associated with higher serum C-reactive protein in patients as well (r = 0.43, p = 0.02) (Figure 4).

**CORRELATES OF THE PRESENCE OF CACHEXIA.** In univariate logistic regression, lower LVEF, higher blood pro-ANP, higher NYHA class, lower intestinal flow in the CT or SMA, and a trend toward lower intestinal flow in IMA were correlated with the presence of cachexia (Table 5). These correlations of lower LVEF, higher blood pro-ANP, higher NYHA class, and lower intestinal flow in the CT or SMA with the presence of cachexia remained significant after adjustment for age and sex (p < 0.02, p < 0.003, p < 0.008, p < 0.03, or p < 0.01, respectively).

In contrast, age, sex, resting arterial limb blood flow (arm), and bowel wall thickness were not correlated with the presence of cachexia serving as the dependent variable (Table 5).

In multivariate regression analysis, lower intestinal blood flow in the SMA and CT (p < 0.04 for all) and a trend toward lower intestinal blood flow in the IMA (p < 0.058) were independently associated with the presence of cardiac cachexia in distinct models, each adjusted for NYHA functional class, LVEF, and pro-ANP. The probability of having cachexia for intestinal flows, each adjusted for NYHA functional class, LVEF, and pro-ANP, was 0.1 for an increase in SMA flow (odds ratio: 0.1; 95% confidence interval: 0.02 to 0.8), 0.2 for an increase in SMA flow (odds ratio: 0.2; 95% confidence interval: 0.04 to 0.8), and 0.4 for an increase in IMA flow (odds ratio: 0.4; 95% confidence interval: 0.1 to 1.0).

There was a trend toward higher NYHA functional class to be independently associated with the

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**TABLE 3** Bowel Wall Thickness of Terminal Ileum, Ascending Colon, Transverse Colon, Descending Colon, and Sigmoid in Noncachectic and Cachectic Patients With Chronic HF and Control Subjects

<table>
<thead>
<tr>
<th>Thickness</th>
<th>Controls (n = 25)</th>
<th>Patients With Noncachectic Chronic HF (n = 51)</th>
<th>Patients With Cachectic Chronic HF (n = 12)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminal ileum</td>
<td>1.0 ± 0.3</td>
<td>1.3 ± 0.4†</td>
<td>1.3 ± 0.4†</td>
<td>0.0005</td>
</tr>
<tr>
<td>Ascending colon</td>
<td>1.2 ± 0.5</td>
<td>1.6 ± 0.6†</td>
<td>1.6 ± 0.4†</td>
<td>0.008</td>
</tr>
<tr>
<td>Transverse colon</td>
<td>1.2 ± 0.4</td>
<td>1.6 ± 0.5†</td>
<td>1.5 ± 0.3†</td>
<td>0.005</td>
</tr>
<tr>
<td>Descending colon</td>
<td>1.4 ± 0.6</td>
<td>1.9 ± 0.7†</td>
<td>1.9 ± 0.5†</td>
<td>0.003</td>
</tr>
<tr>
<td>Sigmoid colon</td>
<td>1.5 ± 0.6</td>
<td>2.1 ± 0.9†</td>
<td>2.0 ± 0.6†</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Values are mean ± SD. *Patients with chronic HF versus controls. †p < 0.05 versus controls.

**TABLE 4** Concentration of Bacteria in Patients With Chronic HF and Control Subjects

<table>
<thead>
<tr>
<th>Concentration (count/g in stool)</th>
<th>Controls (n = 17)</th>
<th>Patients With Chronic HF (n = 21)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bacteria</td>
<td>22 x 10⁻⁷ (27 x 10⁻⁷)</td>
<td>23 x 10⁻⁷ (15 x 10⁻⁷)</td>
<td>0.80</td>
</tr>
<tr>
<td>Aerobes</td>
<td>0.1 x 10⁻⁷ (0.0 x 10⁻⁷)</td>
<td>0.2 x 10⁻⁷ (0.9 x 10⁻⁷)</td>
<td>0.80</td>
</tr>
<tr>
<td>Gram-negative aerobes</td>
<td>0.6 x 10⁻⁵ (0.8 x 10⁻⁵)</td>
<td>0.5 x 10⁻³ (1.5 x 10⁻³)</td>
<td>0.80</td>
</tr>
<tr>
<td>Anaerobes</td>
<td>22 x 10⁻⁷ (68 x 10⁻⁷)</td>
<td>23 x 10⁻⁷ (15 x 10⁻⁷)</td>
<td>0.70</td>
</tr>
<tr>
<td>Anaerobes/total bacteria</td>
<td>1.0 (0.07)</td>
<td>1.0 (0.13)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Values are median (interquartile range). HF = heart failure.
presence of cardiac cachexia in models including either CT or SMA flow (p < 0.097).

DISCUSSION

This is the first study to evaluate blood flow in all 3 arteries supplying the stomach and the small and large intestines in patients with and without cardiac cachexia (Central Illustration). Endothelial function of the forearm vessels revealed both lower resting blood flow and lower post-ischemic flow in patients with HF compared with control subjects. A higher concentration of juxtamucosal anaerobic bacteria in the sigmoid colon in patients was correlated with a higher systemic concentration of anti-LPS IgA antibodies.

Furthermore, there was an increase in GI symptoms in patients compared with controls. Patients more often reported feelings of repletion, burping, flatulence, and murmurs from the intestine. Symptoms were most pronounced in cachectic patients. Patients with abdominal discomfort had lower mean systolic flow in the CT.

Impaired intestinal blood flow correlated with severity of HF and was in accord with greater

![Figure 2](image1.png)  
**Figure 2** Correlation of Concentration of Bacteria in Mucosal Biofilm of the Sigmoid Colon in Patients, With Their Serum Concentrations of IgA-Anti-LPS

IgA = immunoglobulin A; LPS = lipopolysaccharide.

![Figure 3](image2.png)  
**Figure 3** Mean Systolic Blood Flow in the Celiac Trunk

Correlation of mean systolic blood flow in the celiac trunk in 9 patients, with their serum concentrations of immunoglobulin A (IgA)-anti-lipopolysaccharide (LPS).

![Figure 4](image3.png)  
**Figure 4** Lower Mean Systolic Blood Flow in Patients With Heart Failure

Correlation of lower mean systolic blood flow (A) in the celiac trunk (CT) and (B) in the superior mesenteric artery (SMA) with higher serum C-reactive protein in patients with heart failure.
thickness of the bowel wall in patients with chronic HF, suggestive of bowel wall edema. Patients with intestinal murmurs had the greatest bowel wall thickness of the sigmoid and descending colon.

However, patients did not have symptoms of mesenteric ischemia, such as abdominal pain, diarrhea, or obvious intestinal bleeding. The only symptoms found were minor and could be ascribed to changes in intestinal motor function.

**Mucosal Biofilm.** One explanation for the increased number of bacteria in the mucosal biofilm is that entirely new phylogenotypes of bacteria are present in patients with HF. Some differences were found, such as a greater proportion of patients with chronic HF had *Bacteroides/Prevotella, E. rectale*, and *F. prausnitzii* (3), all representing species of normal intestinal flora. Overall, the range of bacteria within biofilm was broadly similar in patients and controls. It is therefore likely that the environment in the mucosal biofilm is altered in patients with HF in such a way that the growth of bacteria is encouraged. In particular, the higher occurrence rate of the strictly anaerobic *E. rectale* group and the strictly anaerobic *F. prausnitzii* in intestinal biofilm indicates better conditions for these specific anaerobes directly at the surface of the mucus membrane in patients with chronic HF.

A major candidate for the cause of the environmental change in the mucosal biofilm is reduced mesenteric blood flow and endothelial dysfunction, as we report here. The correlation of lower systolic flow in the IMA supplying the sigmoid colon with the higher proportion of juxtamucosal strictly anaerobic *E. rectale* found in patients indicates this. Reduced intestinal blood flow results in limited oxygen supply to the mucosa, which may cause this selective enrichment of obligate anaerobic gut flora in patients with HF.

The increase in biofilm bacteria on the luminal side of the gut wall seems to be an initial local mucosal phenomenon not resulting in changes of the global composition of stool, at least in patients with HF in stable condition. The finding that stool bacteria did not correlate with the total amount of bacteria in the mucosal biofilm of the sigmoid colon indicates future studies must be undertaken on samples of mucosal biofilm.

**GI Symptoms.** Consequences of reduced blood flow do not seem to be restricted to the mucosal biofilm, as the increased GI symptoms described here suggest motor dysfunction of the intestine ([Central Illustration](#)). As of now, the precise pathophysiological basis of the symptoms of burping, flatulence, sensation of repletion, and intestinal murmur is not yet known, although a disturbance in motor patterns is a possible explanation. Strictly anaerobic *E. rectale*, a bacterial species we found to be higher in proportion at the surface of the mucus membrane in the congestive HF group, is known to produce high amounts of hydrogen gas and therefore may contribute to the increase in intestinal symptoms such as flatulence and intestinal murmurs in patients with HF. The fact that a higher proportion of juxtamucosal *E. rectale* in patients with HF was correlated with lower systolic flow in the IMA supplying the sigmoid colon suggests that reduced intestinal blood flow in patients with HF may contribute to a consecutive increase in juxtamucosal bacteria, thereby promoting intestinal symptoms ([Central Illustration](#)).

It cannot be completely ruled out that influences of long-term medications or a diet rich in carbohydrates and fibers contribute to these symptoms in patients with HF, though we have no evidence that patients with HF had diets higher in fiber than controls. However, the fact that lower CT blood flow was correlated with abdominal discomfort suggests that the GI symptoms may furthermore be due to motor defects in the gut secondary to ischemia.

Altered arterial intestinal blood flow has not been directly described in patients with chronic HF in stable condition. Intramucosal acidosis occurs in about 50% of patients with circulatory failure (16-18), pointing indirectly to an inadequate oxygen supply and intestinal ischemia (19). The present findings of

| TABLE 5 | Logistic Regression Model With Presence of Cachexia Serving as the Dependent Variable |
|------------------------|-----------------------------------|-----------------|-----------------|
| **Dependent Variable** | **Univariate OR** | **95% CI** | **p Value** |
| Age, per 1-yr increase | 0.98 | 0.92-1.05 | 0.50 |
| Female | 2.30 | 0.26-20.16 | 0.50 |
| NYHA functional class, per 1-class increase | 4.80 | 1.32-17.53 | 0.02 |
| LVEF, per 1% increase | 0.89 | 0.81-0.97 | 0.01 |
| Intestinal blood flow | | | |
| CT, per log Fmean systolic/SD | 0.324 | 0.129-0.815 | 0.017 |
| SMA, per log Fmean systolic/SD | 0.361 | 0.174-0.751 | 0.006 |
| IMA, per log Fmean systolic/SD | 0.519 | 0.250-1.078 | 0.079 |
| Pro-ANP, per log nmol/l/SD | 5.448 | 1.704-17.417 | 0.004 |
| Arm resting blood flow, per ml/100 ml/min | 0.97 | 0.68-1.39 | 0.90 |
| Bowel wall thickness, per 1-mm increase | | | |
| Sigmoid colon | 0.89 | 0.41-1.92 | 0.80 |
| Descending colon | 1.10 | 0.44-2.75 | 0.80 |
| Transverse colon | 0.69 | 0.17-2.88 | 0.60 |
| Ascending colon | 0.89 | 0.26-3.00 | 0.80 |
| Terminal ileum | 1.01 | 0.17-5.90 | 0.90 |

CI = confidence interval; LVEF = left ventricular ejection fraction; OR = odds ratio; other abbreviations as in Tables 1 and 2.
diminished mean and peak systolic resting intestinal blood flow are likely to cause decreased oxygen supply, and this latent intestinal ischemia thereby challenges mucosal barrier integrity.

**INTERACTION BETWEEN MUCOSAL INTESTINAL BACTERIA AND THE IMMUNE SYSTEM.** The intestine investigated in this study is a highly sensitive region, because the bowel wall establishes the barrier to a huge amount of bacteria that are potentially immunogenic to the host when entering the circulation. As a potential result, patients with chronic HF have been reported to display higher blood concentrations of IgA–anti-Enterobacteriaceae endotoxin compared with controls (3), reflecting higher endotoxin bioactivity and mucosal interaction in patients.

Higher endotoxin (LPS) concentrations have been found in the hepatic veins compared with the left ventricle during acute HF, suggestive of bacterial translocation from the gut into the systemic circulation (20). Therefore, the intestine is a very likely reason for triggering IgA antibodies against LPS.

Higher endotoxin concentrations have been found in the hepatic veins compared with the left ventricle during acute HF, suggestive of bacterial translocation from the gut into the systemic circulation (20). Therefore, the intestine is a very likely reason for triggering IgA antibodies against LPS.

The present study shows a correlation between lower blood flow in the CT and higher systemic serum LPS IgA antibodies and an association of increased growth of juxtamucosal bacteria with a higher serum concentration of IgA anti-LPS in patients with HF. Above a certain threshold, the more bacteria there are in the biofilm, the higher the LPS antibodies. This finding points to an interaction between mucosal intestinal bacteria and the immune system (Central Illustration) in patients with HF in stable condition that may contribute to the prognostically relevant systemic inflammation in HF.

However, the extent of contribution to the systemic increase in proinflammatory mediators cannot be concluded from this study.

**BOWEL WALL THICKNESS.** Reduced arterial intestinal blood flow in patients is in accord with greater bowel wall thickness of both the small and large intestines, suggestive of bowel wall edema due to hemodynamic perturbations. Increased bowel wall thickness is a frequent finding in various conditions, such as acute ischemic colitis (21), inflammatory bowel disease (22), and food hypersensitivity (23). The finding of increased bowel wall thickness was previously described in 22 patients with chronic stable HF. In this study of 65 patients, we were able to confirm this finding of the thickened bowel wall in a larger cohort and to investigate its relation to the arterial perfusion in the corresponding intestinal vessels and, furthermore, to intestinal symptoms in HF. There was no direct correlation of diminished arterial blood supply with the extension of swelling of the intestinal wall, which points to cofactors, such as venous congestion that may further influence the degree of bowel wall edema.
Greater bowel wall thickness of the sigmoid and descending colon was associated with increased intestinal murmurs, indicating a contribution of swelling of the intestine to intestinal symptoms.

**CORRELATION OF INTESTINAL BLOOD FLOW WITH FOREARM BLOOD FLOW.** Impaired vasodilator capacity due to endothelial dysfunction may further aggravate this critical perfusion of the intestinal mucosa. Impaired vasodilator capacity was indicated in our patients by lower forearm post-ischemic flow. Higher blood midregional proadrenomedullin levels in patients further underscore the suspected endothelial dysfunction. However, there was no correlation of this reduced arterial forearm blood flow with the reduced intestinal flow, reflecting adaptive mechanisms in the different zones within the vascular bed. Arm blood pressure was not correlated with reduced intestinal flow either. This indicates that both arm blood flow and blood pressure are insufficient markers of decreased intestinal flow and points to a need for the assessment of intestinal flow in patients with HF.

**CARDIAC CACHEXIA.** Cachexia is a serious complication of advanced HF and among the most important predictors of prognosis. Cachectic patients who had more severe HF in this study, as reflected by higher blood concentration of pro-ANP, showed both more severe nausea or vomiting and burping and the lowest intestinal blood flow. In multivariate regression analysis with limited statistical power, the lower intestinal blood flow in the SMA and the CT and the trend toward lower intestinal blood flow in the IMA were correlates of the presence of cardiac cachexia. This suggests a contribution of restricted arterial intestinal blood flow to cardiac cachexia (Central Illustration).

**STUDY LIMITATIONS.** The number of participants in this study is limited. Larger studies are required to provide further insight into intestinal alterations in heart failure.

**CONCLUSIONS**

Intestinal arterial blood flow is reduced in patients with chronic HF, which may contribute to increased growth of juxtamucosal bacteria, inflammation, GI symptoms, and cardiac cachexia complicating advanced stages of HF.

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**PERSPECTIVES**

**COMPETENCY IN MEDICAL KNOWLEDGE:** Chronic HF is associated with low-grade systemic inflammation and anabolic-catabolic imbalance that leads to cardiac cachexia at the terminal stage of the disease. Patients with chronic HF develop reduced intestinal blood flow and bowel wall edema that impede absorptive function and permit bacterial overgrowth in the mucus layer adjacent to the apical surface of the colonic mucosa.

**TRANSLATIONAL OUTLOOK:** Research is needed to determine whether interventions that specially increase mesenteric blood flow inhibit the growth of juxtamucosal bacteria, reduce inflammation and GI symptoms, and ameliorate cardiac cachexia in patients with advanced HF.

**REFERENCES**


KEY WORDS bacteria, gastrointestinal symptoms, heart failure, intestinal blood flow