Title:

Intestinal blood flow in patients with chronic heart failure – a link with bacterial growth, gastrointestinal symptoms and cachexia

Short Title:

Intestinal blood flow in chronic heart failure.

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Abstract:

Background: We hypothesize that blood flow in the intestinal arteries is reduced in patients with stable HF and relates to gastrointestinal symptoms (GIS) and cardiac cachexia.

Objectives: To measure arterial intestinal blood flow (BF) and its role for juxtamucosal bacterial growth, GIS and cachexia in heart failure (HF).

Methods: We investigated 65 patients and 25 controls. Twelve patients were cachectic. Intestinal BF and bowel wall thickness (BWT) were measured using ultrasound. GIS 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-(LPS)-antibodies were measured.

Results: Patients showed a 31-45% reduced mean systolic BF in the superior and inferior mesenteric arteries (SMA and IMA) and celiac trunk (CT) compared to controls (all $p<0.004$). Cachectic patients had lowest BF ($p=0.0007$). Lower BF in SMA and CT correlated with HF severity (all $p<0.04$). Patients had more feelings of repletion, flatulences, intestinal murmurs and burping (all $p<0.04$). Burping and nauseas/vomiting were most severe in cachexia ($p<0.05$).

Patients with lower CT BF had more abdominal discomfort and immunoglobulin A-anti-LPS ($r=0.76$, $p<0.02$). Anti-LPS-response correlated with increased growth of juxtamucosal and not stool bacteria. Patients with intestinal murmurs had greater BWT of sigmoid/descending colon suggestive for edema contributing to GIS ($p<0.05$).

In multivariable regression, lower BF in SMA, CT (p<0.04) and IMA (p=0.056) correlated with the presence of cardiac cachexia.

Conclusions: Intestinal BF is reduced in HF. This may contribute to juxtamucosal bacterial growth and GIS in advanced HF complicated by cachexia.

Key words

heart failure, intestinal blood flow, bacteria, gastrointestinal symptoms

Abbreviations

FISH	Fluorescence In Situ Hybridisation
HF	Heart Failure
LPS	Lipopolysaccharide
NYHA	New York Heart Association Classification
peak VO$_2$	peak oxygen consumption
SD	Standard Deviation
IQR	Interquartile Range

Introduction

Chronic HF is a multisystem disease and along with increased sympathetic tone and chronic low-grade systemic inflammation there is an anabolic/catabolic inbalance 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 chronic HF ranges from 16–42% (2).

The role of the gut in the pathophysiology of chronic HF has only recently started to be investigated in detail. There is increasing evidence for the gut playing an important pathophysiological role for malnutrition and cachexia in chronic HF. Significant morphological and functional alterations of the intestine in chronic HF have been previously shown (3). Patients display a thickened bowel wall, suggestive for bowel wall edema, an intestinal barrier dysfunction and a 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 an increased permeability of both small and large intestine have been demonstrated. A 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 symptoms in cachectic and non-cachectic patients with HF have not been analyzed yet.

We here hypothesize that (1) arterial blood flow in the main intestinal arteries is reduced in patients with stable compensated HF and (2) relates to possible gastrointestinal symptoms and to the (3) prevalence of cardiac cachexia.

Methods

Patients.

We prospectively studied intestinal blood flow in 65 patients with chronic HF and 25 control subjects (for demographic and clinical details see 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 independently of their absolute BMI if they had experienced a non edematous, non intentional weight loss of ≥ 5% within the previous 6-12 months (6). All patients were clinically stable (NYHA 2.5 ± 0.1) and received unchanged medication for at least four weeks prior to assessments. Patients were allowed to take aspirin 100 mg once daily, but not other non-steroidal anti-inflammatory drugs, steroid hormones, or antibiotics within at least 4 weeks prior to being studied. In HF patients, medication consisted of angiotensin converting enzyme (ACE) inhibitors (71%), angiotensin receptor antagonists (32 %), beta-blockers (88 %), aldosterone receptor antagonists (52 %), other diuretics (72 %), glycosides (20 %) and statins (80 %) in varying combinations. None of the control subjects were taking any cardiovascular medication except for calcium channel blocker in one subject and ACE 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 history of autoimmune disorders were excluded. None of the subjects had any 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 following standard procedures. LVEF was measured using biplane Simpson's technique. All subjects underwent a symptom-limited treadmill exercise testing (instantaneous breath by breath method) using the modified Naughton protocol (Innocor™ system; Innovision, Odense, Denmark and treadmill HP cosmos®; HP Cosmos sports & medical GmbH, Nussdorf-Traunstein, Germany). The following variables were measured: peak oxygen consumption (peak VO_2), total exercise time, ventilatory response to exercise (VE/VCO_2-slope), anaerobic threshold, peak heart rate (beats per minute), and peak systolic and diastolic blood pressures.

Blood flow velocities in the celiac trunk (CT), superior mesenteric artery (SMA) and the inferior mesenteric artery (IMA) were measured by high resolution duplex ultrasonography (8-5-MHz vector-array transducer HDI 5000, Philips, Belgium) by a single observer (JB). Blood flow measurements were performed three times in each patient and the mean of three measurements used for statistical analysis. In brief, the investigator measured the diameter of the artery during systole from magnified B-mode longitudinal images of the artery. Blood flow (ml/min) measurements were calculated using the formula: $\pi \times r^2 \times TAMV \times 60$, where r is the radius of the artery and TAMV is the time-averaged mean velocity as previously described (7). The angle between the doppler and the mesenteric 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 20 controls.

Transcutaneous abdominal sonography (12-MHz linear-array transducer, HDI 5000, Philips, Belgium) was used to measure bowel wall thickness in the middle segment of the sigmoid (in subjects 1 to 65), descending, transverse and ascending colon

(subject 7 to 65). Measurement of the terminal ileum (subject 7 to 65) was performed 5 cm proximal to ileocecal valve. Due to obesity, the sigmoid colon was not assessed in three subjects; transverse colon was not assessed in three subjects, the ascending colon in one subject and the terminal ileum in one 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 three times at different positions of the intestinal wall and the mean was calculated.

All sonographic recordings were performed in a standardized way, and readings were analysed by the same experienced physician (JB), who was blinded as to the subjects' study group. 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, USA) system in 55 patients and 17 control subjects, as previously described (8). The subjects rested in a supine position for at least 15 minutes, and forearm blood flow was determined using a mercury-in-silastic strain gauge (Hokanson Inc., Bellevue, USA). A cuff around the right upper arm was connected to a rapid inflation pump with an air source and solenoid valves, used to inflate and deflate the occlusion cuff rapidly to the required pressure of 40 mmHg. To measure the peak forearm blood flow, the cuff was inflated to suprasystolic pressure (30 mm Hg above systolic blood pressure) for 3 minutes. Blood flow was measured after release of the cuff in ten

second intervals for at least two minutes. The highest flow results were considered to represent peak forearm blood flow.

Results for plethysmography are given in milliliters per 100 mL tissue per minute (mL/100 mL/min). All the above assessments were performed in a dedicated quiet room between 9 a.m. and 10 a.m. to prevent data bias from noise and circadian rhythms.

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

Mucosal bacterial biofilm was assessed by Fluorescence in situ hybridization (FISH) in biopsies taken during sigmoidoscopy in 22 patients with chronic HF and 20 control subjects as previously described (3) according to the 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 FISH and epifluorescence microscopy in blinded faecal samples as previously described (11). In 13 controls (subject 10-22) and 12 patients (subject 9-20) intestinal blood flow was assessed in that group. Blood immunoglobulin A-anti-Lipopolysaccharide (LPS) by were assessed in these patients and controls by ELISA (12, 13).

In 27 patients and 18 control subjects, C-reactive protein was measured. Plasma concentrations of mid-regional pro-adrenomedullin and mid-regional pro-atrial natriuretic peptide 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 5.0 software (SAS Institute Inc., Cary, USA). Normality of distribution was assessed using the Kolmogorov-Smirnov test. Results are reported as mean ± SD (indicating normal distribution of data; statistical comparisons were made using unpaired t-test) or median (interquartile range) (indicating non-normal distribution of data; statistical comparisons were made using Mann-Whitney-U-test). Analysis of variance (ANOVA), Student's unpaired *t*-test, Fisher's exact test, Pearson's simple regression, and logistic regression were used as appropriate. Non-normally distributed data were common-log-transformed to achieve a normal distribution where indicated. Parameters that were significantly different between non-cachectic and cachectic patients were tested using multivariable regression analysis. Variables of interest were adjusted for age and gender as indicated. A two-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 gender (Table 1). As expected, patients had a lower ejection fraction and peak VO_2. Patients with cardiac cachexia had a lower BMI and were haemodynamically more severely compromised as reflected by lower peak VO_2, lower LVEF and higher blood levels of proANP compared to patients without cachexia (Table 1). Patients with heart failure had higher blood concentration of white blood cells as compared to control subjects (Table 1). Serum concentrations of C-reactive protein were higher in patients compared to controls with highest levels in cachectic patients compared to non cachectic patients (Table 1).

Intestinal blood flow

Systolic blood flow

Patients with chronic HF had a lower mean and peak systolic blood flow in SMA, IMA and CT as compared to control subjects (Table 2). The lowest systolic blood flow in SMA, IMA and CT was in patients with cardiac cachexia with a flow reduction by 52%, 50% and 53% compared to control subjects. Lower mean systolic flow in both SMA and CT correlated with severity of heart failure in patients according to higher blood pro ANP (Figure 1a and b).

We did not detect any stenoses of the mesenteric arteries or celiac trunk in either patients or controls.

Diastolic blood flow

Mean diastolic blood flow was lower In CT and IMA in patients compared to controls (Table 2). There was a trend for a lower diastolic flow in CT in patients with more

severe HF according to blood pro ANP (r=0.25; p=0.096). Lower maximal diastolic flow and in trend lower minimal diastolic flow in SMA correlated with severity of HF in patients according to higher blood proANP (r=0.3; p<0.03, r=0.25; p=0.077).

Correlation of intestinal blood flow with forearm resting and peak post-ischemic blood flow and arm systolic blood pressure

In patients with HF, both resting arterial limb blood flow (arm) and peak post-ischemic flow are reduced, the latter indicating impaired vasodilator capacity due to endothelial dysfunction as compared to controls (Table 2). Higher blood mid-regional 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 reflecting adaptive mechanisms in the different zones within the vascular bed (all p>0.12). Arm blood pressure did not correlate with mean intestinal blood flow either, indicating that arm blood pressure is an insufficient marker for decreased intestinal flow (all p>0.4).

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 compared to control subjects (all p<0.01, Table 5). However, bowel wall thickness did not correlate with patients' edema status at lower legs and lower arterial intestinal blood flow.

Gastrointestinal symptoms

Patients compared to controls complained more often feelings of repletion (34/58 vs. 4/18, p=0.014), burping (15/59 vs. 0/18, p=0.016), flatulence (43/59 vs. 8/18, p=0.03) and murmurs from the intestine (34/59 vs. 5/18, p=0.027). In cachectic vs. non cachectic patients, burping was more often and more severe (5/11 vs. 8/46, p<0.05 and 1.8±0.4 vs. 1.3±0.3, p=0.01) and murmurs from the intestine were in trend more severe (p<0.08). Nauseas/vomiting, if present, were more severe, too (2.25±0.5 vs. 1.1±0.1, p<0.02).

In those patients with abdominal discomfort, we found a lower mean systolic flow in celiac trunk (274±36 vs. 480±38 mL/min, p=0.02). In univariate regression, both high NYHA class and low CT flow correlated with abdominal discomfort (all p<0.04).

Patients with intestinal murmurs had a greater bowel wall thickness of the sigmoid and descending colon (0.23±0.017 vs. 0.18±0.01 cm, p=0.03 and 0.20±0.014 vs. 0.16±0.01 cm, p=0.04) and a similar bowel wall thickness of terminal ileum and the ascending colon (all p>0.2).

There was a consistent trend for increased heartburn, reflux and constipation in patients with chronic HF compared to controls (21/59 vs. 2/18, p=0.075, 21/59 vs. 2/18, p=0.075 and 15/58 vs. 1/18, p=0.097). However, pain in the upper abdomen (14/58 vs. 2/18 individuals, p=0.3), defecation frequency (2/18 vs. 13/56, p=0.3) and nausea/vomiting (13/59 vs. 2/18 individuals, p=0.5) were similarly reported in patients vs. controls.

Stool bacteria

Amount of bacteria in stool

Concentrations and proportions of both anaerobic and aerobic bacteria in the stool were similar in patients compared to controls (Table 4).

Relation of stool bacteria to increased specific bacteria in mucosal biofilm

The number and composition of stool bacteria did neither reflect the higher concentration of mostly anaerobic bacteria in the mucosal biofilm of patients nor the increased proportion of strictly anaerobic *Eubacterium rectale (EREC)*, *bacteroides/prevotella* and *Fusobacterium prausnitzii* in biofilm of patients (r=0.4 and 0.3, p=0.12, p>0.17, p>0.5 and p>0.37, respectively). This points to an increase in bacteria restricted to the juxtamucosal zone.

Correlation of intestinal blood flow with stool and juxtamucosal bacteria

The concentration of total stool bacteria, aerobes, gram-negative aerobes, anaerobes, lactobacilli, enterococci, bacteroides, bifidobacteria or yeast in stool were not associated with lower intestinal blood flow (all p>0.1).

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

Correlation of stool and juxtamucosal bacteria with serum IgA-LPS-antibodies

In 13/22 patients with a high concentration of juxtamucosal bacteria of $\geq 10^8$/mL there was a strong trend for an association of increased growth of juxtamucosal bacteria

and serum concentrations of immunoglobulin A-anti-LPS (p=0.05, r=0.55, Figure 2). Luminal stool bacteria did not correlate with serum IgA-LPS-antibodies.

Correlation of intestinal blood flow with inflammatory markers in blood

Lower blood flow in CT correlated with higher serum IgA-LPS-antibodies (Figure 3, r=0.76, p<0.02) and with higher serum C-reactive protein (r=0.61, p=0.003, Figure 4). Lower intestinal blood flow in SMA was associated with higher serum C-reactive protein in patients, too (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 CT or SMA and in trend IMA were correlated with the presence of cachexia (Table 3). These correlations of lower LVEF, higher blood pro ANP, higher NYHA class, lower intestinal flow in CT or SMA with the presence of cachexia remained significant after adjustment for age and gender. (p<0.02, p<0.003, p<0.008, p<0.03 or p<0.01, respectively).

In contrast, age, sex, arm resting blood flow and bowel wall thickness were not correlated with the presence of cachexia serving as the dependent variable (Table 3).

In multivariate regression analysis, lower intestinal blood flow in SMA, CT (all p<0.04) or in trend lower intestinal blood flow in IMA (p<0.058) were independently associated with the presence of cardiac cachexia in distinct models each adjusted for NYHA, LVEF and pro ANP. The probability to be cachectic for intestinal flows each adjusted for NYHA, LVEF and pro ANP was 0.1 for increase in CT flow, 0.2 for

increase in SMA flow or 0.4 for increase in IMA flow (OR 0.1, 95% CI 0.02-0.8; OR 0.2, 95% CI 0.04-0.8 or OR 0.4, 95% CI 0.1-1.0, respectively).

There was a trend for higher NYHA class to be independently associated with the presence of cardiac cachexia in models including either CT or SMA flow ($p < 0.097$).

After adjustment of intestinal blood flow for age and gender, lower intestinal blood flow in CT or SMA remained correlated with the presence of cachexia ($p < 0.03$ or $p < 0.01$, respectively).

Discussion

This is the first study to evaluate blood flow in all three arteries supplying stomach, small and large intestine in patients with and without cardiac cachexia.

Endothelial function of the forearm vessels revealed both a lower resting blood flow and a lower flow mediated flow in patients with HF compared to control subjects.

Higher concentration of juxtamucosal anaerobic bacteria in the sigmoid colon of the patients correlated with the higher systemic concentration of anti-LPS IgA antibodies. Furthermore, there was an increase in GI symptoms in patients compared to controls. Patients complained more often of feelings of repletion, burping, flatulences and murmurs from the intestine. Symptoms were most pronounced in cachectic patients. Patients with abdominal discomfort had a lower mean systolic flow in celiac trunk. Impaired intestinal blood flow correlated with severity of HF and was in accord with greater thickness of the bowel wall in patients with chronic HF, suggestive of bowel wall edema. Patients with intestinal murmurs had 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 can be ascribed to changes in intestinal motor function.

One explanation for the increased number of bacteria in the mucosal biofilm is that entirely new phylotypes of bacteria are present in patients with HF. Some differences were found, e.g. a greater proportion of patients with chronic HF had Bacteroides/Prevotella, Eubacterium rectale group (EREC), Fusobacterium Prausnitzii (3), all representing a standing 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 HF patients in such a way that the growth of bacteria is encouraged. In particular, the higher occurrence rate of the strictly anaerobic *Eubacterium rectale* group and the strictly anaerobic *Fusobacterium prausnitzii* in intestinal biofilm indicates better conditions for these specific anaerobes directly at the surface of the mucus membrane in 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 IMA supplying sigmoid with the higher proportion of juxtamucosal strictly anaerobic EREC 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 HF patients.

Consequences of reduced blood flow do not seem to be restricted to the mucosal biofilm as the increased GI symptoms we describe here suggest a motor dysfunction of the intestine. As of now, the precise pathophysiological basis of the symptoms of burping, flatulence, sensation of repletion and borborygmi is not yet known a disturbance of motor pattern is one possible explanation. Strictly anaerobic EREC – a bacterial species we found to be higher in proportion at the surface of mucus membrane in CHF 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 CHF. The fact that higher proportion of juxtamucosal EREC in CHF correlated with lower systolic flow in IMA supplying the sigmoid suggests that reduced intestinal blood flow in heart failure may contribute to a consecutive increase in juxtamucosal bacteria thereby promoting intestinal symptoms.

It can not completely ruled out that influences of long-term medication or a diet rich in carbohydrates and fibers contribute to these symptoms in patients with HF though we have no evidence that HF patients have a diet higher in fibre than controls.

However, the fact that lower CT blood flow 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 stable patients with chronic HF. Intramucosal acidosis occurs in about 50% of patients with circulatory failure (16,17,18) pointing indirectly to an inadequate oxygen supply and intestinal ischemia (19). An increase in gastric intramucosal carbon dioxide pressure has been documented in recompensated patients with chronic HF even at low levels of exercise such as 25 Watt (20). The present findings of a diminished mean and peak systolic resting intestinal blood flow are likely to be causal for a decreased oxygen supply and this latent intestinal ischemia thereby challenging mucosal barrier integrity.

The intestine investigated in this study is a highly sensitive region due to the fact that 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 of this, patients with chronic HF have been reported to display higher blood concentrations immunoglobulin A (IgA)-anti- E.coli J5 endotoxin compared to controls (3) reflecting a higher endotoxin bioactivity and mucosal interaction in patients. Niebauer et al. have found higher LPS concentrations in hepatic veins as compared to the left ventricle during acute HF suggestive of bacterial translocation from the gut into the systemic circulation (21). Therefore, the intestine is a very likely reason for triggering IgA-antibodies against LPS.

The present study shows a correlation of lower blood flow in CT with higher systemic serum LPS IgA antibodies and an association of an 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 points to an interaction between mucosal intestinal bacteria and patients' immune system in stable HF that may contribute to the prognostically relevant systemic inflammation in heart failure.

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

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 stable patients with HF. The finding that stool bacteria did not correlate with total amount of bacteria in mucosal biofilm of sigmoid colon points to that future studies must be undertaken on samples of mucosal biofilm.

Reduced arterial intestinal blood flow in patients is in accord with greater bowel wall thickness of both small and large intestine suggestive for bowel wall edema due to hemodynamic perturbations. An increased bowel wall thickness is a frequent finding in various conditions, such as acute ischemic colitis (22), inflammatory bowel disease

(23), and food hypersensitivity (24). The finding of an increased bowel wall thickness we previously described in 22 patients with chronic stable HF. In this current study on 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 heart failure. There was no direct correlation of diminished arterial blood supply with the extend of swelling of the intestinal wall. This 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.

Impaired vasodilator capacity due to endothelial dysfunction may further aggravate this critical perfusion of the intestinal mucosa. Higher blood mid-regional pro-adrenomedullin levels in patients further underscore the suspected endothelial dysfunction. Impaired vasodilator capacity is indicated in our patients by the lower forearm post-ischaemic flow. However, there was no correlation of this reduced resting arterial limb blood flow (arm) or peak post-ischemic arm flow or arm blood pressure with the reduced intestinal flow. This points to the need of assessment of intestinal flow in HF.

Cachexia is a serious complication of advanced HF and one of 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 nauseas/vomiting and burping and lowest intestinal blood flow. In multivariate regression analysis with limited statistical power, the lower intestinal blood flow in SMA, CT and in trend lower intestinal blood flow in IMA were correlates of the presence of cardiac cachexia. This suggests a contribution of restricted arterial

intestinal blood flow to cardiac cachexia.

Conclusion: Intestinal arterial blood flow is reduced in patients with chronic HF. This may contribute to increased growth of juxtamucosal bacteria, inflammation, gastrointestinal symptoms and cardiac cachexia complicating advanced heart failure.

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