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Intestinal fatty acid binding protein is associated with infarct size and cardiac function in acute heart failure following myocardial infarction

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► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/openhrt-2024-002868).

To cite: Nendl A, Andersen GØ, Seljeflot I, *et al*. Intestinal fatty acid binding protein is associated with infarct size and cardiac function in acute heart failure following myocardial infarction. *Open Heart* 2024;**11**:e002868. doi:10.1136/openhrt-2024-002868

Received 29 July 2024
Accepted 24 August 2024

Check for updates

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ABSTRACT

Background In acute heart failure (HF), reduced cardiac output, vasoconstriction and congestion may damage the intestinal mucosa and disrupt its barrier function. This could facilitate the leakage of bacterial products into circulation and contribute to inflammation and adverse cardiac remodelling. We aimed to investigate gut leakage markers and their associations with inflammation, infarct size and cardiac function.

Methods We examined 61 ST-elevation myocardial infarction (STEMI) patients who developed acute HF within 48 hours of successful percutaneous coronary intervention (PCI). Serial blood samples were taken to measure lipopolysaccharide (LPS), LPS-binding protein (LBP), soluble cluster of differentiation 14 (sCD14) and intestinal fatty acid binding protein (I-FABP). Cumulative areas under the curve (AUCs) from baseline to day 5 were calculated. Serial echocardiography was performed to assess left ventricular ejection fraction (LVEF), global longitudinal strain (GLS) and wall motion score index (WMSI). Single-photon emission CT (SPECT) was performed at 6 weeks to determine infarct size and LVEF.

Results I-FABP$_{AUC}$ correlated positively with infarct size (r_s=0.45, p=0.002), GLS (r_s=0.32, p=0.035) and WMSI (r_s=0.45, p=0.002) and negatively with LVEF measured by SPECT (r_s=−0.40, p=0.007) and echocardiography (r_s=−0.33, p=0.021) at 6 weeks. LPS$_{AUC}$, LBP$_{AUC}$ and sCD14$_{AUC}$ did not correlate to any cardiac function marker or infarct size. Patients, who at 6 weeks had above median GLS and WMSI, and below-median LVEF measured by SPECT, were more likely to have above median I-FABP$_{AUC}$ during admission (adjusted OR (aOR) 5.22, 95% CI 1.21 to 22.44; aOR 5.05, 95% CI 1.25 to 20.43; aOR 5.67, 95% CI 1.42 to 22.59, respectively). The same was observed for patients in the lowest quartile of LVEF measured by echocardiography (aOR 9.99, 95% CI 1.79 to 55.83) and three upper quartiles of infarct size (aOR 20.34, 95% CI 1.56 to 264.65).

Conclusions In primary PCI-treated STEMI patients with acute HF, I-FABP, a marker of intestinal epithelial damage, was associated with larger infarct size and worse cardiac function after 6 weeks.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Haemodynamic changes in acute heart failure after a myocardial infarction can damage the intestinal mucosa and disrupt its barrier function. The subsequent leakage of bacterial products into the circulation may contribute to inflammation in the heart. The inflammatory response aids in tissue repair but also contributes to further injury to the myocardium.

WHAT THIS STUDY ADDS

⇒ We found that intestinal fatty acid binding protein (I-FABP) in the acute phase of an ST-elevation myocardial infarction (STEMI) complicated by acute heart failure is associated with infarct size and several parameters of cardiac function after 6 weeks.

⇒ The relationship between I-FABP, cardiac function and infarct size is likely not mediated by the interleukin-6/C reactive protein axis.

⇒ Lipopolysaccharide (LPS) and I-FABP are elevated early in acute heart failure.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The current study highlights LPS and I-FABP as potential markers of gut involvement in new-onset acute heart failure following a STEMI. Our results suggest that gut hypoperfusion in the setting of new-onset acute heart failure after a STEMI may impact cardiac remodelling. This observation underscores the necessity for additional mechanistic studies to elucidate the underlying pathophysiological mechanisms.

INTRODUCTION

Acute heart failure (HF) is a clinical syndrome related to raised intracardiac filling pressures and/or reduced cardiac output. Patients usually display a continuum of symptoms and signs, depending on the degree of congestion and/or peripheral hypoperfusion.[1]

The development of acute HF in the setting of an acute coronary occlusion is associated with large myocardial infarctions (MI) with substantial myocardial tissue loss and a worse

prognosis.[2] The necrotic debris and ischaemic condition in the myocardium, as well as reperfusion injury, trigger an inflammatory response that aids in tissue repair but also contributes to further injury to the myocardium.[3–5] It has been proposed that persistent inflammation in acute HF may contribute to infarct expansion and adverse ventricular remodelling, ultimately leading to the poor prognosis in these patients.[5] In its most severe state, namely cardiogenic shock, the resulting hypoperfusion may potentiate the inflammatory response and increase the degree of end-organ damage, which is one of the main determinants of short-term prognosis in these patients.[6 7]

Accumulating evidence suggests a role of gut-related inflammation in various cardiovascular diseases, however, there is a scarcity of data on this phenomenon in acute HF.[8] Normally, the intestinal mucosa limits the translocation of whole bacteria or bacterial products from the gut into systemic circulation. With a breakdown in this barrier function, such as with hypoperfusion or congestion, lipopolysaccharide (LPS) and other bacterial products might leak into the circulation.[9] The presence of LPS in the circulation is referred to as endotoxaemia. In the blood, LPS interacts with LPS-binding protein (LBP) and cluster of differentiation 14 (CD14), which in turn activates the Toll-like receptor 4 (TLR4) and triggers downstream inflammatory pathways.[10]

Intestinal fatty acid binding protein (I-FABP) is an intracellular protein most abundant in enterocytes of the small intestine.[11] When the gut mucosa is injured, I-FABP leaks from enterocytes into the systemic circulation and can be measured in the blood as a marker of intestinal epithelial cell damage.[12]

We hypothesised that (1) gut leakage-related markers may be used as early markers of gut involvement in acute HF through damage of the gut wall mucosa and increased intestinal permeability and that (2) gut leakage markers are associated with systemic inflammation, infarct size and cardiac function in patients with acute HF complicating ST-elevation myocardial infarction (STEMI).

Thus, the aims of the present study were (1) to examine temporal profiles of gut leakage markers (LPS, LBP, soluble CD14 (sCD14) and I-FABP) after a primary percutaneous coronary intervention (PCI)-treated STEMI complicated with acute HF and (2) to examine whether gut leakage markers are associated with systemic inflammation, infarct size and cardiac function assessed by echocardiography, single-photon emission CT (SPECT) and cardiac biomarkers.

MATERIALS AND METHODS

Study design

We used data from the LEAF (LEvosimendan in Acute heart Failure following myocardial infarction) trial (NCT00324766), a randomised, double-blind, placebo-controlled, single-centre, parallel-group trial conducted at Oslo University Hospital, Ullevål in Oslo, Norway between April 2006 and May 2011. A detailed description of the study design and main results of the trial have previously been published.[13 14]

Briefly, 61 adults with acute STEMI treated with primary PCI who developed clinical signs and symptoms of acute HF within 48 hours of PCI were included. Additional inclusion criteria were echocardiographic signs of decreased wall motion in at least three of the 16 segments of the left ventricle and successful revascularisation of the infarct-related artery. Additional criteria in the subgroup of patients with cardiogenic shock included both of the following: (1) systolic blood pressure (SBP) <90 mm Hg or SBP between 90 and 100 mm Hg in spite of inotropic support and (2) signs of organ hypoperfusion. Median time from PCI to inclusion was 22 hours. The primary endpoint was a change in the wall motion score index (WMSI) from baseline to day 5. A detailed list of inclusion and exclusion criteria has been previously published.[13]

Blood sampling

Blood samples were taken at the time of inclusion (baseline), after 25 hours (day 1), day 2, day 5 and at week 6 for routine analyses and for determination of LPS, LBP, sCD14, I-FABP, interleukin-6 (IL-6) and C reactive protein (CRP). Blood without additives was separated within 1 hour of sampling by centrifugation at room temperature at 2500×G for 10 min, and blood containing EDTA was separated within 1 hour of sampling by centrifugation at 4°C at 2500×G for 20 min. All blood samples were stored at −80°C until analysed.

LPS levels were analysed using the Kinetic Chromogenic limulus amoebocyte lysate (LAL) assay (Lonza BioScience, Basel, Switzerland). Commercially available ELISAs were used for sCD14, IL-6 (R&D Systems Europe, Abingdon, Oxford, UK), LBP and I-FABP (Hycult Biotech, Uden, the Netherlands) and high-sensitivity CRP (DRG instruments, Marburg/Lahn, Germany). The interassay coefficients of variation were LPS 8.7%, sCD14 6.4%, IL-6 10.5%, LBP 12.3%, I-FABP 11.2% and high-sensitivity CRP <5%.

Echocardiography

Echocardiography was performed at inclusion, after 25 hours, on day 5 and at week 6. Examinations were performed by two experienced echocardiographers and a single observer analysed all images. The echocardiography devices used were digital ultrasonic device systems (Vivid I or Vivid 7, GE Vingmed Ultrasound, Horten, Norway). Images were analysed using dedicated software (Echopac, GE Vingmed Ultrasound). In the present investigation, we measured WMSI, left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS) as measures of contractility and cardiac function,[15] and E/e' ratio as a measure of left ventricular filling pressure.[16] Note that GLS is given as a negative value, representing the percentage of deformation or shortening; therefore, less negative GLS (closer to zero) means worse cardiac function.

Measurement of infarct size

ECG-gated SPECT with 99m-tetrofosmin was performed 6 weeks after inclusion to determine LVEF and infarct size, expressed as a percentage of left ventricular mass.

Statistics

We used non-parametric statistics, as most variables were not normally distributed. Bivariate Spearman's correlation was used for simple correlations. Mann-Whitney U-test was applied for between-group differences. Friedman test was used to check for differences in the levels of gut leakage markers across repeated samples, and Wilcoxon signed-rank test was performed to assess within-group changes from baseline to 25 hours (day 1), day 2, day 5 and week 6 in cases where Friedman's test showed statistically significant changes. To estimate the cumulative impact of each gut leakage marker, we determined area under the curve (AUC) from baseline to day 5 using the trapezoidal rule. The AUCs were determined for 53 patients (47 without shock and 6 with shock) due to missing blood samples on day 2. Binomial logistic regression was used to further explore the relationship between gut leakage markers and selected echocardiographic and SPECT parameters. I-FABP$_{AUC}$ was categorised into quartiles and dichotomised into high and low levels based on natural cut-offs, as were echocardiographic and SPECT parameters. For the multiple regression analyses, we identified age and creatinine at baseline as relevant covariates, as they are known to influence levels of gut leakage markers.[17] Sex was not included as a covariate, as there were no significant correlations with any gut leakage marker AUCs or any of the parameters of cardiac function and infarct size. Peak troponin T (TnT) was included due to significant correlations with LVEF, GLS, WMSI and infarct size at 6 weeks (p=0.03–0.11). A significance level of 0.05 was considered statistically significant. When testing for confounders in logistic regression models, a significance level of 0.2 was used. STATA-SE V.17.0 was used for all statistical analyses. The corresponding author had full access to all the data in the study and took the responsibility for its integrity and the data analysis.

Table 1 Baseline characteristics of LEAF trial participants

Characteristic	Whole population n=61
Age, years	65 (56, 74)
Female sex	18 (30%)
Hypertension	21 (34%)
Dyslipidaemia	13 (21%)
Diabetes mellitus	6 (10%)
Current smokers	22 (26%)
Previous myocardial infarction	11 (18%)
Chronic heart failure	1 (2%)
Cardiogenic shock	9 (15%)
Intra-aortic balloon pump at inclusion	17 (28%)
Hours from PCI to baseline	22 (14, 19)
Wall motion score index	1.97 (1.83, 2.16)
Left ventricular ejection fraction, %	42 (37, 47)
Global longitudinal strain, %	–8.7 (–9.7, –7.2)
E/e' ratio	14.9 (11.6, 19.3)
NT-proBNP, pg/mL	434 (268, 745)
Peak troponin T, ng/L	12 730 (7964, 16 990)
Creatinine, µmol/L	82 (68, 95)
CRP, mg/L	54 (31, 110)
IL-6, pg/mL	27.4 (31.3, 33.7)
LPS, pg/mL	60 (52, 79)
LBP, ng/mL	32 067 (24 937, 38 616)
sCD14, ng/mL	1843 (1613, 2145)
I-FABP, pg/mL	621 (325, 1261)

Continuous variables are given as median (quartile 1, quartile 3). Proportions are given as n (%).
CRP, C-reactive protein; I-FABP, intestinal fatty acid binding protein; LBP, lipopolysaccharide-binding protein; LEAF, LEvosimendan in Acute heart Failure following myocardial infarction; LPS, lipopolysaccharide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCI, percutaneous coronary intervention; sCD14, soluble cluster of differentiation 14.

RESULTS

Baseline characteristics

The population was predominantly male (70%) and median age was 65 years (table 1). Of the 61 patients in total, 9 patients developed cardiogenic shock. Only a single patient had a diagnosis of chronic HF prior to inclusion. The LEAF study randomised patients to treatment with either levosimendan or placebo. Therefore, we tested for differences in gut leakage markers between the two groups at all time points. As the only significant difference between the groups was in I-FABP levels on day 1 (p=0.03), we did not perform any further analyses with respect to the intervention groups (online supplemental file 1) and further analyses are based on the total population.

Temporal profiles of gut leakage markers

Temporal profiles of the selected gut leakage markers are shown in figure 1. In short, I-FABP levels peaked early, followed by a decrease by day 2. Notably, high levels of LPS were present both at baseline and day 5. LBP reached its peak levels on day 2 and sCD14 on day 5.

We also examined the gut leakage markers separately in patients with (n=9) and without (n=52) cardiogenic shock (figure 2). The most striking profile difference was the higher baseline level of I-FABP in the shock group. However, due to the low number of

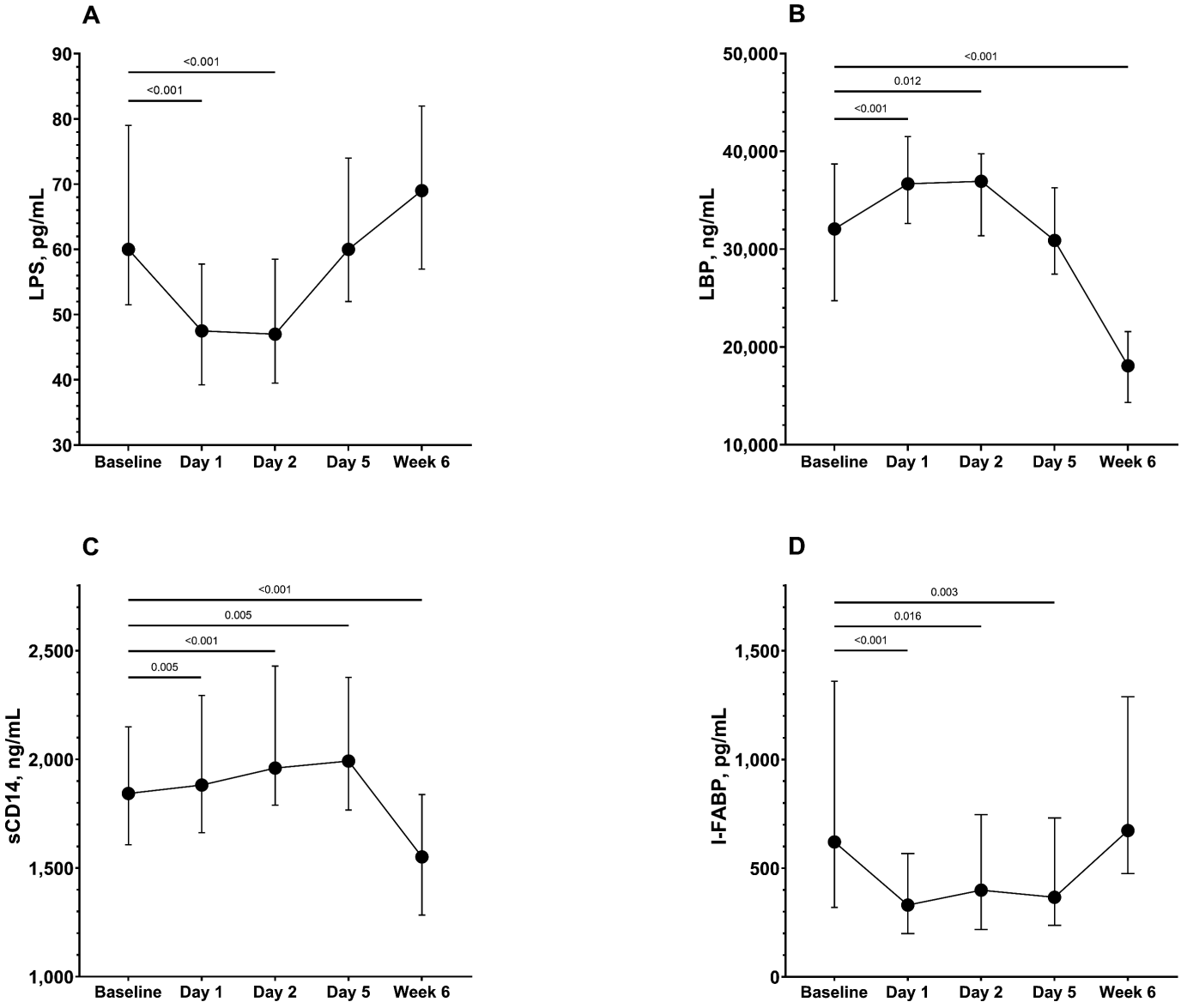

Figure 1 Time profiles of gut leakage markers lipopolysaccharide (A), lipopolysaccharide-binding protein (B), soluble cluster of differentiation 14 and intestinal fatty acid binding protein (D). Circles represent median values and whiskers show IQRs. Significant differences from baseline were obtained with Wilcoxon signed-rank tests and are represented with a line and a p-value. I-FABP, intestinal fatty acid binding protein; LBP, lipopolysaccharide-binding protein; LPS, lipopolysaccharide; sCD14, soluble cluster of differentiation 14.

patients with cardiogenic shock, all further analyses were performed in the population as a whole.

Gut leakage markers and association with troponin T and cardiac function measured by echocardiography

In order to explore associations between gut leakage markers and cardiac function during the initial acute phase (first 5 days), we explored peak values of gut leakage markers and changes in WMSI, GLS, LVEF and E/e' ratio from baseline to day 5. We found that change in LVEF from baseline to day 5 and peak TnT correlated with peak sCD14 level on day 5 (r_s=–0.32, p=0.02 and r_s=0.33, p=0.01, respectively). There were no other significant correlations. A summary of the performed correlations is presented in table 2.

Gut leakage markers and association with infarct size and cardiac function at 6 weeks

To determine the relationship between gut leakage markers measured during admission and the subsequent infarct size and cardiac function determined at 6 weeks, we computed the cumulative AUCs for all gut leakage markers and calculated the median values for infarct size and cardiac function at 6 weeks. The cumulative median AUC values for LPS were 274 pg/mL·days (231, 327), for LBP 173 346 ng/mL·days (154 563, 201 581), for sCD14 9911 ng/mL·days (8764, 11 793) and for I-FABP 2372 pg/mL·days (1668, 3746). At 6 weeks the median value of infarct size was 45% (36.5, 51), LVEF measured by SPECT at 46.5% (36, 54), LVEF measured by echocardiography

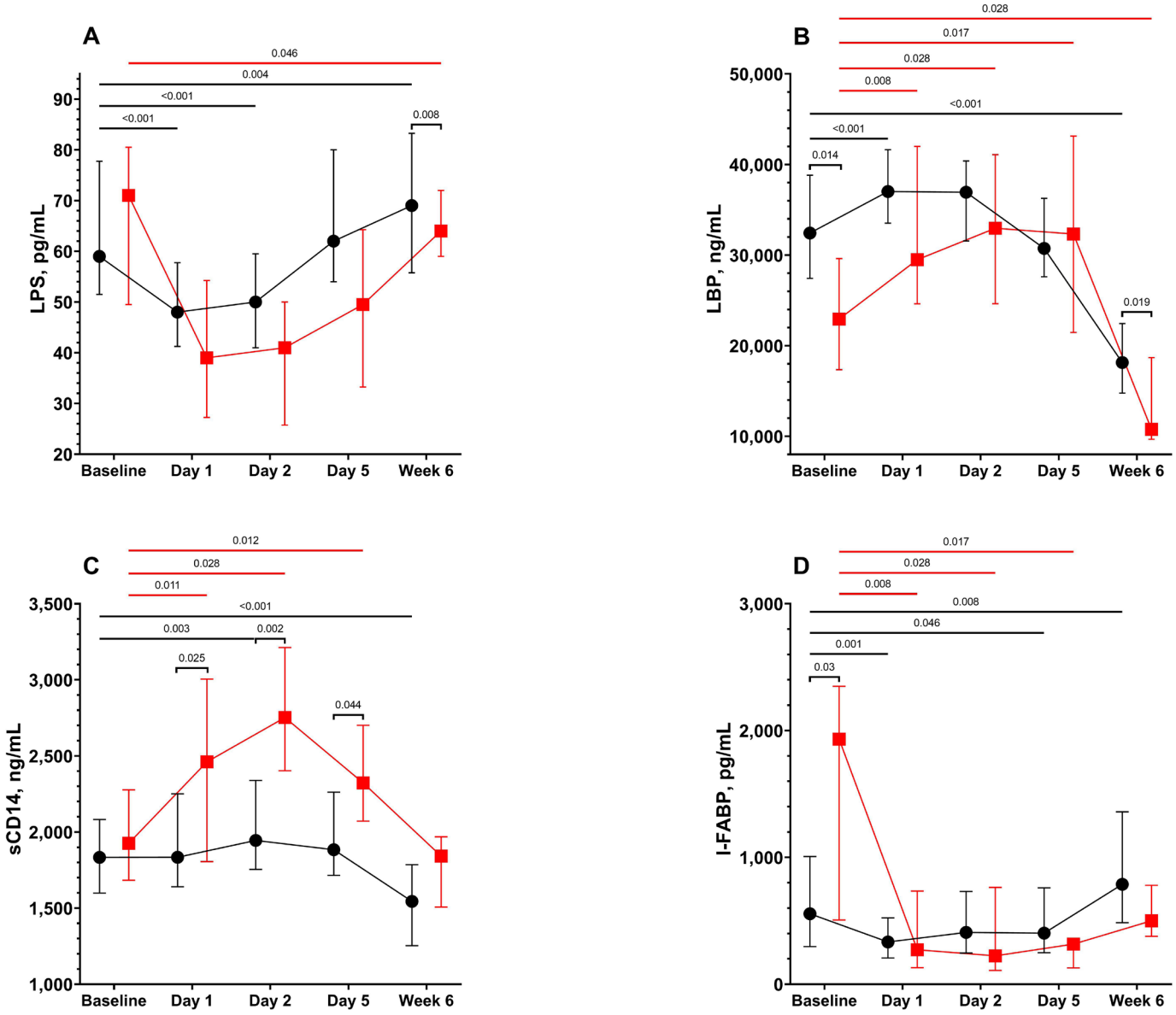

Figure 2 Time profiles of gut leakage markers lipopolysaccharide (A), lipopolysaccharide-binding protein (B), soluble cluster of differentiation 14 and intestinal fatty acid binding protein (D) according to the presence or absence of cardiogenic shock. Red denotes patients with shock and black patients without shock. Circles represent median values and whiskers show IQRs. Significant changes from baseline were obtained with Wilcoxon signed-rank tests and are represented with a straight line and a p-value. Significant differences between groups with and without shock were obtained with Mann-Whitney U-tests and are indicated with a hooked line and a p-value. I-FABP, intestinal fatty acid binding protein; LBP, lipopolysaccharide-binding protein; LPS, lipopolysaccharide; sCD14, soluble cluster of differentiation 14.

48.5% (40, 54), GLS −12.7% (−14.4, −10.3), WMSI 1.63 (1.5, 1.88) and E/e' ratio 15.5 (12.8, 21.2).

I-FABP$_{AUC}$ correlated positively to infarct size (r_s=0.45, p=0.002) and negatively to LVEF measured by SPECT (r_s=−0.40, p=0.007) and by echocardiography (r_s=−0.33, p=0.021) at 6 weeks. It also correlated positively to GLS and WMSI (r_s=0.32, p=0.035 and r_s=0.45, p=0.002, respectively), but not to E/e' ratio (r_s=0.23, p=0.13) at 6 weeks. The scatter plots for the correlations are shown in Online supplemental file 1 . LPS$_{AUC}$ correlated to NT-proBNP at 6 weeks (r_s=−0.29, p=0.045). None of the other gut leakage marker AUCs correlated to NT-proBNP or any of the echocardiographic or SPECT parameters at 6 weeks (range: r_s=−0.18 to 0.28, p=0.07 to 0.99).

We further examined the relationships between I-FABP$_{AUC}$, infarct size and cardiac function using a binominal logistic regression model. The model incorporated age, creatinine at baseline and peak TnT as covariates, as detailed in the statistics section. We found that patients with above median GLS, above median WMSI and below median LVEF measured by SPECT at 6 weeks were more likely to have above median I-FABP$_{AUC}$ during admission. The lowest quartile of LVEF measured by echocardiography and the three upper quartiles of infarct size were

Table 2 Correlations between peak levels of gut leakage markers and change in echocardiographic parameters from baseline to day 5 and peak troponin T

		ΔLVEF BL-D5	ΔGLS BL-D5	ΔE/e' ratio BL-D5	ΔWMSI BL-D5	Peak TnT
LPS on D5	r_s	0.22	0.10	0.12	−0.08	−0.17
	p-value	0.10	0.50	0.36	0.56	0.21
LBP on D2	r_s	0.06	0.20	0.07	0.13	0.11
	p-value	0.68	0.20	0.63	0.35	0.45
sCD14 on D5	r_s	−0.32	−0.07	0.02	0.17	0.33
	p-value	0.02*	0.65	0.89	0.21	0.01*
I-FABP at BL	r_s	−0.05	−0.28	−0.04	−0.02	0.16
	p-value	0.70	0.055	0.78	0.89	0.21

Statistically significant correlations are marked with an asterisk.
BL, baseline; D1, day 1 (25 hours); D2, day 2; D5, day 5; I-FABP, intestinal fatty acid binding protein; LBP, lipopolysaccharide-binding protein; LPS, lipopolysaccharide; Peak TnT, peak troponin T; r_s, Spearman's rho; sCD14, soluble cluster of differentiation 14; ΔE/e' ratio BL-D5, change in E/e' ratio from baseline to day 5; ΔGLS BL-D5, change in global longitudinal strain from baseline to day 5; ΔLVEF BL-D5, change in left ventricular ejection fraction from baseline to day 5; ΔWMSI BL-D5, change in wall motion score index from baseline to day 5.

also more likely to be in the above median $\text{I-FABP}_{\text{AUC}}$ group (table 3). Figure 3 illustrates values of $\text{I-FABP}_{\text{AUC}}$ in groups of infarct size and cardiac function at 6 weeks.

Gut leakage markers and inflammation

In order to explore a putative mechanism underlying the interplay between gut leakage markers and cardiac function, we explored their cumulative AUCs against selected markers of inflammation at 5 days and 6 weeks.

LPS_{AUC} correlated negatively with CRP on day 5 (r_s=−0.32, p=0.02), whereas LBP_{AUC} and $\text{sCD14}_{\text{AUC}}$ correlated positively with CRP (r_s=0.54, p<0.001 and r_s=0.32, p=0.02, respectively) and IL-6 (r_s=0.39, p=0.004 and r_s=0.43, p=0.001, respectively) on day 5. None of the AUCs correlated with either CRP or IL-6 at 6 weeks.

DISCUSSION

This substudy of the LEAF trial is to our knowledge the first to report on the potential contribution of gut-related inflammation in patients who develop acute HF following an acute MI.

We found that I-FABP in the first few days following an acute HF event was associated with infarct size and cardiac function at 6 weeks. Consequently, patients with high I-FABP levels in the acute phase had lower LVEF and worse GLS and WMSI at 6 weeks. Furthermore, levels of the specific gut leakage markers LPS and I-FABP were high at baseline following a STEMI complicated by acute HF, and then decreased on days 1 and 2, whereas LBP and sCD14 increased from baseline to days 1 and 2 following the acute event.

Our results are in concordance with reports of I-FABP being associated with 30-day mortality and adverse clinical outcomes in acute HF.[18 19] A possible explanation of this finding would be that I-FABP may reflect the extent of myocardial injury, degree of HF and end-organ damage. However, I-FABP did not correlate to peak TnT or NT-proBNP in our study. As I-FABP did not correlate

Table 3 Multivariate logistic regression models examining the relationships between infarct size and cardiac function at 6 weeks, and $\text{I-FABP}_{\text{AUC}}$ above median

				95% CI for OR	
	n	p-value	OR	Lower	Upper
LVEF by SPECT below median	44	0.014*	5.67	1.42	22.59
LVEF by echo in quartile 1	49	0.009*	9.99	1.79	55.83
GLS above median	43	0.027*	5.22	1.21	22.44
WMSI above median	48	0.023*	5.05	1.25	20.43
Infarct size in quartiles 2–4	44	0.021*	20.34	1.56	264.65

Statistically significant p-values are marked with an asterisk.
Covariates used were age, creatinine at baseline and peak troponin T.
GLS, global longitudinal strain; LVEF by echo, left ventricular ejection fraction measured by echocardiography; LVEF by SPECT, left ventricular ejection fraction measured by single-photon emission CT; n, number of patients examined in statistical analysis; WMSI, wall motion score index.

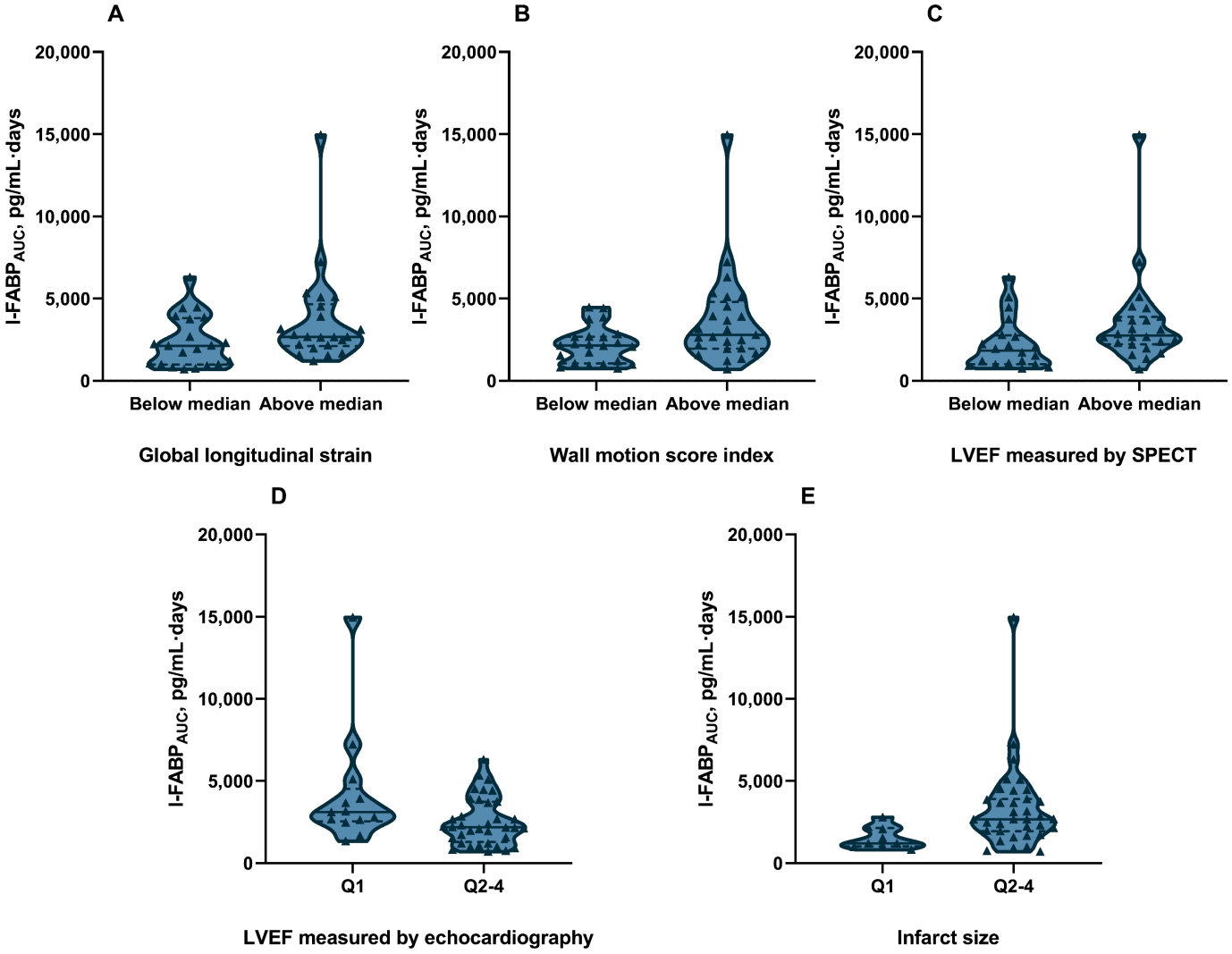

Figure 3 I-FABP$_{AUC}$ values in groups of global longitudinal strain (A), wall motion score index (B) and LVEF measured by SPECT (C) dichotomised at median, and LVEF measured by echocardiography (D) and infarct size (E) dichotomised at 25th percentile at 6 weeks. Solid horizontal line in violin plots represents median, dotted lines are 25th and 75th percentiles. I-FABP$_{AUC}$, intestinal fatty acid binding protein cumulative area under the curve from baseline to day 5; LVEF, left ventricular ejection fraction; Q1, quartile 1; Q2-4, quartiles 2–4; SPECT, single-photon emission CT.

to IL-6 or CRP, we find it less likely that I-FABP itself is mechanistically involved in a hypothesised gut-related inflammation. However, given the correlation observed between I-FABP and cardiac function and injury 6 weeks post-admission, it is reasonable to consider that I-FABP could influence these outcomes in ways that are currently unknown. In the intestines, I-FABP plays a role in fatty acid absorption and transportation. Knockout of the fatty acid binding protein 2 (FABP2) gene, the gene that encodes I-FABP, has been shown to lead to changes in both lipid and glucose metabolism in experimental animals.[20] Importantly, altered lipid metabolism has been implicated in the presence and progression of HF.[21] In contrast, LPS, LBP and sCD14 were moderately associated with CRP, which may indicate their involvement in the observed inflammatory response in acute HF and later possibly adverse remodelling.

The temporal profiles of gut leakage markers support our hypothesis that injury to gut wall epithelial cells occurs in the setting of acute HF and suggests subsequent leakage of bacteria or bacterial products. The late surge of LBP and sCD14 may represent the innate response to LPS and other microbial by-products from the gut, as they are produced in response to LPS, bind up LPS in the circulation and induce an acute inflammatory response.[22 23] However, they may also increase in response to other sources of inflammation, as both are essentially acuete-phase proteins.

It is important to note that baseline blood samples were taken at a median time of 22 hours after PCI. Therefore, we do not know the true peak of the markers, but it is fair to assume that both LPS and I-FABP may be early markers of gut involvement in the setting of acute HF, more so than LBP and sCD14. We suggest that the release

of LPS and I-FABP is most pronounced shortly after the development of acute HF when the degree of congestion and hypoperfusion is greatest, and with treatment by consequent correction of end-organ damage, the levels decline. Notably, nearly all patients in the LEAF trial (59 of 61) received intravenous diuretics, and it has been shown that diuretic treatment in patients with acute decompensated HF normalises LPS levels.[24]

There was a significant increase in LPS at 6 weeks in the group without cardiogenic shock, but not in the population as a whole. Previous studies have reported that MI patients have an altered gut microbiota that remains unchanged 1 week after the MI, and it has been suggested that this persists after 6 weeks and thus may contribute to increased gut leakage.[25] Furthermore, our patients were highly medicated during treatment, which in turn could affect the microbiota and contribute to the observed LPS increase. For example, proton pump inhibitors are known to promote detrimental alterations of the gut microbiota.[26] A final factor may be the LAL assay, which is the method most commonly used to assess endotoxaemia.[27] LPS in the blood is found in biologically active (e.g., monomers or micelles) and inactive forms (e.g., bound to lipoproteins).[28] The assay detects only biologically active LPS that can interact with the lysate, not the total amount of LPS in the sample and may, therefore, underestimate LPS levels in critically ill patients.[29]

The persistent decrease in I-FABP from baseline in the first days and a return to baseline levels at 6 weeks is somewhat in contrast to a previous report.[19] It has been shown that damage to the epithelial gut barrier is completely repaired within 1 hour of reperfusion after 30 min of experimentally induced ischaemia, with I-FABP levels falling in concert.[30] We, therefore, believe that with the initiation of treatment and reestablishment of splanchnic perfusion, I-FABP levels fell rapidly and had already fallen a certain degree at baseline (median 22 hours after admission), similar to LPS described above. Notably, I-FABP was significantly higher at baseline in the shock group, although with wide variation. This difference can probably be attributed to more severe ischaemic damage to enterocytes in these patients. The return to baseline levels at 6 weeks may be due to gut leakage in the setting of chronic HF.[31] Additionally, a persistently altered gut microbiota and the introduction of certain drugs may contribute, as discussed above to LPS.

Our study has several limitations. First, the study population was relatively small, particularly the shock group. The LEAF trial was not designed to examine gut leakage markers and their relationship to inflammation, echocardiographic parameters or MI sequelae. The sample size may, therefore, have been too small to detect certain associations. Due to the explorative design of the study, we did not adjust for multiple comparisons. Furthermore, we have no data on microbiota composition from the trial, which would have added to the observations. Finally, due to the requirement of acute HF being manifest before inclusion, the first samples were obtained after a median time of 22 hours after PCI, which precluded us from examining the initial hours of disease development.

To conclude, in our population of primary PCI-treated STEMI patients with acute HF, LPS and I-FABP are early markers of gut involvement. I-FABP, a marker of intestinal epithelial damage, was associated with larger infarct size and worse cardiac function after 6 weeks, but not with any of our selected markers of systemic inflammation. Thus, our findings suggest that I-FABP in acute HF following a STEMI may influence cardiac function and contribute to infarct size through pathways that are not yet fully understood.

Acknowledgements Thanks to Sissel Åkra and Jeanette K. Steen for invaluable laboratory assistance, as well as other staff at the Center for Clinical Heart Research and the Coronary Intensive Care Unit at Oslo University Hospital Ullevaal for their contributions to the LEAF trial.

Contributors Conceptualisation: AN, AA, GØA, IS and MT; Formal analysis: AN; Investigation: GØA; Writing–original draft preparation: AN and AA; Writing–review and editing: AN, AA, GØA, IS and MT; Funding acquisition: GØA; Resources: GØA and IS; Supervision: AA, IS, MT and GØA. All authors listed have contributed sufficiently to the project to be included, and all those qualified to be authors are listed in the author by-line. All authors read and approved the final manuscript. AN is the guarantor of this research work.

Funding This research was funded by The Centre for Heart Failure Research, University of Oslo, South-Eastern Norway Regional Health Authority, The Scientific Council at Oslo University Hospital Ullevål, The Research Council of Norway and an unrestricted educational grant from Orion Pharma.

Disclaimer The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests The Department of Cardiology, Oslo University Hospital Ullevaal received an unrestricted educational grant from the manufacturer of levosimendan, Orion Pharma in 2005. Orion Pharma did not, however, provide study medication or participate in the design, monitoring or analyses of the present study. The authors declare no conflict of interest.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Regional Ethics Committee South-Eastern Norway Regional Health Authority (reference 538-04218). Participants gave informed consent to participate in the study.

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement Data are available on reasonable request. The data are available on request from the corresponding author, following the establishment of a material and data transfer agreement between the institutions and the approval of an amendment application to the Regional Committees for Medical Research Ethics to ensure that the aim of the planned research is covered by the participant consent forms.

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