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# FGF21 defines a potential cardio-hepatic signaling circuit in end-stage heart failure

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## Abstract

**Background:** Extrinsic control of cardiomyocyte metabolism is poorly understood in heart failure. Fibroblast growth factor-21 (FGF21), a hormonal regulator of metabolism produced mainly in the liver and adipose tissue, is a prime candidate for such signaling.

**Methods:** To investigate this further, we examined blood and tissue obtained from human subjects with end-stage heart failure with reduced ejection fraction (HFrEF) at the time of left

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DISCLOSURES

None.

SUPPLEMENTAL MATERIALS

Supplemental Methods

References 50–55

ventricular assist device (LVAD) implantation, and correlated serum FGF21 levels with cardiac gene expression, immunohistochemistry, and clinical parameters.

**Results:** Circulating FGF21 levels were substantially elevated in HFrEF, compared to healthy subjects (HFrEF: 834.4 [95% confidence interval: 628.4, 1040.3] pg/mL, n = 40; controls: 146.0 [86.3, 205.7] pg/mL, n = 20, $p = 1.9 \times 10^{-5}$). There was clear FGF21 staining in diseased cardiomyocytes, and circulating FGF21 levels negatively correlated with the expression of cardiac genes involved in ketone metabolism, consistent with cardiac FGF21 signaling. FGF21 gene expression was very low in failing and non-failing hearts, suggesting extracardiac production of the circulating hormone. Circulating FGF21 levels were correlated with BNP and total bilirubin, markers of chronic cardiac and hepatic congestion.

**Conclusions:** Circulating FGF21 levels are elevated in HFrEF and appear to bind to the heart. The liver is likely the main extracardiac source. This supports a model of hepatic FGF21 communication to diseased cardiomyocytes, defining a potential cardio-hepatic signaling circuit in human heart failure.

### Keywords

fibroblast growth factor; congestive hepatopathy; venous congestion; ketone metabolism; left ventricular assist device; BDH1; total bilirubin; B-type natriuretic peptide

### Subject terms:

Heart failure; cardiomyopathy

## INTRODUCTION

A central feature of heart failure across different etiologies is a profound alteration in cardiomyocyte metabolism[1]. In heart failure with reduced ejection fraction (HFrEF), notable changes include increased reliance on glucose, ketones, and short-chain fatty acids, reduced pyruvate uptake by mitochondria and a consequent shunting of glycolysis towards the pentose-phosphate pathway[2–5]. Such adaptations are associated with altered expression of cardiomyocyte genes involved in the transport and metabolism of these different substrates. Some of these changes are dependent on cardiomyocyte-intrinsic signaling pathways triggered by cardiac dysfunction, but extrinsic control of cardiomyocyte metabolism is not well understood.

To explore extrinsic cardiometabolic signaling, we focused on fibroblast growth factor-21 (FGF21). This cytokine of the FGF19/21/23 family is produced primarily in the liver and adipose tissue, and is a potent regulator of fuel utilization and metabolism. Due to the absence of heparin-binding domains, secreted FGF21 can travel into the bloodstream and act as a hormone, binding to a receptor complex composed of a tyrosine kinase FGF receptor isoform and the β-Klotho (KLB) co-receptor. FGF21 regulates fatty acid oxidation in the liver, insulin sensitivity, glucose metabolism in adipose cells, and ketone usage[6]. In humans, FGF21 has been explored as a metabolic biomarker. In healthy subjects, it is induced late during the adaptive response to starvation[7], but also during short-term carbohydrate

overfeeding[8], alcohol consumption[9], and cold-induced thermogenesis[8]. Increased hepatic and adipose secretion is widely noted in diabetes and obesity, and skeletal muscle expression is noted after exercise or in hyperinsulemic states[10–14].

FGF21 signaling appears to be protective in several animal models of cardiac disease, possibly by direct action on the heart[15–17]. However, FGF21 signaling in heart disease remains unresolved in humans. In particular, whereas FGF21 appears protective in most animal models of heart disease, elevated levels are poor prognostic indicators in humans. In two studies of diabetic patients with coronary disease, higher levels of FGF21 were predictive of poorer outcomes[18, 19]. In cardiomyopathies, FGF21 elevations predicted adverse events in both heart failure with reduced or preserved ejection fraction, though >40% of patients in both these studies had diabetes[20, 21]. Additionally, it is unclear whether the elevated blood FGF21 is synthesized in the heart itself or is produced in other organs. In mouse studies, FGF21 appears to be synthesized in diseased or metabolically-altered hearts, but not healthy cardiomyocytes, though cardiac expression was not seen in other studies[15, 16, 22–24]. Human data is scant, with one study showing an increase in FGF21 transcripts and two showing FGF21 staining in cardiomyocytes in alcoholic cardiomyopathy or hypertensive heart disease[23, 25, 26]. Thus, the extent of FGF21 elevation during HFrEF, what signals trigger this elevation, and whether it is active in the heart, remain open questions. Here, to investigate human cardiac FGF21 biology independent of its well-established elevation during diabetes, we took advantage of cardiac tissue collection during the implantation of left ventricular assist devices (LVAD) in non-diabetic patients with end-stage HFrEF.

## METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### Study Population

The HFrEF cohort was taken from a larger sample of patients enrolled at the time of LVAD implantation. Patients who required LVAD support due to acute heart failure (acute myocardial infarction, acute myocarditis, and others) were prospectively excluded. Patients (age ≥ 18-years) were consecutively enrolled in institutions comprising the Utah Transplantation Affiliated Hospitals (U.T.A.H.) Cardiac Transplant Program (University of Utah Health Science Center, Intermountain Medical Center, and the Veterans Administration Salt Lake City Health Care System) with clinical characteristics consistent with dilated cardiomyopathy and chronic advanced heart failure, who required circulatory support with continuous-flow LVAD. Non-failing donor hearts, not allocated for heart transplantation due to non-cardiac reasons (size, infection, and others) were used as controls. The study was approved by the institutional review board of the participating institutions, and informed consent was provided by all patients.

In the current study, we selected patients from the overall study who had blood samples available and who did not have diabetes (clinical diagnosis or hemoglobin A1c < 6.5%),

overt renal failure (creatinine < 1.2 mg/dL), a clinical diagnosis of non-alcoholic fatty liver disease or viral hepatitis.

Blood samples used as the control reference were from healthy subjects recruited from the University of Utah and the surrounding Mountain West states. We obtained 20 samples of the same gender and within 2 years of the age to samples from our heart failure cohort. Healthy donors were medication free and without acute or chronic illnesses. All subjects provided written, informed consent and all study protocols were IRB approved.

### Blood and Myocardial Tissue Acquisition

Myocardial tissue was prospectively collected from the LV apical core at the time of LVAD implantation and was frozen before storage at −80 °C. Control samples were acquired from hearts that were not transplanted due to non-cardiac reasons. Donor LV apical tissue was harvested and processed the same way as the failing hearts. For HFrEF and donor samples, blood was collected immediately prior to the beginning of the operation. For healthy control samples, blood was collected by venipuncture. Samples were centrifuged and serum or plasma collected and stored for later analysis.

### Clinical Data Collection

Donor information like age, sex, and cause of death were collected with the help of DonorConnect. For HFrEF patients, clinical data including demographics, comorbidities, echocardiographic parameters, laboratory results, and other clinical data were collected within one week before LVAD implantation using our institutional research electronic data capture system (REDCap). We followed the echocardiographic data of each participant after surgery for up to 12 months. Based on left ventricular functional and structural changes following at least 3 months on LVAD support, patients were categorized as either responder or non-responder (see definitions in Results).

### Blood FGF21 measurements

FGF21 levels were measured using the Quantikine ELISA Human FGF21 kit (R&D Systems, Minneapolis).

### Immunohistochemistry

Formalin-fixed, paraffin-embedded cardiac tissue pieces were stained with anti-FGF21 antibody (Abcam, ab171941).

### Cardiac FGF21 gene expression measurement

RNA isolation and cDNA synthesis from LV tissue samples were performed using commercially-available kits, and quantitative PCR was performed with Power SYBR Green PCR Master Mix (Thermo) and gene-specific primers.

### Statistics

Distributions were checked for normality visually, and skewed distributions were transformed by a base 10 logarithm to make them normal. Student’s *t*-test with unpaired,

unequal variance samples were used for two-sample comparisons, assuming significance for $p < 0.05$. Correlations were performed using linear regression, with p-values for the coefficient of determination ($r^2$) calculated from an analysis of variance using the *F*-statistic. For multiple hypothesis testing, a Benjamini-Hochberg procedure was used to derive corrected p-values (q-values) using a false discovery rate of 0.05. Analyses were performed in Excel and OriginPro 2020.

Additional methodological details are available in supplemental information.

## RESULTS

### FGF21 is elevated in end-stage HFrEF

We retrospectively analyzed serum samples, obtained at the time of left ventricular assist device (LVAD) implantation, in 40 patients with ischemic and nonischemic HFrEF. Because we specifically wanted to determine the effect of heart failure on FGF21 levels, none of these patients had diabetes, end-stage renal failure, viral hepatitis, or non-alcoholic fatty liver disease (NAFLD), conditions known to alter FGF21 levels[11, 27–29]. A description of patient characteristics is included in Table 1. For controls, we utilized plasma from 20 healthy controls.

Circulating FGF21 levels were more than fivefold higher in HFrEF patients compared to controls (834.4 [628.4, 1040.3] pg/mL vs. 146.0 [86.2, 205.7] pg/mL, mean [two-sided 95% confidence interval], Figure 1A). In prior studies of FGF21 in human cardiomyopathies, a substantial fraction of patients had diabetes, a comorbidity expected to raise FGF21. Our results here show the increase in FGF21 during HFrEF is not due only to concurrent diabetes or NAFLD. Within the HFrEF group, no significant difference was observed in serum FGF21 between females and males (822.7 [487.0, 1158.4] pg/mL vs. 841.4 [561.7, 1121.1] pg/mL, Figure 1B), or between ischemic and non-ischemic etiologies (691.1 [396.4, 985.9] pg/mL vs. 895.8 [622.1, 1169.4] pg/mL, Figure 1C). There was no correlation with the age of the subject (Figure 1D).

In a subset of patients with mechanically-unloaded failing hearts, cardiac structure and function improves to the point that some of these patients can be weaned from mechanical support, and we assessed whether FGF21 level might predict such myocardial function improvement. In our cohort, recovery was defined as an improvement in left ventricular ejection fraction to >40% and reduction in left ventricular end-diastolic diameter to ≤59 mm. However, there was no significant difference in serum FGF21 between patients who recovered left ventricular function during mechanical unloading (responder, 774.2 [395.8, 1152.5] pg/mL, Figure 1E) and those that did not (non-responder, 860.2 [599.5, 1120.9] pg/mL).

### FGF21 present in the heart appears to have substantial extra-cardiac synthesis.

Next, we addressed whether FGF21 is found within heart tissue in HFrEF, and whether the elevated serum levels are due to cardiac FGF21 synthesis. To address the first question, we stained cardiac sections with anti-FGF21 antibodies in a subset of the HFrEF patients. As control, we examined cardiac sections in structurally intact hearts obtained from non-failing

donors, but unused for human heart transplantation due to non-cardiac reasons. Although hearts in these donors were structurally and functionally normal, the donors themselves were deceased due to traumatic or anoxic brain injury, critical illnesses in which circulating FGF21 levels have been found to be elevated[30–33]. Our results replicated these findings, with donor serum FGF21 levels elevated (809.8 [185.9, 1433.7] pg/mL, n = 5) as in HFrEF serum. This set of conditions allows us to clearly identify if cardiac dysfunction leads to FGF21 signaling. In fact, whereas sections from donors showed essentially no cardiac FGF21 staining, sections obtained from HFrEF patients showed robust labeling throughout cardiomyocytes (Figure 2). This difference in cardiomyocyte staining is not due to altered levels of circulating FGF21, as serum levels were similarly elevated in both donor and HFrEF subjects. Rather, this result establishes that the failing heart is preferentially primed for FGF21-mediated metabolic signals.

Next, we addressed whether the FGF21 staining seen in heart sections represented a fraction bound from the elevated circulating levels or protein synthesized within cardiomyocytes. To address this issue, we assessed the expression of cardiac genes related to FGF21 signaling (Figure 3). Because the limited amounts of tissue obtained per patient are used in various assays across multiple studies, precluding Western blot analyses of protein levels, we restricted our analysis to measuring transcript levels via quantitative reverse-transcriptase polymerase chain reaction (qPCR). When we examined *FGF21* transcripts with qPCR, we found expression was low, near the limits of detection. Moreover, there was no clear change in expression between donor and HFrEF patients, nor any correlation with serum FGF21 levels (Figure 3), suggesting the *FGF21* gene may have low cardiac expression. To further assess cardiac *FGF21* transcription, we examined 7 published RNA-seq datasets obtained from cardiac tissue in human patients with ischemic, non-ischemic, restrictive, and hypertrophic cardiomyopathies (Table 2)[34–40]. *FGF21* transcripts were detectable in only 14 out of 167 samples, primarily in cardiomyopathy samples, and in most of these cases corresponded to 1–2 reads. Given limited cardiac FGF21 synthesis, it appears elevated circulating FGF21 during HFrEF may have a primarily extracardiac source. However, though FGF21 is synthesized elsewhere, it clearly signals to the heart, given the robust FGF21 staining we found in cardiac tissue in HFrEF, but not donors. Taken together, these results reveal an unexpected metabolic signaling axis to the heart from organs synthesizing FGF21.

### Correlation of circulating FGF21 with cardiac metabolic gene expression.

As a first step towards examining cardiac FGF21 signaling in humans, we also assayed genes involved in the FGF response and fuel metabolism via qPCR (Figure 3). FGF21 exerts its effects primarily by binding to a receptor complex composed of one of four tyrosine kinase FGF receptor isoforms, typically FGFR1, and the β-Klotho (KLB) co-receptor[41]. In our hands, there was no evidence for a net increase in gene expression of FGF receptors nor the co-receptor β-Klotho between HFrEF versus donor samples. Intriguingly, however, there was a strong positive correlation between serum FGF21 and cardiac *FGFR3* expression. In contrast, most samples had suppressed *FGFR4* expression. We then turned to genes involved in the metabolism of glucose, fatty acids, and ketones. Compared to donor heart tissue, HFrEF cardiac samples had increased levels of *pyruvate dehydrogenase kinase 4* (*PDK4*),

which inhibits the conversion of pyruvate into acetyl-CoA, as well as several genes involved in the transport and metabolism of ketones, including *solute carrier family 16 member 7* (*SLC16A7* or *MCT2*), a monocarboxylate transporter responsible for ketone uptake, *3-hydroxybutyrate dehydrogenase* (*BDH1*), which catalyzes the interconversion between the ketones β-hydroxybutyrate and acetoacetate, and *3-oxoacid-CoA transferase* (*OXCT1* or *SCOT*), which transfers the CoA group to the ketone acetoacetate. Unexpectedly, we found a negative correlation between serum FGF21 levels and *BDH1* transcripts, and similar but much weaker trends with the *SLC16A1* and *SLC16A7* transporters. This result was intriguing, as prior mouse studies revealed that inhibition of FGF21 reduced *Bdh1* transcripts, opposite to the correlation found here[42]. Although these analyses of correlations do not establish a particular mechanism for cardiac FGF21 activity, they do lend support to the hypothesis that FGF21 may act as a hormonal regulator of cardiac metabolism.

### Clinical parameters suggest elevated circulating FGF21 may be due to hepatic congestion.

To investigate the source of FGF21 production, we correlated serum FGF21 levels with the available clinical data on adiposity and cardiac, hepatic, and renal function (Figure 4). Notably, advanced HFrEF is associated with a cachectic phenotype, and elevated FGF21 levels have been attributed to muscle wasting during cardiac cachexia or prolonged fasting[7, 43]. In our cohort, however, we found no correlation with body-mass index (BMI) or aspartate aminotransferase (AST), a liver marker also released during muscle breakdown in cachectic states. Intriguingly, we observed a significant correlation with B-type natriuretic peptide (BNP) and total bilirubin, a marker of hepatic dysfunction. Moreover, we observed strong negative correlations with triglycerides and total cholesterol, which also partly reflect hepatic synthesis. We did not pursue correlations with invasive hemodynamic data because of confounding factors. Hemodynamic values are instantaneous measures, but in our study cohort were obtained on average 10 days apart from blood samples. Moreover, hemodynamic values were often targeted for optimization in the immediate preoperative period prior to LVAD implantation. Taken together, our data here supports the hypothesis that one main source of elevated circulating FGF21 observed in HFrEF is due to hepatic release.

## DISCUSSION

This study describes three major findings defining human cardiac FGF21 biology. First, serum levels of FGF21 are elevated in the setting of HFrEF independent of other comorbidities, such as diabetes, that can raise hormone concentration. Second, FGF21 is present in cardiomyocytes from failing but not donor hearts, suggesting that it may activate downstream cardiac signals. Third, the origin of the elevated FGF21 appears to be partly extracardiac, with the liver as the most likely extracardiac source.

Elevated serum FGF21 levels have been seen in prior studies of heart failure biomarkers with either reduced or preserved ejection fraction[20, 21, 43]. In two studies, diabetes was a significant comorbidity in >40% of subjects, confounding the ability to interpret the basis for elevated FGF21[20, 21]. Notably, the HFrEF study by Shen *et. al.* was powered to detect cardiovascular outcomes, and elevated FGF21 levels predicted cardiac death independently

of N-terminal pro-BNP levels[21]. More broadly, elevated FGF21 levels have been associated with adverse cardiac events in individuals with coronary disease and/or diabetes[18, 19, 44, 45]. Thus, elevated FGF21 is a potential biomarker for severity in cardiac disease, raising the question of what derangements are causing this elevation, and whether the elevated FGF21 is an intrinsic or hormonal signal for the diseased heart.

The source of FGF21 signaling to the heart has been difficult to resolve. Though some studies suggested minimal expression in the mouse heart, others found upregulation during cardiac hypertrophy[15, 16, 46]. In the only study of human cardiac gene expression, transcriptomic analysis revealed somewhat increased FGF21 expression during end-stage HFrEF[23]. In our qPCR data, whereas elevated transcription was seen in particular HFrEF samples, a uniform increase was not detected, corroborated by analysis of previously published transcriptomic datasets. Taken together, this suggests that cardiac FGF21 gene expression is low at baseline, with perhaps a slight, heterogeneous increase in cardiomyopathies.

Nevertheless, our data here is consistent with mouse and human data showing direct activity of circulating FGF21 on the heart[15, 24–26]. Robust cardiac FGF21 staining was seen in all the HFrEF samples but none of the non-failing donors, suggesting that elevated circulating FGF21 binds to the failing heart. In terms of cardiac regulation, exogenous FGF21 reduced fibrosis, inflammation, apoptosis, and maladaptive changes in cardiac energy metabolism[15–17]. In this report, we queried a range of genes involved in cardiac metabolism. Surprisingly, we found an overall negative correlation between FGF21 and genes involved in the synthesis and transport of ketones. Whereas some prior data has suggested a direct relationship between FGF21 and fasting-induced ketogenesis, in humans the ketogenic response seems to precede the release of FGF21, suggesting a more circuitous relationship[7, 42]. Since our data is entirely correlational, we can only speculate that FGF21 acting on the heart may be a compensatory signal to preserve energetic homeostasis during progressive contractile failure. Intriguingly, there must definitely be changes in the response or susceptibility to circulating FGF21 during cardiomyopathies, as we saw no significant FGF21 staining in functionally normal hearts collected from donors, despite these individuals having similarly elevated serum FGF21 levels. In examining the FGF receptor family, we saw no obvious transcriptional upregulation that would indicate how FGF21 binds cardiomyocytes during HFrEF, though there was a strong positive correlation with *FGFR3*, and possibly transcriptional suppression of *FGFR4*.

Finally, we investigated the pathology responsible for elevating blood FGF21. The liver is the primary source of FGF21, though adipose tissue also produces it. It is likely the elevated FGF21 in HFrEF derives from the liver rather than adipose tissue, as we saw no relationship with BMI, and, when increased FGF21 levels are due to adipose release, it shows a positive correlation with lipid profile[11, 47]. Instead, here we find higher FGF21 associated with a lower lipid levels, which may reflect the triglyceride-lowering effect of hepatic FGF21[48, 49]. In regards to the mechanism activating hepatic FGF21 secretion, our data revealed a strong correlation between FGF21 and BNP levels, a sensitive marker of chronic pathological myocardial stretch and vascular congestion. We also showed a correlation between FGF21 and elevated bilirubin, but not elevated liver function enzymes (AST). This pattern is most

consistent with congestive hepatopathy, which is also due to chronic vascular congestion. This suggests that chronic venous congestion may be a proximal signal for hepatic FGF21 secretion. In summary, pathological hepatic venous congestion in HFrEF may cause FGF21 release, with elevated FGF21 feeding back on the heart to regulate its metabolism. Thus, FGF21 defines a potential cardio-hepatic metabolic signaling loop in HFrEF.

## LIMITATIONS

First, although we assay a variety of clinical indexes, cardiac gene expression, and cardiac FGF21 protein, our analysis is based on correlations between these parameters, and a causal pathway has not been established. Without corresponding liver samples from these patients, we cannot confirm that elevated circulating FGF21 is due to hepatic congestion. Second, we did not study clinical outcomes. Our study was not powered or designed for clinical outcomes, as HFrEF patients went on to LVAD implantation and, for a substantial number of individuals, cardiac transplants. Third, we studied a subset of patients without diabetes, end-stage renal failure, or several other forms of liver disease. The biological activity of FGF21 may be more complex when these comorbidities are present. Finally, our study population consisted of patients with end-stage HFrEF. Whether FGF21 alters cardiac metabolism during earlier periods in HFrEF with relatively preserved cardiac output has not been established.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## SOURCES OF FUNDING

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**What is new?**

- There are pronounced changes in metabolism during the progression of heart failure with reduced ejection fraction (HFrEF), including in the fuels the heart uses. We investigated if levels of a signaling molecule, fibroblast growth factor 21 (FGF21), which is known to alter fuel utilization, were altered in end-stage HFrEF. We found large increases in circulating FGF21 in HFrEF.
- In addition, though FGF21 protein was present in failing but not structurally normal hearts, there appeared to be a lack of cardiac FGF21 gene expression in either condition, suggesting FGF21 acts as a hormonal signal from another organ, most likely the liver.

**What are the clinical implications?**

- Our results expand the idea that HFrEF is in part a metabolic disease. Subclinical alterations in the behavior of other organs, such as the liver, may be leading to changes in cardiac fuel metabolism and impacting HFrEF progression, possibly defining different HFrEF subgroups.
- FGF21 analogs are also in development as therapies for metabolic diseases, and these may alter cardiac function in patients with cardiomyopathies.

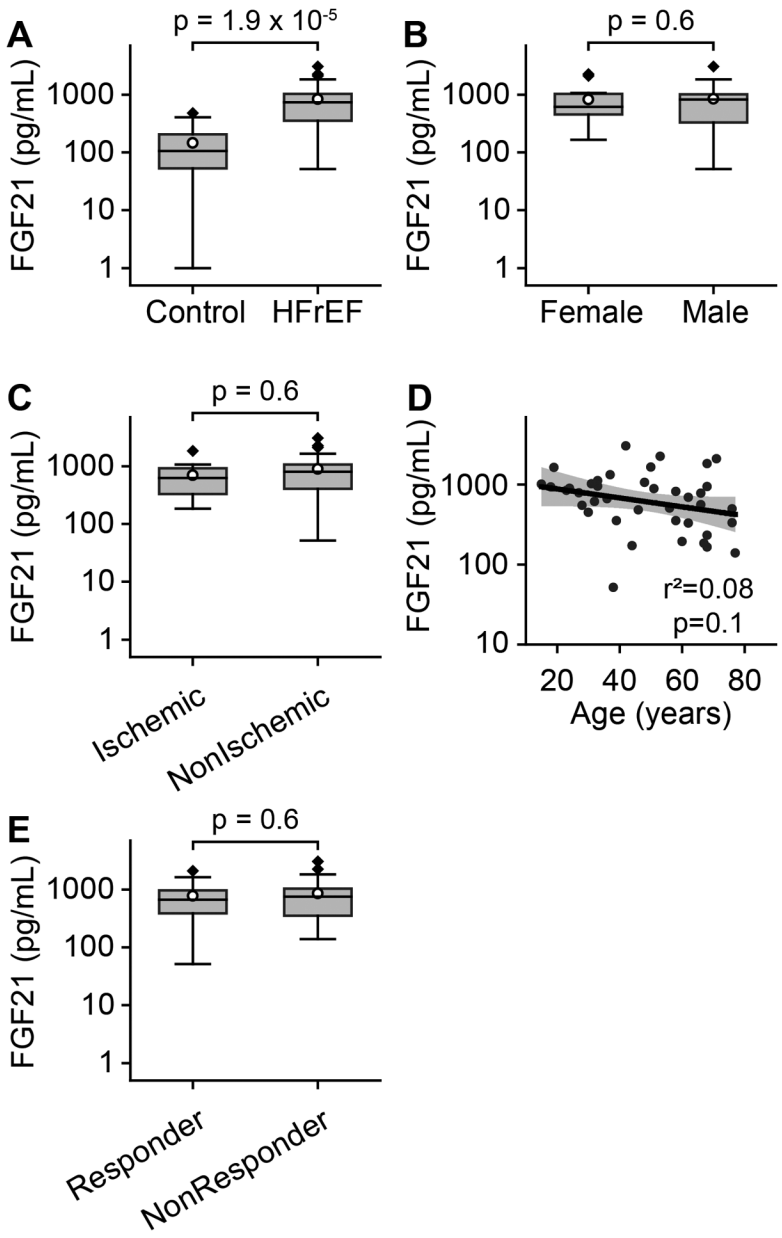


**Figure 1. Circulating FGF21 levels are elevated in HFrEF.**

**A.** FGF21 levels in healthy controls (n=20) versus patients with heart failure with reduced ejection fraction (HFrEF, n=40) displayed as Tukey boxplots, with mean shown as white circle. Note logarithmic scales. Student's *t*-test used for two-sample comparisons. **B.** No significant difference in FGF21 levels across gender in HFrEF patients (female = 15, male = 25). **C.** No significant difference in FGF21 levels between ischemic (n=12) and non-ischemic (n=28) HFrEF. **D.** No correlation with age of patient. Black line represents linear regression fit to the data, with shaded area representing 95% confidence bands. **E.** No significant difference in FGF21 between responders (n=18) and non-responders (n=22). Coefficient of determination ($r^2$) and corresponding p value are shown.

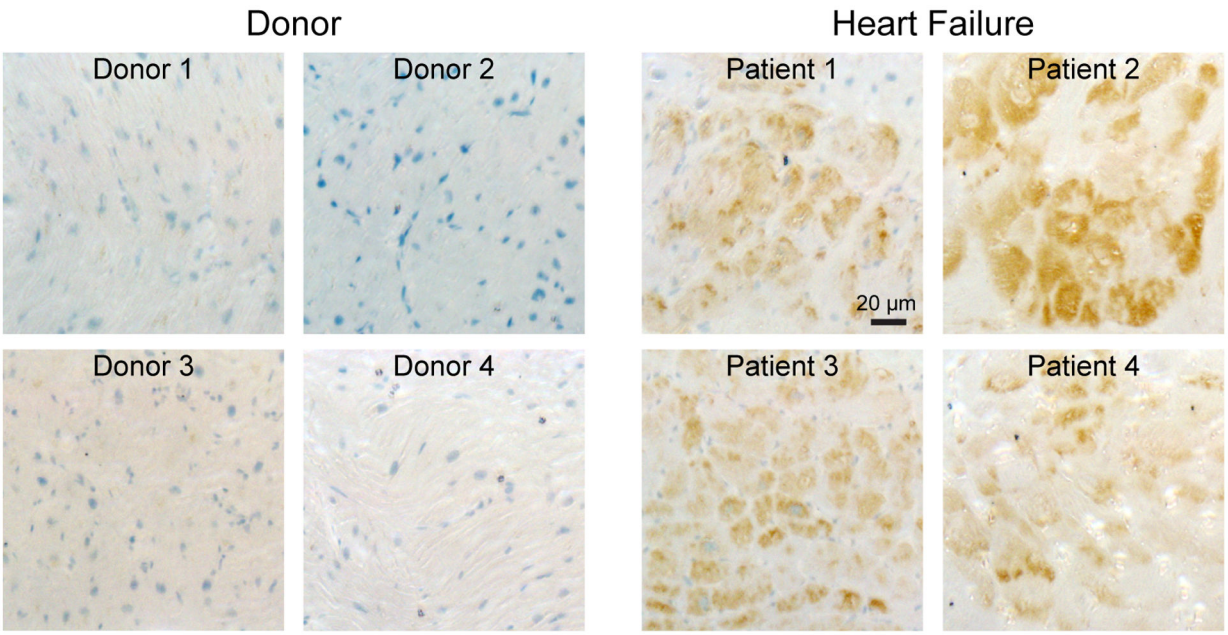


**Figure 2. FGF21 is present in cardiomyocytes from HFrEF patients.**

Immunostaining for FGF21 in human heart slices reveals little FGF21 present in donor hearts but robust staining in HFrEF hearts. Nuclei are labelled in blue and FGF21 immunostaining is brown. Each panel is from a different patient.

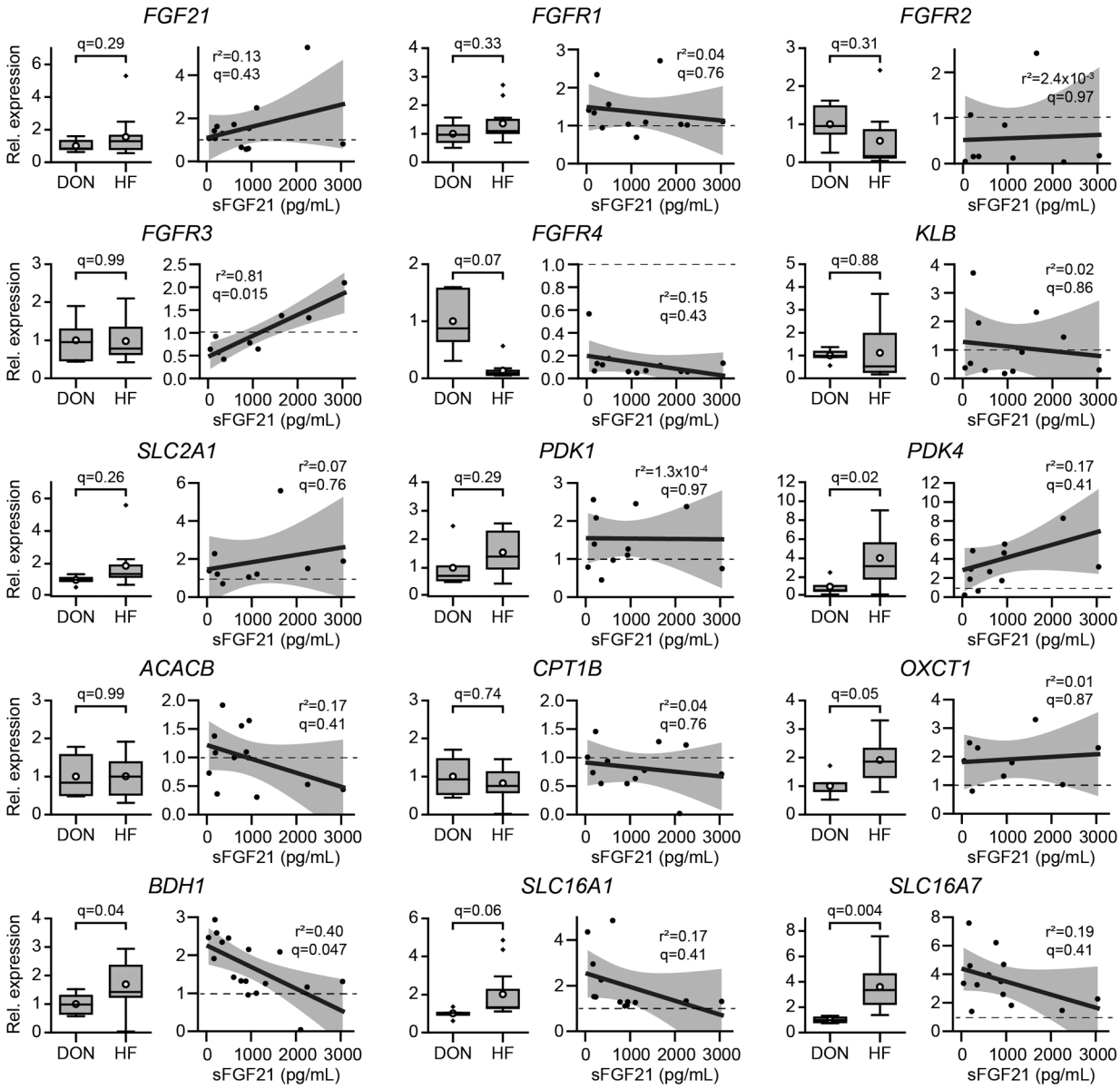


**Figure 3. Correlations between serum FGF21 and cardiac gene expression.**

For each gene listed above, the left panel is the relative gene expression between normal donor (DON, n=4–6) and HFrEF hearts (HF, n=9–17). The right panel for each gene shows the linear regression for the HFrEF hearts against serum FGF21 (sFGF21) levels. The black line is the linear regression, with shaded area corresponding to 95% confidence bands. Coefficient of determination ($r^2$) and corresponding Benjamini-Hochberg corrected p value (q) for a false discovery rate of 0.05 are shown.

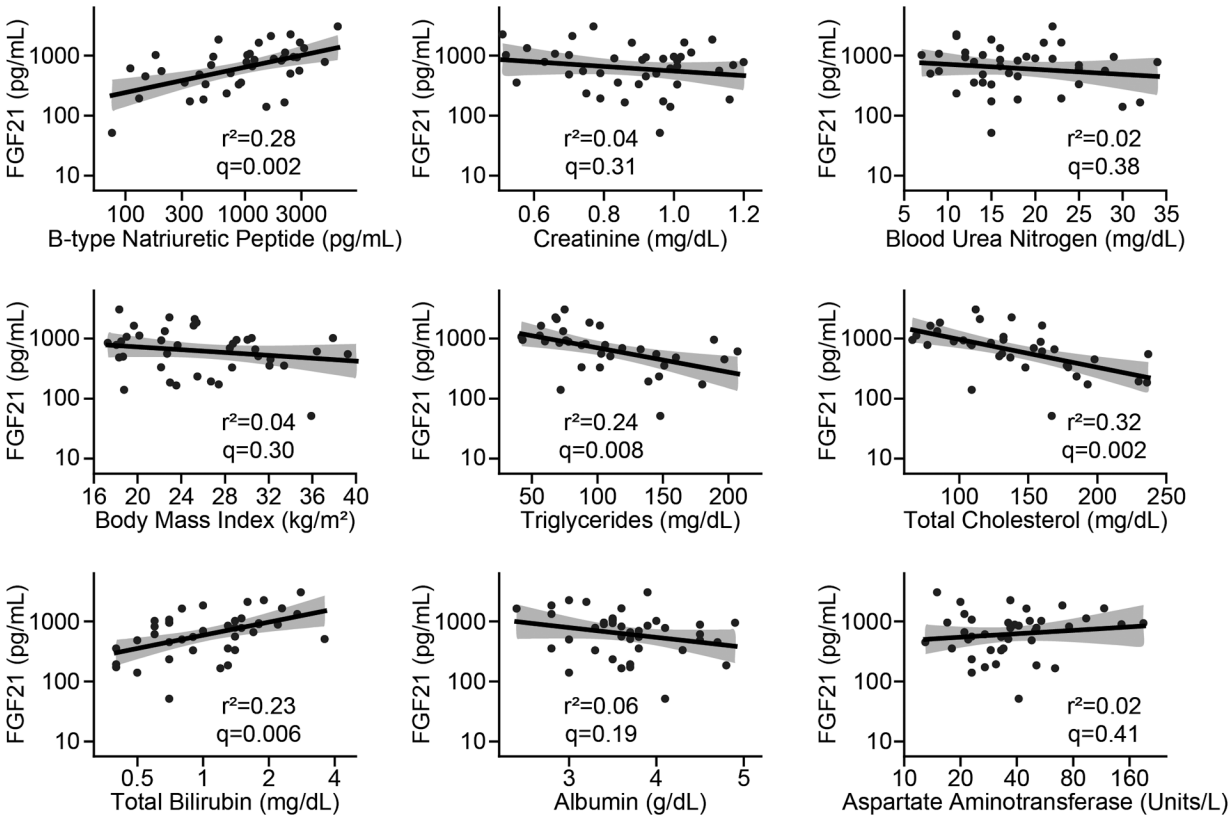


**Figure 4. Correlations between serum FGF21 and clinical parameters.**

Correlation of serum FGF21 values with clinical index via linear regression (n=34–40). The black line is the linear regression, with shaded area corresponding to 95% confidence bands. Coefficient of determination ($r^2$) and corresponding Benjamini-Hochberg corrected p value (q) for a false discovery rate of 0.05 are shown. Note logarithmic scale for FGF21, BNP, AST, and total bilirubin.

**Table 1.**

Characteristics of study population

| | Heart Failure | Controls | Donors |
|---|---|---|---|
| N | 40 | 20 | 9 |
| Age (years) | 48 [38, 54] | 48 [39, 57] | 44 [38, 50] |
| Women | 15 (37.5%) | 11 (55%) | 5 (55.6%) |
| Hispanic/Black/White/Other | 3/2/33/2 | NA | 0/0/8/1 |
| Smoker | 17 (42.5%) | NA | NA |
| Body Mass Index (kg/m$^2$) | 26 [22, 28] | NA | 25 [22, 28] |
| Left ventricular ejection fraction (%) | 19 [17, 21] | NA | 60 [55, 66] |
| Left ventricular end-diastolic diameter (cm) | 6.5 [6.3, 6.7] | NA | 4.1 [3.7, 4.4] |
| Ischemic HFrEF | 12 (30%) | 0 | 0 |
| Non-ischemic HFrEF: | 28 (70%) | 0 | 0 |
| Idiopathic | 19 (48%) | | |
| Peripartum | 3 (8%) | | |
| Drug-induced | 2 (5%) | | |
| Valvular | 2 (5%) | | |
| Other | 2 (5%) | | |
| B-type natriuretic peptide (pg/mL) | 1440 [1027, 1853] | NA | NA |
| Hemoglobin A1C | 5.7 [5.6, 5.8] | NA | 5.4 [5.1, 5.7] |
| Serum creatinine (mg/dL) | 0.9 [0.8, 0.9] | NA | 0.9 [0.6, 1.2] |
| Blood urea nitrogen (mg/dL) | 17.9 [15.7, 20.1] | NA | 16.3 [8.8, 23.9] |
| Aspartate aminotransferase (Units/L) | 45.6 [34.1, 57.0] | NA | 99.8 [34.8, 164.7] |
| Albumin (g/dL) | 3.7 [3.5, 3.9] | NA | 2.7 [2.4, 3.1] |
| Total bilirubin (mg/dL) | 1.2 [1.0, 1.5] | NA | 1.0 [0.7, 1.3] |
| Triglycerides (mg/dL) | 107.1 [91.3, 122.9] | NA | NA |
| Total Cholesterol (mg/dL) | 139.7 [123.7, 155.6] | NA | NA |
| Central venous pressure (mmHg) | 12 [10, 14] | NA | 9 [6, 11] |
| Mean pulmonary arterial pressure (mmHg) | 35 [32, 39] | NA | NA |
| Pulmonary capillary wedge pressure (mmHg) | 24 [21, 27] | NA | NA |
| Beta-blocker | 22 (55%) | NA | NA |
| ACE inhibitor | 20 (50%) | NA | NA |
| Angiotensin receptor blocker | 4 (10%) | NA | NA |
| Aldosterone Blocker | 19 (47.5%) | NA | NA |
| Diuretics | 37 (92.5%) | NA | NA |
| Aspirin | 17 (42.5%) | NA | NA |
| Clopidogrel | 3 (7.5%) | NA | NA |
| Anti-arrhythmics | 14 (35%) | NA | NA |

Values are counts or mean [95% confidence intervals]. NA: not available

**Table 2.**

Human cardiomyopathy RNA-Seq datasets

| Dataset (Ref.) | Cardiomyopathy Type | Total Samples | Detectable FGF21 transcripts – Non-failing (positive/total) | Detectable FGF21 transcripts – Cardiomyopathy (positive/total) |
|---|---|---|---|---|
| GSE135055 [34] | HFrEF | 30 | 0/7 | 0/23 |
| GSE71613 [35] | HFrEF, Restrictive | 8 | 0/4 | 2/4 |
| GSE57344 [36] | HFrEF | 6 | 1/3 | 1/3 |
| GSE46224 [37] | HFrEF | 40 | 0/8 | 1/32 |
| GSE160997 [38] | Hypertrophic | 23 | 0/5 | 2/18 |
| GSE133054 [39] | HFrEF, Hypertrophic | 23 | 0/8 | 5/15 |
| GSE130036 [40] | Hypertrophic | 37 | 0/9 | 2/28 |
| | | 167 | 1/44 | 13/123 |