FGF-23 is associated with increased disease severity and early mortality in cardiogenic shock

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Abstract

Background: Despite the increased use of percutaneous interventions, infarction-related cardiogenic shock (CS) is still associated with high mortality. Biomarkers might be helpful to identify patients at risk, and point towards novel therapeutic strategies in CS. The phosphaturic hormone fibroblast growth factor 23 (FGF-23) has recently been introduced as a predictor for mortality in patients with chronic systolic heart failure. However, its predictive role in CS has not been investigated so far.

Methods and results: FGF-23 was measured in 51 patients with CS. Eighteen patients with uncomplicated acute myocardial infarction (AMI) and 940 patients with stable coronary artery disease (CAD) undergoing elective coronary angiography included in a previous study served as control groups. Compared with patients with stable CAD, FGF-23 was profoundly elevated in patients with CS, but not in patients with uncomplicated AMI (CAD: 131.1 ± 9.5 ; AMI: 175.3 ± 57.2 ; CS: 1684.4 ± 591.7 rU/ml, $p < 0.0001$ CS vs. CAD). In patients with CS, FGF-23 correlated significantly with the SAPS II score ($r = 0.461$, $p = 0.0003$) and NT-pro BNP levels ($r = 0.489$, $p = 0.001$). Patients were stratified as “survivors” and “non-survivors” according to their 28-day mortality. The overall 28-day-mortality-rate was 37%. Non-survivors of CS showed significantly higher FGF-23 levels compared with survivors (3260.1 ± 1514.7 vs. 847.9 ± 182.4 rU/ml, $p = 0.028$). In the ROC curve analysis, FGF-23 levels predicted 28-day mortality (area under the curve (AUC) 0.686, $p = 0.028$), and FGF-23 level of 1180 rU/ml was identified as optimal cut-off value. In a multivariate Cox proportional hazard model adjusted for gender, blood pressure, ejection fraction and levels of creatine kinase, FGF-23 levels above 1180 rU/ml significantly predicted 28-day mortality (hazard ratio (HR) 2.74, 95% CI 1.01–7.04, $p = 0.037$).

Conclusion: In CS, a tremendous increase in FGF-23 occurs, and high levels of FGF-23 are associated with poor outcome.

Keywords

Cardiogenic shock, FGF-23, outcome predictors

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Introduction

Cardiogenic shock (CS) is one of the clinical entities representing acute heart failure syndromes.¹ Despite the broad use of early percutaneous intervention, the mortality rate is still high. Indeed, CS represents the leading cause of in-hospital death in patients with acute myocardial infarction.^{2–4} A growing body of evidence indicates that CS is not simply a hemodynamic problem caused by severe myocardial ischemia leading to decreased cardiac output. Its complex pathophysiology involves neurohormonal responses,

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which initiate a downward spiral resulting in tissue hypoperfusion, hypoxemia, and systemic inflammatory response syndrome (SIRS) and finally death.⁵ Identification of markers may contribute to a better understanding of the underlying mechanisms and may improve identification of patients at risk, in order to initiate appropriate treatment.

A deranged calcium-phosphate metabolism is associated with various cardiovascular diseases. Epidemiologic evidence suggests an association between hyperphosphatemia and coronary calcification,^{6,7} cardiovascular and mortality^{8,9} not only in patients with chronic kidney disease but also in patients with normal renal function. The phosphaturic hormone fibroblast growth factor 23 (FGF-23) is produced by osteoblasts and osteocytes.¹⁰ It is an important negative regulator of serum phosphate levels and is considered to reflect a biomarker of long-term total phosphate burden.¹¹ In the presence of its co-factor Klotho, FGF-23 reduces gastrointestinal phosphate absorption, promotes renal phosphate excretion, and lowers renal conversion of 25-(OH)-D3 into 1,25-(OH)-D3.¹² Circulating levels of FGF-23 have been shown to predict mortality and cardiovascular events in patients with chronic kidney disease.¹³⁻¹⁵ Recently, this relationship has also been observed in patients with normal renal function and documented coronary artery disease,¹⁶ as well as in the general population.¹⁷

Increasing evidence suggests an association between FGF-23 and structural myocardial damage. Three studies showed increased left ventricular hypertrophy in patients with elevated FGF-23 levels.¹⁸⁻²⁰ In over 800 patients undergoing elective coronary angiography with mainly preserved renal function, FGF-23 concentration was associated with atrial fibrillation and left ventricular dysfunction.²¹ Furthermore, FGF-23 is an independent predictor of survival in patients with stable systolic heart failure.^{22,23} Data investigating the role of FGF-23 in CS or critically ill patients are lacking. The present study examined the prognostic value of circulating FGF-23 levels in patients with infarction-related CS.

Methods

Patients and study design

Patients with infarction-related cardiogenic shock. In a prospective mono-centric study, FGF-23 was measured in 51 patients with infarction-related CS who had a TIMI-III-flow²⁴ after acute coronary intervention. The study was approved by and performed according to the institutional review board and according to the WHO guidelines for good clinical practice.^{25,26} Critical illness was defined as a minimum Simplified Acute Physiology Score II (SAPS II) of 30 points.²⁷ Informed written consent was obtained from patient or substitute decision makers. CS was defined as clinical signs of hypoperfusion, such as cool extremities owing to centralization, decreased urine output or alteration in mental status. Clinical diagnosis was confirmed by hemodynamic parameters: systolic blood pressure <90 mmHg in the absence

of hypovolemia or the need for vasopressors, a reduction of cardiac index (<1.8 l/min/m²) and/or an elevation in pulmonary capillary wedge pressure >18 mmHg.²⁵ Patients resuscitated before admission to the intensive care unit (ICU) were excluded. Percutaneous coronary intervention (PCI) was performed in all patients. The physician in charge decided according to clinical needs whether or not to implant an Intraaortic balloon pump (IABP). The use of inotropes, vasopressors and further concomitant treatments was decided according to judgment of the treating intensive care physician. The primary endpoint of the study was 28-day mortality.

Patients with stable coronary artery disease and patients with uncomplicated acute myocardial infarction. Nine-hundred and forty HOM SWEET HOME study¹⁹ participants with stable CAD undergoing elective coronary angiography, who had been included in a prospective study performed in our hospital, served as a primary control group; subjects were recruited between May 2007 and June 2010. FGF-23 measurements from these stable patients have been reported previously.¹⁹ Eighteen patients with uncomplicated acute myocardial infarction defined according to the current guidelines served as a second control group.^{28,29}

Laboratory measurements

Blood samples were collected under standardized conditions immediately after admission to the ICU. The samples were centrifuged at 3000 g for 10 minutes at room temperature. Supernatants were stored in aliquots at -80° C until further use. C-terminal FGF-23 levels were measured from plasma samples by ELISA (Immunotopics, San Clemente, CA, USA; low cut-off value 3 rU/ml, high cut-off value 2000 rU/ml. Samples with FGF-23 >2000 rU/ml were measured after dilution). Plasma levels of creatinine, calcium, phosphate were measured by standard methods. NT-proBNP was assessed by electrochemoluminescence (Cobas 8000, Roche, Mannheim, Germany).

Hemodynamic measurements

According to the recommendations and guidelines for treatment of CS, hemodynamic assessment was performed using pulmonary artery catheters.^{1,30} The following hemodynamic parameters were measured: heart rate (HR), mean arterial blood pressure (MAP), mean pulmonary capillary wedge pressure (PCWP), mean pulmonary artery pressure (PAP), cardiac index (CI), mixed venous oxygen saturation (SvO₂), cardiac power index (CPI), and systemic vascular resistance (SVR).

Statistics

Data management and statistical analysis was performed with SPSS statistics version 20.0 and GraphPad Prism version 5.0. Two-sided *p*-values <0.05 were considered

Table 1. Baseline characteristics at admission of patients with stable coronary artery disease (CAD) and cardiogenic shock (CS).

Characteristic	Stable CAD (n=940)	CS (n=51)	p
Age (years)	66 ± 0.3	68 ± 2.0	0.007
Male gender (%)	728/940 (77.4)	38/51 (74.5)	0.367
Systolic blood pressure (mmHg)	150 ± 0.7	90 ± 2.4	< 0.0001
Diastolic blood pressure (mmHg)	82 ± 0.4	46 ± 1.5	< 0.0001
Heart rate (bpm)	68 ± 0.4	101 ± 3.0	< 0.0001
Cardiovascular risk factors			
Diabetes mellitus (%)	382/940 (40.6)	15/51 (29.4)	0.072
Nicotine (%)	130/940 (13.8)	20/51 (39.2)	< 0.0001
Hemodynamic parameters			
Ejection fraction (EF) (%)	64 ± 0.6	33 ± 2.0	< 0.0001
NT pro-BNP (pg/ml)	630 ± 45.6	12782 ± 1790.0	< 0.0001
Laboratory parameters			
Creatinine (mg/dl)	1.0 ± 0.01	1.5 ± 0.1	< 0.0001
Phosphate (mg/dl)	3.3 ± 0.02	4.1 ± 0.2	= 0.001
Calcium (mmol/l)	2.3 ± 0.004	2.1 ± 0.03	< 0.0001

Categorical variables are presented as percentage of patients and compared by χ^2 test. Continuous data are expressed as means $\pm$ standard error of the mean, and compared by Mann-Whitney test. p values are shown for stable CAD compared with CS.

statistically significant. Categorical variables are presented as percentage of patients and compared using a χ^2 test. Continuous data are expressed as means $\pm$ standard error of the mean, and compared by Mann-Whitney or Kruskal-Wallis tests, as appropriate. The associations between continuous variables were assessed by Spearman's rank correlation testing. The cut-off-point with a specificity of 80% was determined by performing Receiver Operating Characteristic (ROC) analysis. A Cox regression survival plot was created with separate lines for patients with FGF-23 < 1180 and $\geq$ 1180 rU/ml, respectively. Multivariate Cox proportional hazards regression analysis was performed to test whether FGF-23 might represent an independent predictor variable for 28-day-survival.

Results

Patient characteristics

Baseline patient characteristics are shown in Table 1. Compared with patients with stable CAD, CS patients had lower systolic and diastolic BP, a higher HR, were more often smokers, had a lower ejection fraction (EF) and higher NT pro-BNP levels. Furthermore, levels of creatinine, phosphate, and calcium differed significantly.

Nineteen of the 51 CS patients died within 28 days, which corresponds to a mortality rate of 37%. When comparing major demographic characteristics (Table 2), non-survivors had lower BP and a higher HR compared with survivors. No significant differences existed with regards to the main cardiovascular risk factors. As expected, non-survivors had a lower CPI compared with survivors, and they tended to have lower SvO₂ and higher SAPS II score.

FGF-23 is increased in cardiogenic shock and related to survival and disease severity

Compared with patients with stable CAD, circulating FGF-23 levels were profoundly elevated in patients with CS (CAD: 131.1 $\pm$ 9.5 vs. CS: 1684.4 $\pm$ 591.7 rU/ml, p <0.0001). In contrast, FGF-23 levels among patients with uncomplicated AMI (175.3 $\pm$ 57.2 rU/ml) did not differ from patients with stable CAD (Figure 1(a)). Within CS patients, non-survivors had significantly higher FGF-23 levels compared with survivors (3260.1 $\pm$ 1514.7 vs. 847.9 $\pm$ 182.4 rU/ml, p =0.028) (Figure 1(b)). FGF-23 levels correlated with both SAPSII score (r =0.461, p =0.0003) and NT-pro BNP levels (r =0.489, p =0.001) in CS patients (Figure 2(a) and (b)). Furthermore, there was a significant inverse correlation with SvO₂ (r = -0.323, p =0.021) as a marker of tissue hypoperfusion. There was no significant correlation with left ventricular EF or with plasma phosphate.

When stratifying CS patients by FGF-23 levels into quartiles, significantly more non-survivors had increased FGF-23 levels above the third quartile compared with survivors (47.4 vs. 9.4%, p =0.003).

FGF-23 is a predictor for survival in patients with cardiogenic shock

As shown in the ROC analysis, FGF-23 levels showed a high diagnostic accuracy in predicting mortality in CS patients. Figure 3 depicts the ROC curve for FGF-23 and the AUC and p -values for different prognostic variables. FGF-23 showed a higher AUC (0.686) compared with the established prognostic markers SAPS II score and SvO₂. From these ROC curve data, we arbitrarily selected the FGF-23 concentration which

Table 2. Baseline characteristics of patients with cardiogenic shock (CS) ($n=61$) according to the 28-day survival; of the 51 included CS patients, 32 were classified as survivors, 19 as non-survivors.

Characteristic	Survivors ($n=32$)	Non-survivors ($n=19$)	<i>p</i>
Age (years)	66.4 ± 2.9	72.2 ± 2.2	0.30
Male gender (%)	71.9	79	0.74
Heart rate (bpm)	97 ± 4	108 ± 5	0.03
Systolic blood pressure (mmHg)	92 ± 3	83 ± 3	0.01
Diastolic blood pressure (mmHg)	49 ± 2	42 ± 3	0.03
Cardiovascular risk factors			
Hyperlipidemia (%)	62.5	79	0.35
Diabetes mellitus (%)	31.3	26.3	0.76
Hypertension (%)	53.1	52.6	1.00
Nicotine (%)	43.8	31.6	0.56
Hemodynamic parameters			
CPI (W/m ²)	0.4 ± 0.04	0.2 ± 0.02	0.003
SVO ₂ (%)	54.4 ± 2.4	50.1 ± 3.3	0.24
Ejection fraction (EF) (%)	33.2 ± 2.5	32.2 ± 3.4	0.80
SAPS II Score	36.4 ± 2.9	41.7 ± 3.7	0.25
Inotropes (%)	75.0	84.2	0.50
IABP (%)	96.9	100	1.00
Mechanical ventilation (%)	18.8	31.6	0.33
Laboratory parameters			
NT pro-BNP (pg/ml)	$11,168.1 \pm 2160.6$	$15,250.4 \pm 3080.5$	0.17
CK max (U/l)	2129.1 ± 556.2	4326.2 ± 1593.0	0.16
Creatinine (mg/dl)	1.4 ± 0.1	1.7 ± 0.2	0.30
Phosphate (mg/dl)	3.7 ± 0.2	4.4 ± 0.4	0.09
Calcium (mmol/l)	2.2 ± 0.03	2.1 ± 0.1	0.05

Categorical variables are presented as percentage of patients and compared by χ^2 test. Continuous data are expressed as means $\pm$ standard error of the mean, and compared by Mann-Whitney test.

Figure 1. (a) FGF-23 serum levels in patients with stable coronary artery disease (CAD), uncomplicated acute myocardial infarction (AMI) and cardiogenic shock (CS). Data are shown as mean $\pm$ SEM. (b) FGF-23 serum levels in survivors ($n=32$) and non-survivors ($n=19$) of cardiogenic shock. Data are shown as mean $\pm$ SEM.

Figure 2. Spearman correlations of FGF-23 serum levels with (a) SAPS II Score and (b) NT pro-BNP serum concentrations. To allow better visibility, results from four patients with FGF-23 > 6000 rU/ml are not depicted.

predicted mortality with a specificity of 80% (1180 rU/ml) as the best cut-off value for further analyses.

As shown in the multivariate Cox regression survival plot in Figure 4, patients with FGF-23 levels above the cut-off level of 1180 rU/ml had a nearly threefold increased rate of death compared with patients with FGF-23 levels below this cut-off level independently of gender, blood pressure at admission, EF and myocardial infarction size measured by creatine kinase (CK); hazard ratio (HR) 2.74, 95% CI 1.01–7.04, $p=0.037$.

Discussion

The present study reports for the first time a profound increase in plasma FGF-23 in patients presenting with CS. Moreover, patients with highest FGF-23 levels had a worse outcome, and FGF-23 independently predicted short-term mortality.

The clinical implications of these findings may be threefold. Firstly, although further underscoring the idea of a major interplay between high FGF-23 and cardiovascular disease, they challenge our present understanding of its temporal sequences. The presence of such interplay was

first reported by epidemiological studies, which associated hyperphosphatemia with adverse outcome.⁹ Given the tremendous rise in FGF-23 levels in subjects with impaired renal function,³¹ FGF-23 was reported to predict cardiovascular events^{13,15} and overall mortality^{13,14,32} in patients with chronic kidney disease (CKD). Recently, the association between plasma FGF-23 and impaired cardiovascular outcome was expanded towards subjects not pre-selected by prevalent CKD.^{16,17} Of note, all earlier epidemiological studies^{13–17} considered FGF-23 a direct or indirect pathophysiological mediator of cardiovascular disease, the latter potentially via inhibiting activation of vitamin D. This idea was further corroborated by cross-sectional data on associations of FGF-23 levels with left-ventricular hypertrophy,^{18–20} atrial fibrillation and impaired systolic left ventricular function.²¹ Furthermore, recent epidemiological studies reported FGF-23 to predict mortality in patients with chronic systolic heart failure,^{22,23} even after adjusting for conventional risk markers including natriuretic peptides. Notably, experimental evidence showed direct harmful effects of FGF-23 on myocardial tissue in vivo and in vitro,¹⁸ so that it gradually became accepted as a direct inducer of subsequent cardiac disease.³³

Against this background, our finding of increased FGF-23 levels in the acute setting of CS partly challenges the idea that hyperphosphatemia only precedes cardiovascular disease, and it suggests that under certain circumstances, cardiac disease may induce rather than follow hyperphosphatemia. Admittedly we cannot provide patients' data on FGF-23 and kidney function before the onset of CS, as patients were recruited after hospital admission. Nonetheless, we measured FGF-23 levels that by far surpass those found in stable patients with either impaired left-ventricular systolic function²¹ or mild to moderate CKD.³¹ Moreover, all patients suffered from infarction-related CS, and earlier studies failed to associate FGF-23 levels with subsequent myocardial infarction.^{16,17} These arguments refute the idea that severe hyperphosphatemia preceded CS in our patients. Instead, our findings strongly suggest that CS may induce FGF-23 secretion.

The underlying pathophysiological pathways remain to be elucidated. Hypoxemia might be considered a trigger for excess FGF-23 production.³⁴ This hypothesis is supported by the fact that there was a significant inverse correlation between FGF-23 levels and the SVO_2 , a marker of tissue hypoperfusion. Alternatively, given acute heart failure is characterized by a strong activation of the renin-angiotensin system (RAAS), and that hyperphosphatemia has been linked to an increased activity of the RAAS,³⁵ such an interaction might also contribute to the results. Interestingly, in patients with CS after myocardial infarction, the low cardiac output induced by a severe left ventricular dysfunction rather than acute myocardial ischemia *per se* appeared to increase FGF-23 secretion, as FGF-23 was only elevated in CS, but not in uncomplicated AMI patients.

Figure 3. (a) Receiver operating curve (ROC) assessing the prognostic accuracy of FGF-23 in predicting 28-day mortality in patients with cardiogenic shock. (b) Areas under the curve (AUC) for FGF-23 compared with other prognostic parameters in cardiogenic shock. CPI: cardiac power index; SvO₂: mixed venous oxygen saturation, SAPS II score.

It is tempting to speculate that the strong association between FGF-23 and adverse cardiovascular outcome in earlier studies^{13,15-17} might partly be caused by reverse association, where elevated baseline FGF-23 was reflecting prevalent subclinical cardiac disease, rather than being induced by incident cardiac disease. Notably, large cohort studies found FGF-23 concentrations to predict mortality and future heart failure events rather than acute myocardial infarction.^{16,17}

A second implication of our study is the identification of FGF-23 as a predictor for adverse outcomes in CS. If future larger trials confirm this predictive role of FGF-23, stratification of CS patients by FGF-23 at hospital admission might allow to better identify patients with highest risk for mortality, who may need more aggressive treatment than patients at moderate risk.

As a final implication, our findings might point toward new therapeutic strategies in CS. High FGF-23 levels can be reduced by several pharmacological interventions, of

which some have already been introduced into clinical medicine (such as oral phosphate binders), whereas others are still under development (such as direct FGF-23 inhibitors or receptor blockers). Therefore, it will be of considerable interest to learn whether in CS, hyperphosphatemia only represents an innocent bystander, or whether it may exert direct harmful cardiovascular effects.

Our study has some potential limitations. First, the results are only observational. Therefore, they do not prove causality but are hypothesis generating. Second, we used a historical control group of patients included in a previous study conducted between 2007 and 2010. Third, we did not collect urine samples from our study participants; therefore, renal phosphate handling in CS cannot be analyzed in detail. Furthermore, we cannot provide a detailed analysis of renal function in the setting of CS. We did not observe significant differences in plasma creatinine concentrations between survivors and non-survivors. As creatinine is not a valid marker of renal function in acute kidney injury, the

Figure 4. (a) Multivariate Cox regression survival plot with separate lines for patients with FGF-23 < 1180 rU/ml and ≥ 1180 rU/ml, respectively. (b) Results of the multivariate analysis. SBP: systolic blood pressure; EF: ejection fraction; CKmax: maximum of creatine kinase.

latter might have contributed to hyperphosphatemia in our CS patients.

In summary, we report a tremendous acute rise of FGF-23 in patients with infarction-related CS, which challenges our pathophysiological understanding of temporal relationships between hyperphosphatemia and cardiac disease. Moreover, we show that FGF-23 predicts short-term mortality in CS. Future experimental and clinical trials should explore the pathophysiological implications of hyperphosphatemia in CS in order to develop new therapeutic strategies.

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Conflict of interest

JP and SS received speaker honoraria from Sanofi-Aventis. GHH received speaker fees and travel grants from SHIRE.

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