Fibroblast growth factor 23 levels are elevated and associated with severe acute kidney injury and death following cardiac surgery

David E. Leaf[1], Marta Christov[2,3], Harald Jüppner[2], Edward Siew[4], T. Alp Ikizler[4], Aihua Bian[5], Guanhua Chen[5], Venkata S. Sabbisetti[1], Joseph V. Bonventre[1], Xuan Cai[6], Myles Wolf[6,7] and Sushrut S. Waikar[1,7]

[1]*Division of Renal Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA;* [2]*Endocrine Unit and Pediatric Nephrology Unit, Massachusetts General Hospital, Boston, Massachusetts, USA;* [3]*Department of Medicine, New York Medical College, Valhalla, NY;* [4]*Division of Nephrology and Hypertension, Vanderbilt Center for Kidney Disease, Vanderbilt University Medical Center, Nashville, Tennessee, USA;* [5]*Department of Biostatistics, Vanderbilt Center for Kidney Disease, Vanderbilt University Medical Center, Nashville, Tennessee, USA; and* [6]*Division of Nephrology, Department of Medicine and Center for Translational Metabolism and Health, Institute for Public Health and Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA*

Fibroblast growth factor 23 (FGF23) is elevated in chronic kidney disease and associated with increased mortality, but data on FGF23 in humans with acute kidney injury (AKI) are limited. Here we tested whether FGF23 levels rise early in the course of AKI following cardiac surgery and if higher postoperative FGF23 levels are independently associated with severe AKI and adverse outcomes. Plasma C-terminal FGF23 (cFGF23) levels were measured preoperatively, at the end of cardiopulmonary bypass, and on postoperative days 1 and 3 in 250 patients undergoing cardiac surgery. We also measured intact FGF23, parathyroid hormone, phosphate, and vitamin D metabolites in a subgroup of 18 patients with severe AKI and 18 matched non-AKI controls. Beginning at the end of cardiopulmonary bypass, cFGF23 levels were significantly and consistently higher in patients who developed AKI compared with those who did not. The early increase in cFGF23 predated changes in other mineral metabolites. The levels of intact FGF23 also increased in patients who developed severe AKI, but the magnitude was lower than cFGF23. In analyses adjusted for age, preoperative eGFR, and cardiopulmonary bypass time, higher cFGF23 levels at the end of cardiopulmonary bypass were significantly associated with greater risk of severe AKI and the need for renal replacement therapy or death. Thus, cFGF23 levels rise early in AKI following cardiac surgery and are independently associated with adverse postoperative outcomes.

Kidney International (2016) **89,** 939–948; http://dx.doi.org/10.1016/j.kint.2015.12.035

KEYWORDS: AKI; RRT; fibroblast growth factor 23; cardiopulmonary bypass

Correspondence: *David E. Leaf, Renal Division, Brigham and Women's Hospital, 75 Francis St, Boston, Massachusetts 02115, USA. E-mail: deleaf@partners.org*

[7]These authors contributed equally to this work.

Received 17 August 2015; revised 24 November 2015; accepted 3 December 2015; published online 17 February 2016

Acute kidney injury (AKI) is one of the most devastating complications of cardiac surgery. As defined by consensus criteria, AKI occurs in up to 30% of patients after cardiac surgery and is associated with a 6- to 18-fold increased risk of death compared with individuals who do not acquire AKI.[1–4] Severe AKI that requires dialysis occurs in ~1% of patients who undergo cardiac surgery and is associated with in-hospital mortality rates that exceed 40%.[1] Novel markers of early AKI and novel therapeutic targets are thus needed to improve clinical outcomes after cardiac surgery.

Disordered mineral metabolism is a common complication of chronic kidney disease (CKD), but it has been studied less extensively in AKI. Decreased 1,25-dihydroxyvitamin D levels and hypocalcemia associated with reduced or elevated parathyroid hormone (PTH) levels have been reported in small studies of patients with established AKI,[5–8] but the mechanisms are poorly defined. Elevated levels of the osteocyte-derived hormone, fibroblast growth factor 23 (FGF23), may contribute to some of these laboratory abnormalities, because FGF23 normally stimulates urinary phosphate excretion and inhibits activation of 25-hydroxyvitamin D.[9] In the setting of CKD, FGF23 rises early in the course of disease,[10] contributes to the development of secondary hyperparathyroidism,[11] and is strongly associated with increased risk of cardiovascular disease[12–14] and death.[15,16]

Considerably less is known about FGF23 in AKI. In an animal study of AKI induced by either folate or glycerol injection, we reported that FGF23 levels rose soon after the onset of renal injury, independent of changes in serum phosphate, calcium, or PTH- or vitamin D-dependent signaling.[17] In the same study, pilot data from 14 patients undergoing cardiac surgery revealed similar findings.

The primary purpose of this study was to comprehensively define the kinetics of changes in FGF23 and associated mineral metabolites before and soon after AKI onset in a larger prospective cohort study of adults undergoing cardiac surgery. We

tested the hypotheses that FGF23 levels rise early in the course of AKI and that higher postoperative levels are independently associated with an increased risk of severe AKI and other postoperative complications.

RESULTS

Baseline characteristics

Cardiac surgery is an ideal clinical model to investigate the evolution of changes in FGF23 and other mineral metabolites before and during human AKI, because the timing of renal injury can be pinpointed. We enrolled 250 patients who underwent cardiac surgery and were at high risk of the development of postoperative AKI but had no evidence of AKI at baseline. The median age was 79 years (interquartile range [IQR]), 72–83 years), the median baseline estimated glomerular filtration rate (eGFR) was 50 ml/min per 1.73 m^2 (IQR, 41–66 ml/min per 1.73 m^2), and the median baseline C-terminal FGF23 (cFGF23) level was 124 relative units (RU) per ml (IQR, 74–317 RU/ml). Additional baseline and operative characteristics are shown in Table 1.

AKI definition and event rates

AKI was defined as an increase in the serum creatinine level to ≥0.3 mg/dl within 48 hours or ≥50% in 7 days.[18] Patients meeting criteria for AKI were further classified as having mild or severe AKI. Mild AKI was defined as an increase in serum creatinine level <2 times the baseline; severe AKI was defined as doubling of serum creatinine or a need for renal replacement therapy (RRT). Using these definitions, we identified incident AKI in 73 patients (29%), 55 cases (22%) of which were mild and 18 cases (7%) of which were severe.

Kinetics of cFGF23 in AKI after cardiac surgery

Levels of cFGF23 over time were significantly higher in patients who developed AKI compared with those who did not ($P < 0.001$ for global comparison of cFGF23 curves in patients with or without AKI) (Figure 1a). Evaluation of cFGF23 levels at individual time points revealed that levels were similar at baseline, became significantly increased at the end of cardiopulmonary bypass in those with AKI compared with those without AKI ($P \leq 0.01$), and remained significantly higher on postoperative days (PODs) 1 ($P < 0.001$) and 3 ($P < 0.001$) (Figure 1a). Baseline cFGF23 levels were higher among patients with pre-existing CKD, defined as an eGFR < 60 ml/min per 1.73 m^2, versus those without CKD (median, 140 RU/ml; IQR 79–349 RU/ml versus 98 RU/ml; IQR, 69–173 RU/ml; $P < 0.01$). However, postoperative cFGF23 levels increased in similar patterns among patients who acquired

Table 1 | Baseline/operative characteristics

Characteristic	All (n = 250)	No AKI (n = 177)	Mild AKI (n = 55)	Severe AKI (n = 18)	*P* value[a]
Demographics					
Age (yr)	79 (72–83)	79 (74–83)	79 (71–84)	72 (64–79)	0.02
Female	107 (43)	80 (45)	21 (38)	6 (33)	0.46
White	242 (97)	172 (97)	53 (96)	17 (94)	0.80
Preoperative renal function					
Serum creatinine (mg/dl)	1.2 (1.0–1.5)	1.2 (1.0–1.4)	1.3 (1.1–1.6)	1.3 (1.0–1.8)	0.03
eGFR (ml/min per 1.73 m^2)	50 (41–66)	53 (43–66)	48 (36–66)	48 (41–58)	0.09
eGFR < 60 ml/min per 1.73 m^2	170 (68)	117 (66)	39 (71)	14 (78)	<0.001
eGFR 30–59 ml/min per 1.73 m^2	145 (58)	104 (59)	29 (53)	12 (67)	0.54
eGFR 15–29 ml/min per 1.73 m^2	25 (10)	13 (7)	10 (18)	2 (11)	0.06
eGFR < 15 ml/min per 1.73 m^2	0 (0)	0 (0)	0 (0)	0 (0)	NA
Comorbidities					
Hypertension	205 (82)	147 (83)	48 (87)	10 (56)	<0.01
Congestive heart failure	103 (41)	78 (44)	18 (33)	7 (39)	0.32
Diabetes mellitus	93 (40)	67 (38)	22 (40)	4 (22)	0.38
Chronic lung disease	56 (22)	38 (21)	15 (27)	3 (17)	0.55
Malignancy	52 (21)	39 (22)	12 (22)	1 (6)	0.25
Chronic liver disease	8 (3)	4 (2)	1 (2)	3 (17)	<0.01
Operative characteristics					
Type of procedure					
CABG alone	31 (12)	22 (12)	9 (16)	0 (0)	0.19
Valve alone	111 (44)	80 (45)	21 (38)	9 (50)	0.57
CABG and valve	78 (31)	55 (31)	20 (36)	3 (17)	0.29
Urgent procedure	98 (39)	69 (39)	24 (44)	5 (28)	0.49
Previous cardiac surgery	78 (31)	56 (32)	13 (24)	9 (50)	0.11
CPB time (min)	140 (100–196)	133 (98–183)	152 (103–197)	209 (158–288)	<0.001
Cross-clamp time (min)	93 (66–126)	89 (66–123)	98 (65–142)	149 (97–194)	0.002
Preoperative cFGF23 (RU/ml)	124 (74–317)	111 (72–302)	135 (81–257)	295 (155–2564)	0.03

Data are presented as n (%) or median (interquartile range [IQR], 25th–75th percentile). Mild AKI was defined as an increase in serum creatinine level to ≥ 0.3 mg/dl within 48 hours or ≥50% in 7 days. Severe AKI was defined as an increase in serum creatinine level to ≥2.0 times baseline or initiation of renal replacement therapy. eGFR was determined using the (Chronic Kidney Disease Epidemiology Collaboration) equation.

AKI, acute kidney injury; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; CPB, cardiopulmonary bypass; eGFR, estimated glomerular filtration rate; NA, not applicable; RU, relative units.

[a]*P* value for global comparisons among groups by Kruskal-Wallis and chi-square tests for continuous and categorical variables, respectively.