

Relationship between Fibroblast Growth Factor 21 and Extent of Left Ventricular Remodeling after Acute Myocardial Infarction

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Abstract

Background: Fibroblast growth factor 21 (FGF21) is a novel myokine released from skeletal muscle. Recent studies have showed that FGF21-transgenic mice had low plasma levels of insulin-like growth factor-1, a potent tissue survival factor, in ischemic myocardium following acute myocardial infarction (AMI).

Objective: To examine a role of FGF21 in subsequent complication after AMI.

Methods: Patients experiencing their first AMI (n=71, mean age 62.4±10.1 years old) was employed. Successful coronary reperfusion was accomplished within 12 hours in all patients. Plasma FGF21 levels were measured on admission, and 7 days and 6 months after onset. Left ventricular (LV) remodeling was assessed by left ventriculography on the day of admission and 6 months after AMI.

Results: Levels of FGF21 in plasma peaked on admission and had declined by 6 months (admission: 611±40, day 7: 246±23, 6 months: 316±24 pg/ml, P<0.001). The FGF21 levels were correlated with plasma lactate levels on admission (r=+0.26, P=0.03). The LV end-diastolic volume index (LVEDVI) significantly increased 6 months after AMI (admission: 79.5±2.4, 6 months: 84.5±2.9 ml/m², P=0.004). The FGF 21 levels on admission were positively correlated with the changes in LVEDVI (r=+0.23, P=0.04). The multivariate regression analysis showed that the plasma FGF21 levels on admission was a significant explanatory variable for the changes in LVEDVI (β=+0.232, P=0.041).

Conclusions: These results suggest that a novel myokine, FGF21, reflects circulatory insufficiency and could be a marker for late-stage LV remodeling after AMI.

Keywords: Myokine; Ventricular remodeling; ST elevation myocardial infarction; Skeletal muscle

Introduction

Although primary percutaneous coronary intervention (PCI) has improved the survival of patients with acute myocardial infarction (AMI), the development of left ventricular (LV) remodeling, subsequent heart failure, and sudden cardiac death remain significant clinical issues [1,2]. LV remodeling after AMI is the process of infarct expansion followed by progressive LV dilatation and is associated with adverse clinical outcomes [3]. Determining novel factors related to LV remodeling might provide further advances.

Fibroblast growth factor 21 (FGF21) was identified as an atypical member of the FGF family that functions like an endocrine hormone [4]. FGF21 was reported to be expressed predominantly in liver, but has also been found in muscle tissue [5]. FGF21 induces the synthesis of ketone bodies, the principal source of energy during prolonged fasting and starvation [6]. It also sensitizes mice to torpor, an energy-conserving state characterized by decreases in body temperature and physical activity [7]. Recently it has been shown that overexpression of FGF21 in mice reduced growth and decreased plasma insulin-like growth factor-1 (IGF-1) concentrations by inhibiting growth hormone signaling [8]. Interestingly, not only low body mass index but also low levels of IGF-1 in acute phase were associated with a poor prognosis after AMI [9-12].

Myokines are humoral factors produced and released from contracting muscles. Human studies have suggested that levels of blood lactate, hormones and growth factors in blood were higher after low-intensity exercise with blood flow restriction of muscle than that without restriction [13,14]. In this regard, muscle ischemia might be related to release of vasoactive substances, growth factors,

and myokines. Considering the association of IGF-1 and body mass with prognosis of AMI, there might be an effect of ischemia-related myokines on ventricular function after AMI.

AMI patients with inadequate circulation on presentation had higher CADILLAC risk scores leading to greater subsequent mortality [15]. We hypothesized that circulating FGF21 exerts a causal influence on subsequent LV dilatation through its physiological actions. We conducted a prospective study to investigate the relationship between FGF21 in plasma and LV remodeling in the chronic phase of AMI.

Methods

Preliminary study

We employed healthy volunteers to examine the effect of exercise on circulating myokine levels (n=9, all males, mean age=35.3±5.8 years). Treadmill exercise test was started with the standard Bruce protocol. Bruce stage was increased until maximum heart rate was obtained. After maximum heart rate was achieved, the speed of the machine was controlled to maintain the heart rate of 85% of maximum. The subjects

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Received May 09, 2011; Accepted July 06, 2011; Published July 10, 2011

Citation: Kondo H, Hojo Y, Saito T, Ikemoto T, Katsuki T, et al. (2011) Relationship between Fibroblast Growth Factor 21 and Extent of Left Ventricular Remodeling after Acute Myocardial Infarction. J Clin Exp Cardiol 2:139. doi:10.4172/2155-9880.1000139

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then continued exercising for 30 minutes at 85% of maximum heart rate. Anti-coagulated venous blood samples were obtained before and, immediately, 30 minutes, 60 minutes and 240 minutes after the exercise. Samples were centrifuged at 1000 X g for 10 minutes at 4°C. The plasma was stored at -80°C until the assay.

Study population

We prospectively selected 78 consecutive patients experiencing their first ST elevation AMI admitted to Jichi Medical University Hospital. AMI was defined by typical chest pain and a ST-segment elevation of 1 mm or more in two or more contiguous leads on ECG at admission [16]. All patients had a single primary lesion and received primary PCI with a bare-metal stent implantation. Successful coronary recanalization with a Thrombolysis In Myocardial Infarction (TIMI) flow grade of more than 2 was accomplished within 12 hours after the onset of symptom. Patients with cardiac arrest, inflammatory diseases, left main trunk and 3-vessel disease, malignancy, previous coronary artery bypass grafting, severe liver or kidney dysfunction, significant valvular heart disease, stent thrombosis, taking immunosuppressive drugs, or who had undergone defibrillation shock were excluded. The Ethics Committee of Jichi Medical University approved the protocol of the study. All patients enrolled in the study gave informed consent. This investigation conforms to the principles outlined in the Declaration of Helsinki.

Assessment of LV remodeling and hemodynamic status

All patients submitted to coronary angiography and left ventriculography (LVG) on the day of admission and 6 months after onset. During the injection of the contrast medium (30ml of 320mg I/ml at 10ml/sec.), biplane images were obtained at a rate of 30 images per second. The right anterior oblique view was analyzed to calculate left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV) and left ventricular ejection fraction (LVEF), using the area-length method (QCA-CMS, Version 6.0, Medis, Nuenen, The Netherlands). The end-diastolic and end-systolic phases were determined visually [17]. The mean normalized systolic ejection rate (MNSER) was determined as LVEF/ejection time. The contractility index was calculated by dividing LV systolic pressure (P_{syst}) by LVESV. All data obtained from catheterization studies were evaluated by a single observer blinded to the blood test findings.

Enzyme-linked immunosorbent assay and other laboratory analyses

Peripheral blood was taken from patients on the day of admission, on day 7 and at 6 months after onset. Peripheral blood was collected in the morning on day 7 and at 6 months in a fasted condition. Anti-coagulated samples were then centrifuged immediately at 1000 X g (4°C, 10 minutes) and stored at -80°C until the assay. FGF21 concentrations were measured by enzyme-linked immunosorbent assay according to the manufacturer's instructions (BioVender, Brno, Czech Republic). All FGF21 measurements were performed by investigators unaware of the patient's characteristics and outcome. The creatine phosphokinase (CPK)-area under the curve (CPK-AUC) [18] was computed by numerical integration with a zero-line of 100 IU/L using Prism software (Graph Pad Software, Inc., San Diego, California). Values were calculated in IU/l × hr.

Study end point

We set the fold-increase in the LVEDV index (LVEDVI) at 6

months after AMI as the primary endpoint because LVEDV reflects both structural remodeling and diastolic filling. End-diastolic myocyte fiber length and LV dilatation were associated with progressive global cardiac dysfunction leading to an unfavorable clinical outcome [19,20].

Statistical analysis

All values are expressed as the mean±SEM unless otherwise indicated. Changes in parameters induced by exercise stress tests or during the course of AMI were evaluated by a one-way analysis of variance with repeated measures. Changes in parameters over 6 months were analyzed with a paired t-test. Pearson's correlations were performed to determine simple associations between two parameters. A stepwise multivariate regression analysis was used to evaluate significant variables contributing to LV remodeling. Values of P<0.05 were considered significant. All statistical analyses were performed with a commercially available statistical package (SPSS Inc., Chicago, Illinois).

Results

Preliminary study

All subjects accomplished the study protocol. Figure 1 shows the changes in plasma levels of CPK, interleukin-6 and FGF21 induced by exercise stress. As shown in the figure 1, plasma levels of CPK peaked immediately after the exercise and subsequently declined for 240 minutes. Interleukin-6 was significantly elevated immediately post

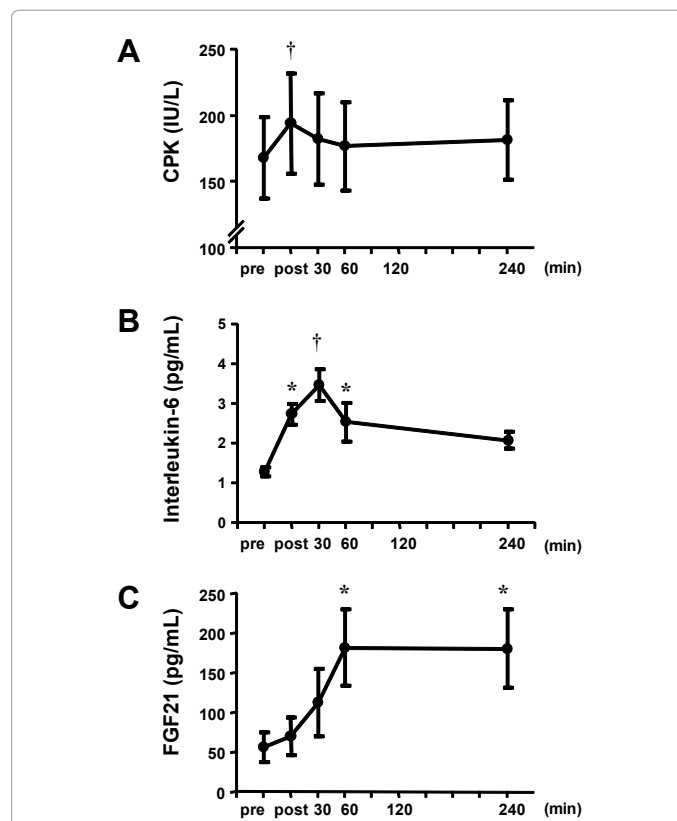
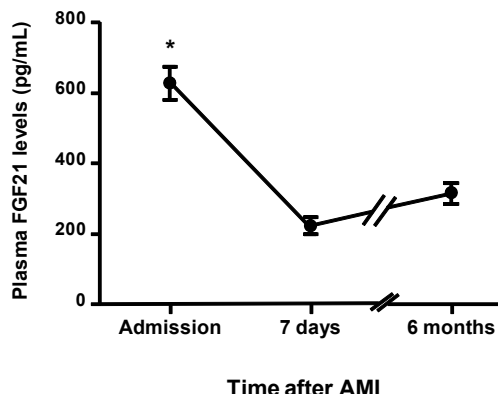


Figure 1: Time course of changes in creatine phosphokinase and myokine levels after exercise. Healthy volunteers (n=9) were made to exercise at 85% of the target heart rate for 30 minutes. Plasma levels of creatine phosphokinase (panel A), interleukin-6 (panel B) and FGF21 (panel C) were measured. †: P<0.001, *: P<0.01 versus before exercise.



*: P<0.001 versus day 7 and versus 6 months

Figure 2: Time course of changes in FGF21 levels after acute myocardial infarction. The figure shows the time course of plasma FGF21 levels after the onset of acute myocardial infarction (AMI) (admission: 611±40, day 7: 246±23, 6 months: 316±24 pg/ml).

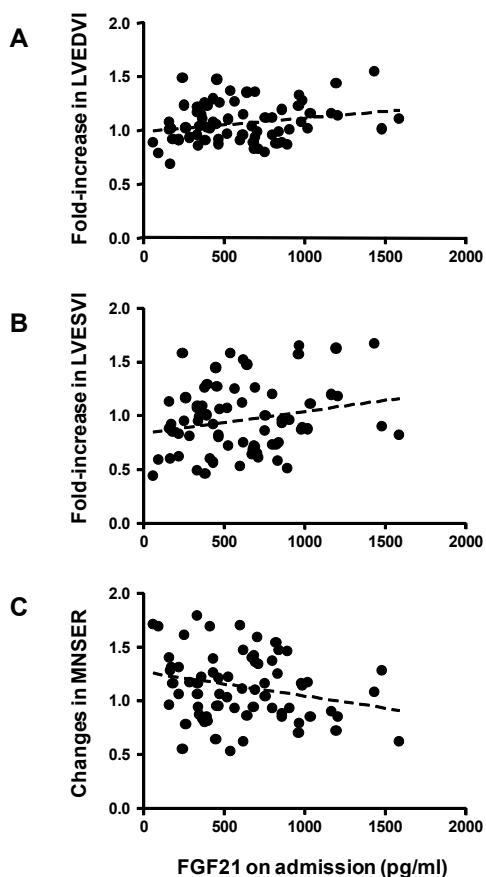


Figure 3: Correlation between plasma FGF21 levels and left ventricular remodeling after acute myocardial infarction. The figure shows simple correlations between plasma FGF21 levels on admission and left ventricular end-diastolic volume index (LVEDVI), left ventricular end-systolic volume index (LVESVI), and the mean normalized systolic ejection rate (MNSER) over 6 months after acute myocardial infarction. There was a significant positive correlation between plasma FGF21 levels on admission and the fold-increase in LVEDVI ($r=+0.23$, $P=0.04$). A positive correlation was also found between plasma FGF21 levels on admission and the fold-increase in LVESVI with marginal significance ($r=+0.22$, $P=0.07$). There was a significant negative correlation between FGF21 on admission and changes in MNSER ($r=-0.24$, $P=0.04$).

exercise, peaked at 30 min, and remained elevated at 60 min. Levels were returned towards baseline by 240 min. In contrast, levels of FGF21 elevated gradually with significant increases at 60 and 240 minutes.

Baseline characteristics

After initial enrolment of the study, 6 patients could not be contacted. One patient died in-hospital from cardiac rupture. Among the remaining 71 patients (59 males and 12 females, aged 62.4 ± 10.1 years, ranging from 34 to 78 years), no death, heart failure or re-admission occurred during the study period. Forty seven patients had hypertension (66%), 23 had diabetes mellitus (32%), 42 had dyslipidemia (59%), 45 were current smokers (63%), and 14 had a family history of coronary artery disease (20%). Their body mass index (BMI) was 24.4 ± 0.4 kg/m². Forty-two patients had anterior, 24 had inferior and 5 had postero-lateral infarctions. All patients were treated with PCI, and a TIMI flow grade of more than 2 was obtained at the primary lesions. One patient had large diagonal branch disease, 46 patients had 1-vessel disease and 24 patients had 2-vessel disease. The mean onset-to-balloon time was 4.7 ± 2.3 hours. LVEF ranged from 30 to 73%, with a mean of 51.4%. CPK-AUC was $99,919 \pm 7,471$ IU/l X hr and the lactate level on admission was 1.6 ± 0.1 mmol/L. After PCI, dual anti-platelet therapy (thienopyridine on top of aspirin) was given to all patients. β -blockers were prescribed to 47 patients, calcium channel blockers to 8 patients, diuretics to 3 patients, nicorandil to 5 patients, rennin-angiotensin system (RAS) inhibitors to 63 patients, and statins to 58 patients. In the acute phase, catecholamine was given intravenously to 4 patients, nicorandil to 15 patients, nitroglycerine to 22 patients, and carperitide to one patient and intra-aortic balloon pumping was used in 19 patients.

Coronary angiographic restenosis, defined as the stenosis of more than 50% of the target vessel diameter was revealed in 15 patients (21.1%) at 6 months follow-up, however all patients showed TIMI flow

Parameter	Admission	After 6 months	P value
LVEDVI (ml/m ²)	79.5±2.4	84.5±2.9	0.004
LVESVI (ml/m ²)	39.3±1.7	37.2±2.0	0.144
LVEF (%)	51.4±1.2	57.8±1.2	<0.0001
SV index (ml/m ²)	40.3±1.4	47.5±1.6	<0.0001
MNSER (/sec.)	1.72±0.05	1.88±0.07	0.02
Psyst/ESV (mmHg/ml)	2.18±0.13	2.74±0.20	<0.0001

Values are expressed as mean±SEM. P values are based on paired tests (versus admission). LVEDVI: Left Ventricular End-Diastolic Volume Index; LVESVI: Left Ventricular End-Systolic Volume Index; LVEF: Left Ventricular Ejection Fraction; SV: Stroke Volume; MNSER: Mean Normalized Systolic Ejection Rate; Psyst: LV systolic pressure; ESV: End-Systolic Volume

Table 1: Quantitative Left Ventriculography and LV Contractility.

	Coefficient (β)	P Value
Age	-0.05	0.66
Body mass index	-0.18	0.13
CPK-AUC	+0.26	0.03
LVEF	+0.12	0.33
eGFR at discharge	-0.17	0.14
Lactate	+0.08	0.49
Onset-to-balloon time	-0.06	0.59
FGF21 on admission	+0.23	0.04

CPK: Creatine Phosphokinase; AUC: Area Under the Curve; LVEF: Left Ventricular Ejection Fraction; eGFR: estimated Glomerular Filtration Rate; FGF21: Fibroblast Growth Factor 21

Table 2: Correlation between clinical parameters and fold-increase in left ventricular end-diastolic volume over 6 months.

	Coefficient (β)	P value
Model 1	F=4.85	P=0.031
CPK-AUC	+0.256	.0031
Model 2	F=4.67	P=0.005
CPK-AUC	+0.257	0.024
Nitroglycerine IV	-0.240	0.034
FGF21 on admission	+0.232	0.041

CPK-AUC: Creatine Phosphokinase-Area Under the Curve; IV: Intravenous injection; FGF21: Fibroblast Growth Factor 21

Table 3: Results of multivariate stepwise regression analysis.

grade 3 at the treated sites. No occlusion of the treated vessel occurred. There was no significant difference in the fold-increase of LVEDVI between the patients with restenosis and those without ($P=0.14$).

Quantitative ventriculography and LV contractility

Table 1 shows the changes in parameters related to LV function over 6 months after AMI. The LVEF, the stroke volume index, MNSER and the $P_{\text{sys}}/\text{LVESV}$ increased significantly. LVEDVI increased significantly 6 months after AMI (admission: 79.5 ± 2.4 , 6 months: 84.5 ± 2.9 ml/m², $P=0.004$). LVEDVI increased in 44 patients, but did not increase in the remaining 28 patients. LVESV index (LVESVI) did not change significantly. The fold-increase in LVEDVI inversely correlated with LVEF at 6 months after AMI ($r=-0.26$, $P=0.03$). Similarly, the fold-increase in LVESVI correlated inversely with LVEF at 6 months after AMI ($r=-0.51$, $P<0.001$).

Changes in FGF21 levels and the association with clinical parameters

Figure 2 shows the time course of the changes in FGF21 levels during 6 months after AMI. Maximum levels were observed on admission with a subsequent decline by 6 months (admission: 611 ± 40 , day 7: 246 ± 23 , 6 months: 316 ± 24 pg/ml, $P<0.0001$). We found a significant positive correlation between lactate and FGF21 levels on admission ($r=+0.26$, $P=0.03$). We did not find any significant correlation between FGF21 levels and other clinical parameters such as age, BMI, coronary risk factors, gender, CPK-AUC, LVEF, onset-to-balloon time, the number of major coronary arteries with significant stenosis, and the treatment used.

Predictive value for left ventricular remodeling

We conducted a regression analysis to determine significant factors that contribute to LV remodeling. We examined the simple correlation between continuous clinical parameters and the fold-increase in LVEDVI over 6 months. By simple regression analysis, CPK-AUC, and FGF21 on admission were associated with the fold-increase in LVEDVI (Table 2). As shown in Figure 3, plasma levels of FGF21 on admission showed a significant positive correlation with fold-increase in LVEDVI ($r=+0.23$, $P=0.04$). FGF21 levels on admission also showed a positive correlation with the fold increase in LVESVI with marginal significance ($r=+0.22$, $P=0.07$). In addition, FGF21 levels on admission negatively correlated with changes in MNSER ($r=-0.24$, $P=0.04$).

Then we performed a stepwise multivariate regression analysis with the forward entry method to determine significant independent variables contributing to the fold-increase in LVEDVI. In model 1, we set the fold-increase in LVEDVI as a responsive variable and observed significant parameters in a simple correlation analysis (CPK-AUC and level of FGF21 on admission). We found that the CPK-AUC was significant ($\beta=+0.256$, $P=0.031$) and that the plasma level of FGF21 on

admission was a marginally significant factor ($P=0.054$) for predictions of the fold-increase in LVEDVI (Table 3). Because of clinical relevance and potential importance, we added the treatment given as explanatory variables (use of intravenous catecholamine, nitroglycerine and carperitide in the acute phase and medications such as RAS inhibitors and beta blockers) into the above model (model 2). In model 2, we found that the CPK-AUC, intravenous injection of nitroglycerine and level of FGF21 on admission were significant factors to predict the fold-increase of LVEDVI (Table 3, $F=4.67$, $P=0.005$). A similar result was obtained when we added BMI and TIMI flow grade as explanatory variables to model 2 (data not shown).

Discussion

The findings from this study showed that the FGF21 level at admission was related to the subsequent LV dilatation at 6 months in patients with AMI after successful coronary reperfusion. The FGF21 levels on admission were significantly related with increased LV volume and reduced LV function. Immediate FGF21 secretion was related to inadequate peripheral circulation and the elevation of FGF21 might have an important role in the subsequent healing of the infarcted myocardium. We also found that the use of intravenous nitroglycerin attenuated the LV remodeling after 6 months, consistent with the previous report [21]. Importantly, in addition to traditional markers, FGF21 levels in the early phase of AMI provide prognostic information for cardiac remodeling in the chronic stage.

We confirmed that exercise induced a significant increase in plasma FGF21 levels in a preliminary study. FGF21 is produced from liver, adipose tissue, and skeletal muscle. Our data suggest that FGF21 was released from skeletal muscle not only in a mouse model but also in human subjects [5]. We still do not know whether this increase in FGF21 is due to a simple release or de novo synthesis from tissues. We found a positive correlation between lactate levels and FGF21 levels in patients with AMI at admission in this study. Our findings suggest that peripheral circulatory insufficiency is involved in the increase of FGF21 in the acute phase of AMI.

Recently Chau et al. have reported that FGF21 regulates energy metabolism by activating AMP-activated protein kinase and sirtuin 1 (SIRT1) [22]. SIRT1 promotes the deacetylation of peroxysome proliferator-activated receptor- γ coactivator-1 α , a downstream target that plays an important role in mitochondrial biogenesis. In this regard, myocardial mitochondrial function is modulated by an elevation of FGF21 levels and downstream molecules, resulting in LV remodeling in the chronic phase. It is quite interesting that metabolic factors affect myocardial performance in the chronic phase of myocardial infarction even after successful coronary reperfusion.

Recent study showed that FGF21-transgenic mice had low plasma levels of IGF-1, a potent pro-survival factor in the ischemic myocardium. A previous report demonstrated a marked decrease of serum IGF-1 levels in the very early phase of AMI [11]. Elevated levels of IGF-1 at the beginning of AMI were accompanied by less ventricular dilatation and better ventricular function [23]. In an animal model of experimental ischemia, constitutive overexpression of IGF-1 attenuated myocyte necrosis and tissue injury [24]. This leads us to speculate that IGF-1 prevents undesirable remodeling of the myocardium after AMI and FGF21 counteracts this protective mechanism.

The increase in FGF21 leads to improved glucose tolerance and insulin sensitivity. A high glucose level on admission is a significant

risk factor in the short term as well as long term after AMI [25]. In this regard, the elevation of FGF21 is one of the mechanisms preventing myocardial injury after AMI. We still do not know whether the elevation of FGF21 is a compensatory mechanism to prevent LV remodeling or deteriorating factor for LV dilatation. At this point we found that FGF21 could be a surrogate marker that predicts LV remodeling and LV systolic function in the chronic phase of AMI. The role of FGF21 in LV remodeling after AMI should be elucidated in other studies such as with animal models. Nonetheless, early modification of FGF21 and its downstream targets may be a novel therapeutic tool to prevent LV remodeling and systolic dysfunction in the chronic phase of AMI.

Study limitations

We set the fold-increase in LVEDVI as a primary endpoint in the study, but we should also investigate the role of FGF21 in the long-term prognosis of AMI patients. Assessments of LV function are an important part of risk stratification in patients with AMI. However, early measurements of LVEF might be misleading, since the improvement in LVEF from myocardial stunning begins within 3 days and is completed by 14 days after successful PCI [26,27].

Although LVESV after recovery from myocardial stunning is an important prognostic indicator, we could not find a significant increase in LVESV in this study. Electrocardiogram-gated single-photon emission computed tomography or cardiac magnetic resonance imaging might provide better accuracy and reproducibility to evaluate LV remodeling after AMI.

Conclusions

To our knowledge, this is the first report of an association of FGF21 with the progression of LV remodeling in the chronic phase of AMI. Measurements of plasma FGF21 levels could provide prognostic information for LV remodeling after AMI. FGF21 might be a target to prevent serious complications after AMI.

Acknowledgements

We thank Takako Takagi for her excellent technical assistance.

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