Title of the article

Predictors of surgery-induced muscle proteolysis in patients undergoing cardiac surgery

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Keywords

Muscle proteolysis, 3-methylhistidine, cardiac surgery, catabolism

Abstract

Background

Muscle proteolysis due to postoperative hypercatabolism is responsible for the functional decline observed in patients undergoing cardiac surgery. The aim of this study was to explore the factors underlying increased muscle proteolysis by measuring the urinary 3-methylhistidine/creatinine ratio (3-MH/Cr) in patients who had recently undergone cardiac surgery.

Methods and results

Sixty-nine patients undergoing elective cardiac surgery participated in this study. The 24-h urinary 3-MH/Cr was collected for three days after surgery. Serum levels of metabolic markers, amino acids and skeletal muscle strength were measured before and after surgery. Cumulative 3-MH/Cr during 3days after surgery (cum3-MH/Cr) was 676.7 ± 169.0 nmol/g.Cr, and was positively associated with the decrease in muscle strength. In multivariate analysis, factors associated with an increased cum3-MH/Cr were: preoperative grip strength (β = – 0.309, p = 0.003), body mass index (β = – 0.299, p = 0.001), hemoglobin (β = – 0.243, p = 0.007), cardiopulmonary bypass time (β = 0.184, p = 0.049), and immediate postoperative IL-6 (β = 0.295, p = 0.002).

Conclusions

Our findings suggest that postoperative muscle proteolysis is facilitated by preoperative catabolic accelerators in patients undergoing cardiac surgery. The factors of muscle proteolysis immediately after surgery may be a novel therapeutic target in rehabilitation intervention.

Introduction

Skeletal muscle atrophy is widely recognised as a complication of the acute phase after cardiac surgery [1], and cause a postoperative muscle weakness. Persistent muscle weakness is also a major factor of general fatigue after surgery [2], which causes functional limitations in daily living after discharge. Prophylaxis of muscle deterioration, therefore, is an important clinical issue in rehabilitation intervention for surgical patients. However, even with intensive mobilisation, systemic muscle weakness is still common in patients undergone cardiac surgery [3].

The deterioration of skeletal muscles is, in part, dependent on proteolysis induced by the surgery [4] and muscle proteolysis is thought to be enhanced via postoperative hyper-catabolism induced by postoperative elevation of inflammatory cytokine production [5-7]. Added to this, we previously suggested that postoperative 3-methylhistidine (3-MH), an established marker of skeletal muscle proteolysis [8,9], may be a useful indicator of surgical invasiveness for skeletal muscle by indicating the association of urinary 3-MH both with postoperative systemic inflammation and with reductions in skeletal muscle strength [10].

We hypothesized this postoperative skeletal muscle breakdown may serve as a trigger to enhance postoperative worsening outcomes when preoperative factors such as

preoperative loss of body tissue, physical inactivity, altered metabolism and aging coexist [11-13]. Our study, therefore, aimed to explore the factors that contribute to facilitated the excretion of 3-MH in patients undergoing cardiac surgery.

Methods

Subjects

Sixty-nine consecutive patients who underwent elective cardiac surgery between April 2012 and March 2013, involving median sternotomy and cardiopulmonary bypass (CPB), were enrolled into this study. Patients requiring mechanical ventilation beyond 24 h post-surgery, reoperation, or with comorbidities of respiratory failure, chronic kidney disease (estimated glomerular filtration rate < 30 mL/min/1.73 m^2), and central nervous system dysfunction, were excluded. After surgery, all patients remained intubated and were transported from the operating room to the intensive care unit (ICU). Artificial ventilation was continued until the patient regained sufficient spontaneous respiration. During this time, patients were infused with fentanyl at 0.01 – 0.02 μg/kg/h for sedation. All patients were extubated upon stabilisation of cardiovascular and respiratory conditions.

After receiving approval from the Nagoya University Ethics Committee (approval

number: 1086), written informed consent was obtained from each patient who participated in this study.

Blood samples

Blood samples were taken at three intervals for each patient as follows: sample 1, the day before surgery; sample 2, 4 h after surgery in the ICU; and sample 3, postoperative day (POD) 1. The samples were immediately centrifuged at 4°C and stored at –80°C until assayed. The serum level of IL-6 was measured using an automated chemiluminescence enzyme immunoassay (CLEIA) system (Lumipulse; Fujirebio Inc., Tokyo, Japan). To confirm the catabolic/anabolic balance, plasma levels of branched-chain amino acids (BCAA) and aromatic amino acids (AAA) were measured by liquid chromatography/mass spectrometry (LC/MS) (LCMS2020; Shimadzu, Kyoto, Japan). Plasma levels of cortisol, growth hormone (GH) and insulin-like growth factor 1 (IGF-1) were also determined using a commercially available direct competitive radioimmunoassay (RIA) (automatic γ-counter; Wallac, Turku, Finland).

Urine samples

The amount of muscle proteolysis was calculated as the urinary 3-MH to creatinine (Cr) ratio (3-MH/Cr) because of the fact that the urinary excretion of 3-MH is proportional to muscle mass as is urinary Cr excretion. Added to this, urinary 3-MH/Cr

yields a smaller inter-individual variation than 3-MH itself. In our previous study, we demonstrated, by analysing 24-h urine samples for 5 days, that the peak of increased urinary 3-MH/Cr after cardiac surgery occurred on POD4 [10]. We also found a strong correlation ($r = 0.873$, $p < 0.0001$) between cumulative 3-MH/Cr (cum3-MH/Cr) excretion over 3 days and that over 5 days after cardiac surgery (unpublished data). Based on these findings, we measured the 3-MH/Cr up to POD3 to provide an index of total postoperative muscle proteolysis following cardiac surgery. The enzyme method was performed to measure the level of urinary Cr, and urinary 3-MH was measured by high performance liquid chromatography using an automated amino acid analyser (L-8500; Hitachi, Tokyo, Japan).

Muscle strength measurements

Muscle strength measurements of grip strength (GS), isometric knee extensor strength (IKES), maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP) were performed within 3 days prior to the operation and then again on POD 7. GS was measured using a JAMAR hand-held dynamometer (Biometrics Ltd., Ladysmith, VA, USA). The patients were seated with the elbow flexed at 90° and the forearm in the neutral position with the wrist between 0° and 30° dorsiflexion. The patients were asked to squeeze the handle as hard as they could. Each hand was tested

three times and the highest value was recorded. IKES was measured with the patient seated at the edge of the treatment table and positioned with the hips and knees flexed at 90°. A hand-held dynamometer (μ Tas F-1; Anima Corporation; Tokyo, Japan) was placed distally anterior to the tibia to measure the isometric knee extension contractions. IKES was expressed in kg and as a percentage of body weight. The highest value from two attempts on the dominant side was recorded. MIP and MEP were measured using a respiratory dynamometer (Vitalopower KH-101; Chest, Tokyo, Japan) as an index of respiratory muscle strength. For each test, patients adopted the sitting position and sustained maximal effort against an occluded airway at functional residual capacity. The best of three consecutive attempts was recorded for MIP and MEP.

6-min walking test (6MWT)

The 6MWT was performed according to the ATS guidelines [14] in a 30m long hallway with a level surface, located in our department. Participants were encouraged to cover as much distance as possible, with all patients being supervised by a physiotherapist during testing. Patients were allowed to stop walking if they developed either shortness of breath or fatigue. This test was conducted twice and the best of the two tests within 7 days prior to the operation was recorded.

Statistics

Statistical evaluation of the data was performed with SPSS 19.0J (SPSS Japan Inc., Tokyo, Japan). Data are expressed as the means ± standard deviation or absolute numbers and percentages. Bivariate analyses between the clinical variables and level of the cum3-MH/Cr during the three days after surgery were tested by Pearson's correlation. Multivariate linear regression analysis was performed to identify predictive factors associated with the cum3-MH/Cr. Potential factors of interest with bivariate $p < 0.2$ were entered into multivariable models; age and gender were entered into these models as exceptions, since muscle mass is known to be affected by both aging and gender. A two-tailed *p*-value less than 0.05 was considered to indicate statistical significance.

Results

Patient characteristics and clinical indicators

Patient characteristics are listed in Table 1. Interleukin-6 and cortisol, the catabolic factors, were significantly increased at 4 hours post-surgery and returned to baseline on POD 1 (Fig. 1 A, B). In contrast, anabolic indicators of the BCAA-to-AAA ratio (BCAA/AAA) and the IGF-1-to-GH ratio (IGF-1/GH) were significantly decreased on POD 1 (Fig. 1 C, D). The 6MWD test before surgery was well-tolerated in all patients

with a mean walking distance of 328.0 ± 78.8 m.

Relationship between cum3-MH/Cr and muscle weakness on POD7

The 3-MH/Cr gradually and significantly increased from 148.2 ± 44.2 nmol/g.Cr on POD1 to 208.9 ± 68.2 nmol/g.Cr on POD2 and 319.5 ± 93.8 nmol/g.Cr on POD 3 (Fig. 2), and the mean value of the cum3-MH/Cr over the 3-day period was 676.7 ± 169.0 nmol/g.Cr. Preoperative average muscle strength in GS, IKES, MIP and MEP were 32.8 ± 11.1 kgf, 0.38 ± 0.19 kgf/kg, 58.6 ± 18.1 cmH_2O and 62.2 ± 21.3 cmH_2O, respectively. The rates of decrease in GS, IKES, MIP and MEP were 29.7%, 18.2%, 23.0% and 19.8% on POD 7, respectively. The decrease in GS, IKES, MIP and MEP on POD 7 were positively associated with log cum3-MH/Cr (Fig. 3).

Factors linked to increased cum3-MH/Cr during 3 days after surgery

We found correlations between cum3-MH/Cr and preoperative GS (r = –0.528, p < 0.0001) and immediate postoperative IL-6 (r = 0.505, p < 0.0001) (Table 2). Using multivariate analysis, BMI, CPB time, level of hemoglobin, preoperative GS and immediate postoperative IL-6 excretion were independently associated with an increase in 3-MH/Cr (adjusted R^2 = 0.53, p < 0.0001) (Table 3).

Discussion

We found that a marked increase in urinary 3-MH/Cr after cardiac surgery was associated with postoperative inflammation and systemic skeletal muscle weakness. Furthermore, this study has indicated that muscle proteolysis after cardiac surgery was affected not only by surgical stress, but also by the conditions before surgery, especially in patients with a low physical function. These findings suggest that, in patients with catabolism enhancer factors, muscle proteolysis immediately after cardiac surgery become a novel therapeutic target in rehabilitation intervention.

A few studies have conducted to focus on the mechanism of skeletal muscle wasting during postoperative phase, but not using distinctive biochemistry [4]. In the present study, we determined that urinary 3-MH/Cr remarkably increased during 3 days after surgery. Because of the fact that 3-MH cannot be reutilised for protein synthesis [8,9] and 12.2 hours of excretion half-life for 3-methylhistidine [15], the urinary 3-MH/Cr in this study is considered to reflect muscle proteolysis immediately after the surgery. Based on these understandings, the finding of the time course in urinary 3-MH/Cr indicates that muscle proteolysis is accelerated 24 hours post-operation (POD 2), suggesting that 48 hours following the operation will become a target period for interventions to preserve skeletal muscle mass.

The findings for the postoperative inflammatory reaction in this study are consistent with previous studies that demonstrated an immediate increase in pro-inflammatory cytokine such as tumour necrosis factor (TNF)-α and IL-6 after surgery [5,6]. The systemic inflammatory reaction may have occurred in response to surgical trauma, extracorporeal circulation, and perioperative hypothermia [16]. TNF-α has been regarded as an important proinflammatory factor to activate the synthesis of cytokines, including IL-6 [17] and to elicit direct muscle protein breakdown through multiple proteolytic mechanisms, such as the nuclear factor-kappa B signalling pathway [18,19]. On the other hand, IL-6 is responsible for the coordination of the acute phase response that consists of fever, leukocytosis, altered vascular permeability, and increased production of acute phase proteins [17]. Therefore, in this study, IL-6 may be considered as an indicator that reflects a catabolic phase, instead of as a factor that directly regulates muscle proteolysis during the postoperative acute phase [18-20].

Hormonal changes and abnormalities in amino acid metabolism also denoted the catabolic state in our results. We observed an increased serum cortisol level, which promotes proteolysis and lipolysis to produce gluconeogenic precursors [21,22] and the resistance of IGF-1 response to GH secretion. These metabolic effects of the hormonal changes indicate increased catabolism, which mobilises substrates to provide energy

sources [23-25]. Finally, a reduced BCAA to AAA ratio also indicated the catabolic state in the early postoperative period [26] because BCAA are the greatest producers of energy in conditions under severe stress. These findings suggested that protein breakdown in the muscle was, in part, due to the metabolic response to surgical stress [27]. We speculated that the postoperative skeletal muscle weakness was most likely the result of catabolism-induced muscle proteolysis due to cardiac surgery, not mere skeletal muscle deconditioning.

The results of multiple regression analysis selected both operative factors (longer CPB time and immediate postoperative IL-6 elevation) and prognostic factors (lower GS, BMI and hemoglobin) as independent predictors of the cum3-MH/Cr. The operative factors selected here are known to be considerable accelerating factors of the catabolic state [13], suggesting that these factors also up-regulated muscle proteolysis after surgery. The immediate postoperative catabolic state in this study was evident from significantly enhanced IL-6 production and suppressed anabolic state as indicated by reduction in IGF-1/GH and BCAA/AAA [26,28,29]. Our previous study indicated that lower GS and BMI was associated elevated IL-6 levels immediately after surgery [30]. CPB has also been reported as a factor facilitating the immune response during cardiac surgery. Hemoglobin levels are also known to be greatly reduced by hepcidin synthesis

through activation of inflammatory cytokines [31]. These reports suggested that postoperative 3-MH excretion may be determined by surgery-induced catabolism and preoperative factors such as enhanced inflammation. Notably, reduced preoperative GS has been reported to be associated with functional decline, disability, mortality and increased postoperative complications in surgical patients [32], and is also regarded as a preoperative catabolic indicator. These data suggest that elevation of muscle proteolysis induced by surgical stress may intervene between preoperative catabolic factors, such as low GS, and postoperative muscle mass, which are linked to muscle weakness after surgery. Thus, patients with predictive parameters for increased postoperative muscle proteolysis, may be candidates for preventive interventions in the perioperative phase. Regarding the perioperative management designed to correct the catabolic/anabolic imbalance, adequate nutrition and neuromuscular electrical stimulation therapy may have possible to help preserve muscle architecture and to improve muscle function in patients after surgery [33-35].

Study limitations

This study had several limitations. First, this was a single-centre study with a relatively small cohort and was observational in nature, making it prone to bias. Second, our study may have been subject to selection bias. For example, factors that enhance the

catabolic response, such as chronic kidney disease [36] and prolonged mechanical ventilation, were excluded. Furthermore, inactivity or immobilisation immediately after surgery may have varied between individuals and may consequently have confounded muscle catabolism. Nevertheless, our findings provide a fundamental source for underlying mechanisms of postoperative functional decline in patients undergoing cardiac surgery.

Conclusions

In conclusion, increased postoperative muscle proteolysis can cause postoperative muscle weakness, and be shown to be associated with a poor preoperative functional status. It may therefore be necessary to develop clinical approaches to counteract the postoperative triggers of muscle proteolysis in these patients.

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Disclosures

There is no conflict of interest.

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Table 1. Patient characteristics and procedural details

Male, n (%)	53 (76.8)
Age, years	69.1 ± 8.8
Body mass index, kg/m^2	23.1 ± 4.1
Brain natriuretic peptide, pg/mL	197.5 ± 174.6
Hemoglobin, g/dL	12.7 ± 1.51
Hemoglobin A1c, %	6.11 ± 0.85
eGFR, ml/min/1.73m^2	67.0 ± 17.6
Surgery, n (%)	
CABG	34 (49.3)
VR	26 (37.7)
CABG+VR	9 (13.0)
Operation time, min	216.6 ± 82.7
CPB duration, min	118.6 ± 67.4
Aortic cross-clamp duration, min	86.7 ± 41.4
ICU stay, day	1.53 ± 0.24
Preoperative comorbidities, n (%)	

Hypertension;	37 (53.6)
Dyslipidemia;	22 (31.9)
Chronic heart failure;	20 (29.0)
Diabetes Mellitus;	18 (26.1)
Left ventricle ejection fraction, %	63.75 ± 13.3
Preoperative medication, n (%)	
Statin	54 (78.3)
β-blockers	50 (72.5)
ACE inhibitors or ARBs	30 (43.5)
Calcium channel blockers	20 (29.0)
Diuretics	18 (26.1)

CABG, coronary artery bypass grafting; VR, valve replacement; CPB, cardiopulmonary bypass; ACE, angiotensin-converting enzyme; ARBs, angiotensin-II-receptor blockers.

Table 2. Correlations of clinical variables with cum3-MH/Cr during the 3 days after surgery

Variable	*r*	95%CI	*p*-value
Preoperative			
Age	0.070	–0.185, 0.302	0.565
Female	0.067	–0.173, 0.980	0.589
Body mass index	–0.432	–0.601, –0.218	0.0002
LVEF	0.145	–0.095, 0.369	0.233
BNP	–0.058	–0.219, 0.104	0.478
Hemoglobin A1c	0.066	–0.174, 0.298	0.591
CRP	0.239	0.002, 0.450	0.048
Hemoglobin	0.255	0.021, 0.464	0.034
Grip strength	–0.528	–0.678, –0.333	< 0.0001
IKES	0.056	–0.183, 0.289	0.648
MIP	–0.036	–0.270, 0.202	0.769
MEP	–0.078	–0.309, 0.162	0.525
6MWD	–0.084	–0.135, 0.238	0.512

Interleukin-6	0.158	–0.079, 0.380	0.195
Cortisol	–0.079	–0.309, 0.161	0.520
IGF-1/GH	–0.039	–0.273, 0.199	0.748
BCAA/AAA	–0.194	–0.412, 0.040	0.109
CPB time	–0.160	–0.382, 0.080	0.189
Immediate postoperative			
Interleukin-6	0.505	0.305, 0.663	< 0.0001
Cortisol	0.103	–0.307, 0.331	0.401
IGF-1/GH	0.121	–0.119, 0.348	0.320
BCAA/AAA	–0.030	–0.269, 0.204	0.780

Cum3-MH/Cr, cumulative 3-methylhistidine; LVEF, left ventricular ejection fraction; CPB, cardiopulmonary bypass; CRP, C-reactive protein; IKES, isometric knee extensor strength; MIP, maximum inspiratory pressure; MEP, maximum expiratory pressure; 6MWD, 6-min walking test; IGF, insulin-like growth factor; GH, growth hormone; BCAA, branched-chain amino acid; AAA, aromatic amino acid.

Table 3. Multiple regression models for independent prediction of cum3-MH/Cr

Variable	β	95%CI	*p*-value	Adjusted R^2
Preoperative				0.531
Body mass index	–0.299	–0.474, –0.125	0.001	
CPB time	0.184	0.0007, 0.364	0.049	
CRP	0.163	–0.014, 0.342	0.071	
Hemoglobin	–0.243	–0.415, –0.070	0.007	
Grip strength	–0.309	–0.504, –0.108	0.003	
Immediately postoperative				
Interleukin-6	0.295	0.107, 0.475	0.002	

Cum3-MH/Cr, cumulative 3-methylhistidine; LVEF, left ventricular ejection fraction; CPB, cardiopulmonary bypass; CRP, C-reactive protein; BCAA, branched-chain amino acid; AAA, aromatic amino acid.

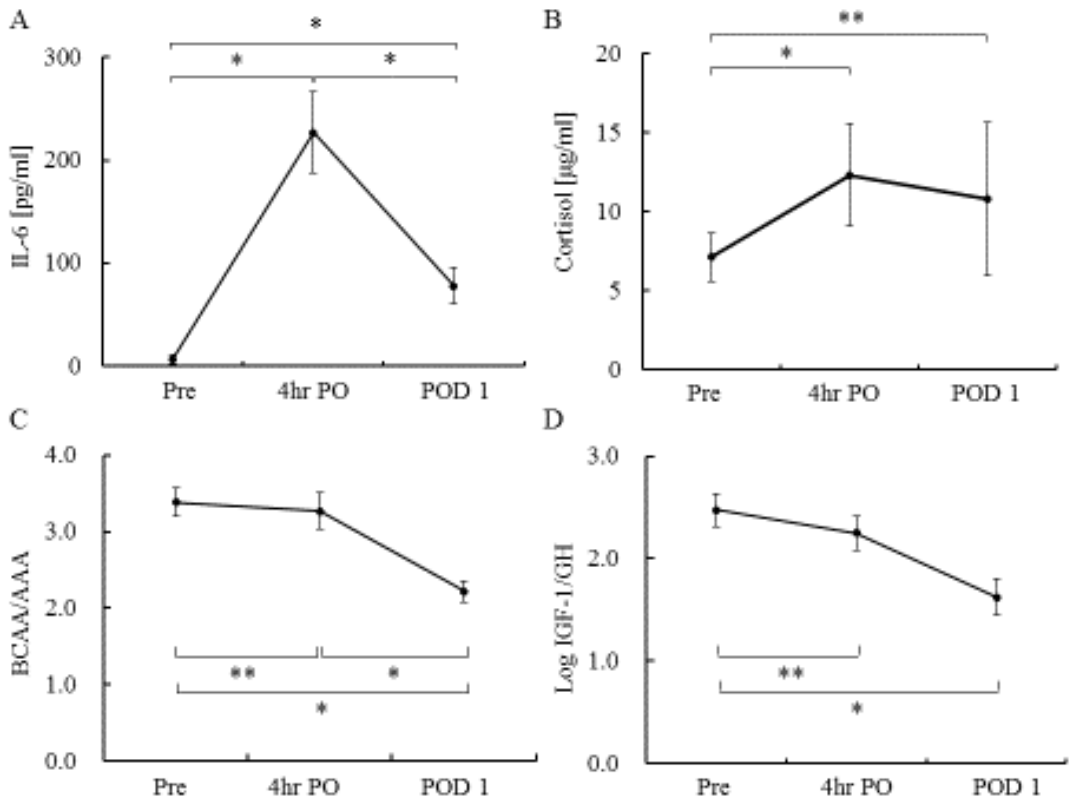

Figure 1. Immediate postoperative time courses of IL-6, BCAA/AAA, Cortisol, and Log IGF-1/GH

Interleukin-6 (A) and cortisol (B) were significantly increased at 4 hours post-surgery. The BCAA to AAA ratio (BCAA/AAA) (C) and IGF-1 to growth hormone ratio (IGF-1/GH) (D) were significantly decreased at post-operative day 1. *p <0·01. **p <0·05. IL-6, Interleukin-6; BCAA, branched chain amino acids; AAA, aromatic amino acids; IGF-1, insulin-like growth factor-1; Pre, preoperative; 4 hr PO, 4 hour postoperative; POD1, postoperative day 1.

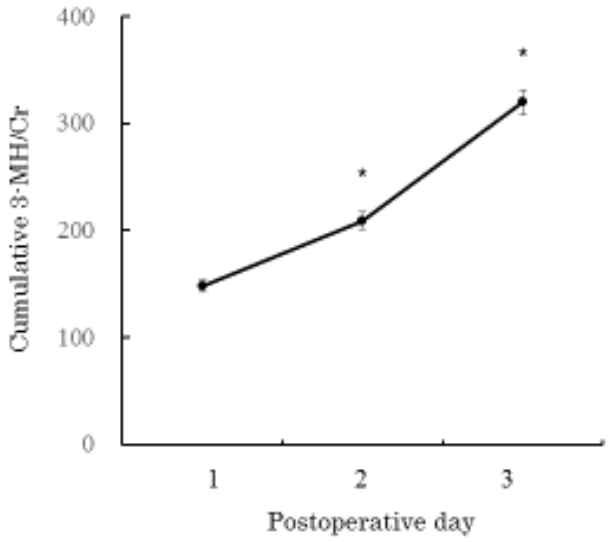

Figure 2. Change in cumulative 3-MH/Cr during 3 days after surgery

*p <0·01 vs POD1. 3-MH, 3-methylhistidine; Cr, creatinine; POD, postoperative day.

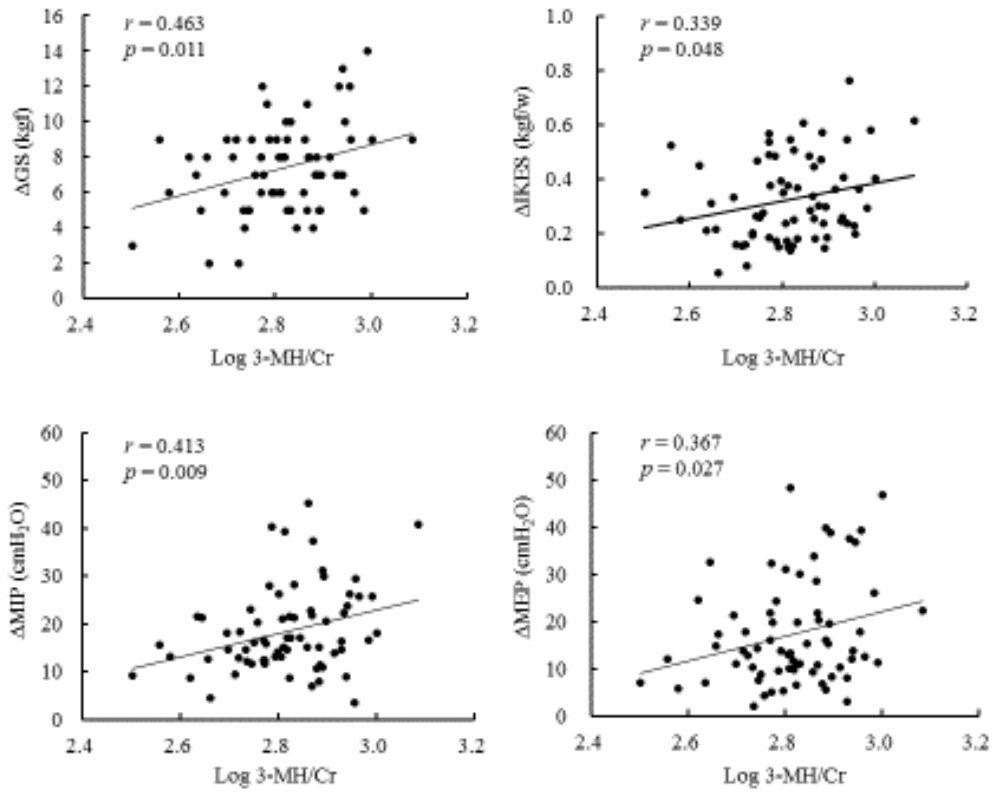

Figure 3. Relationship between cumulative 3-MH/Cr during the 3 days after surgery and decrease in skeletal muscle strength on POD 7

Log cumulative 3-MH/Cr, logarithmic cumulative 3-methylhistidine/creatinine; GS, grip strength; IKES, isometric knee extensor strength; MIP, maximum inspiratory pressure; MEP, maximum expiratory pressure.