Journal of Cardiology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

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

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ARTICLE INFO

Article history:
Received 20 August 2015
Received in revised form 7 November 2015
Accepted 26 November 2015
Available online xxx

Keywords:
Muscle proteolysis
3-Methylhistidine
Cardiac surgery
Catabolism

ABSTRACT

Background: Muscle proteolysis due to post-operative 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 3 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 3 days 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 ($\beta = -0.309$, $p = 0.003$), body mass index ($\beta = -0.299$, $p = 0.001$), hemoglobin ($\beta = -0.243$, $p = 0.007$), cardiopulmonary bypass time ($\beta = 0.184$, $p = 0.049$), and immediate post-operative interleukin-6 ($\beta = 0.295$, $p = 0.002$).

Conclusions: Our findings suggest that post-operative 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 recognized as a complication of the acute phase after cardiac surgery [1], and is a cause of post-operative 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 mobilization, systemic muscle weakness is still common in patients undergoing 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 post-operative hypercatabolism induced by post-operative elevation of inflammatory cytokine production [5–7]. Added to this, we previously suggested that post-operative 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 post-operative systemic inflammation and with reductions in skeletal muscle strength [10].

We hypothesized this post-operative skeletal muscle breakdown may serve as a trigger to enhance post-operative 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 facilitate the excretion of 3-MH in patients undergoing cardiac surgery.

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http://dx.doi.org/10.1016/j.jjcc.2015.11.011
0914-5087/

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 in 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. All patients were administered acetate Ringer's solution, mannitol, sodium bicarbonate, methylprednisolone sodium succinate, and cephem antibiotic as the priming fluid of the CPB circuit. Throughout the period of CPB, the temperature was maintained at 32–34 °C, and CPB flow rate was based on perfusion index 2.5 and 3.0 L/min/m^2. 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 stabilization of cardiovascular and respiratory conditions, and started oral feeding within 24 h after surgery.

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, post-operative day (POD) 1. The samples were immediately centrifuged at 4 °C and stored at −80 °C until assayed. The serum level of interleukin (IL)-6 was measured using an automated chemiluminescence enzyme immunoassay 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 (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 (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 analyzing 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 post-operative 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 analyzer (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

The 6-minute walking test (6MWT) was performed according to the ATS guidelines [14] in a 30 m long hallway with a level surface, located in our department. Participants were encouraged to cover as great a 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 better 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 3 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. IL-6 and cortisol, the catabolic factors, were significantly increased at 4 h 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. 1C, D). The 6MWD test before surgery was well tolerated in all patients with a mean walking distance of 328.0 ± 78.8 m.