

Original Article

# Heparin responsiveness during off-pump coronary artery bypass graft surgery: predictors and clinical implications

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**Aim:** To evaluate the clinical impact of reduced heparin responsiveness ( $HR_{\text{reduced}}$ ) on the incidence of myocardial infarction (MI) following off-pump coronary artery bypass graft surgery (OPCAB), and to identify the predictors of  $HR_{\text{reduced}}$ .

**Methods:** A total of 199 patients scheduled for elective OPCAB were prospectively enrolled. During anastomosis, 150 U/kg of heparin was injected to achieve an activated clotting time (ACT) of  $\geq 300$  s, and the heparin sensitivity index (HSI) was calculated. HSIs below 1.0 were considered reduced ( $HR_{\text{reduced}}$ ). The relationships between the HSI and postoperative MI, cardiac enzyme levels and preoperative risk factors of  $HR_{\text{reduced}}$  were investigated.

**Results:** There was no significant relationship between the HSI and cardiac enzyme levels after OPCAB. The incidence of MI after OPCAB was not higher in  $HR_{\text{reduced}}$  patients.  $HR_{\text{reduced}}$  occurred more frequently in patients with low plasma albumin concentrations and high platelet counts.

**Conclusion:**  $HR_{\text{reduced}}$  was not associated with adverse ischemic outcomes during the perioperative period in OPCAB patients, which seemed to be attributable to a tight prospective protocol for obtaining a target ACT regardless of the presence of  $HR_{\text{reduced}}$ .

**Keywords:** heparin responsiveness; off-pump coronary artery bypass graft surgery; risk factors; myocardial infarction

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## Introduction

Heparin inhibits thrombin generation by binding to anti-thrombin III (AT-III), and heparin is widely used as an anticoagulant during percutaneous coronary interventions (PCI) and coronary artery bypass graft surgery (CABG) to prevent thromboembolic complications<sup>[1–3]</sup>. However, large variability exists in individual heparin responsiveness<sup>[4, 5]</sup>, and despite the theoretical possibility of increased periprocedural ischemic events associated with reduced heparin responsiveness ( $HR_{\text{reduced}}$ ), clinical evidence is either contradictory or limited.

In patients undergoing PCIs, conflicting results exist with regard to the association between  $HR_{\text{reduced}}$  and ischemic complications such as abrupt vessel closure during and after angioplasty<sup>[6–10]</sup>. In the surgical setting, only a single retro-

spective study has been performed to evaluate the relationship between ischemic complications in patients undergoing on-pump CABG, which found a close correlation between  $HR_{\text{reduced}}$  and fatal myocardial infarction (MI)<sup>[11]</sup>.

Surgical revascularization is also widely performed by off-pump coronary artery bypass graft surgery (OPCAB) during which a similar degree of anticoagulation, as used during PCIs, is sufficient. Unlike with PCIs, however, all patients presenting for OPCAB have previous exposure to heparin during coronary angiography, which is one of the well-established risk factors of  $HR_{\text{reduced}}$ <sup>[4, 5, 12]</sup>. Moreover, OPCAB still confers significant inflammatory responses and is associated with a postoperative procoagulant state relative to on-pump CABG<sup>[13, 14]</sup>. Concerning the possible relationship between  $HR_{\text{reduced}}$  and an increased risk of ischemic events, there is still no clear recognition of patients with  $HR_{\text{reduced}}$  or the clinical significance of  $HR_{\text{reduced}}$  in patients undergoing OPCAB at present.

The aim of this study was to prospectively identify

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predictors of HR<sub>reduced</sub> and its clinical impact with regard to the incidences of MI and other major morbidity endpoints in the immediate postoperative period in patients undergoing OPCAB.

## Materials and methods

### Patients

This was a prospective study enrolling all consecutive patients scheduled for elective isolated multivessel OPCAB between April 2007 and March 2008 at a single university hospital. The approval of the institutional review board and patients consent were obtained. Exclusion criteria were the presence of known preoperative coagulopathy, emergency surgery or preoperative use of an intra-aortic balloon pump.

Patients demographics; preoperative medications, including anticoagulant therapy; and preoperative hematological and biochemical laboratory results, including hematocrit, total white cell count, percentage of neutrophils, platelet count, plasma protein and albumin concentrations, C-reactive protein (CRP), fibrinogen concentration, activated partial thromboplastin time, and prothrombin time, as well as levels of myocardial enzymes including creatinine kinase-MB (CK-MB) and troponin (Tn) T, were assessed. Additionally, the preoperative AT-III concentration and activated clotting time (ACT) were assessed.

All patients received standard anesthetic and surgical care according to institutional guidelines by physicians blinded to this study.

### Measurement for ACT

ACT was monitored with the Hemochron<sup>®</sup> Response Whole Blood Coagulation System (International Technidyne Corp (ITC), Edison, NJ, USA) using Hemochron HRFTCA510 celite ACT tubes.

### Heparin sensitivity index

Baseline ACT was determined by blood sampling immediately after the insertion of the arterial line. An initial dose of 150 U/kg of porcine heparin was injected into a central venous line just prior to Y-graft formation; the target ACT value was 300 s<sup>[15]</sup>. Ten minutes after the loading dose, the ACT was measured. An ACT of 300 s or greater was considered adequate. Then, a follow up ACT measurement was taken 30 min after the first ACT measurement. If the ACT fell below the target value of 300 s, an additional dose of heparin was administered. If the ACT was between 250 and 299 s, an additional 2000 U of heparin was administered, and if the ACT was between 200 and 249 s, then an additional 3000 U of heparin was injected. Ten minutes after the injection of additional heparin, the ACT was remeasured. Upon completion of anastomoses, the ACT was measured again, and the heparin activity was neutralized with protamine sulfate. If the ACT was greater than 300 s, 50 mg of protamine sulfate was administered. If the ACT was between 251 and 299 s or between 200 and 250 s, 30 mg or 20 mg protamine sulfate was administered, respectively. Patients were considered to have HR<sub>reduced</sub>

if the heparin sensitivity index [HSI, HSI=(post-heparin ACT - baseline ACT)/heparin loading dose (U/kg)] was below 1.0 after the initial dose of 150 U/kg of heparin<sup>[16]</sup>. Patients with HSI $\geq$ 1 were considered to have normal heparin responsiveness (HR<sub>normal</sub>).

### Variables assessed

Intraoperative variables such as the total amount of heparin and protamine administered, the number and nature of grafts, the amount of blood loss and the amount transfused were recorded. The amount of blood loss and blood transfused during postoperative period, the coagulation profiles and myocardial enzyme levels were recorded.

All of the patients were transferred to the intensive care unit (ICU) after surgery and treated with fentanyl-based intravenous patient-controlled analgesia for 2–3 d for pain control, and anti-platelet therapy was started within 24 h unless contraindicated.

In the immediate postoperative period, the following variables were assessed. The highest postoperative CK-MB and Tn-T levels were recorded during first seven postoperative days. Clinical diagnostic criteria for MI were defined as the occurrence of an increase in cardiac enzyme levels five times above the upper normal limit; new Q waves of greater than 0.04 mm or a reduction in R waves greater than 25% in at least 2 leads, or both; new ST elevation in at least 2 contiguous leads measuring more than 0.2 mV in leads V1–V3 or more than 0.1 mV in all other leads; or a new left bundle branch block<sup>[17]</sup>. Postoperative major morbidity endpoints were defined as permanent stroke, renal dysfunction, hemostatic re-exploration, deep sternal wound infection, and prolonged ventilation (>48 h)<sup>[18]</sup>. For clarification, renal dysfunction was defined as an acute postoperative renal insufficiency resulting in 1 or more of the following: (1) an increase in the serum creatinine level (Cr) to >2.0 mg/dL, (2) a  $\geq$ 50% increase in Cr over the preoperative baseline value, or (3) a new requirement for dialysis. The development of *de novo* atrial fibrillation was also assessed. Patients were followed up for 6 months postoperatively for cardiac morbidities/mortality and restenosis, which was defined as stenosis with a cross-sectional diameter >50% at the site of bypass graft as assessed by computed tomography (CT) angiography. Cardiac morbidities included Q-wave and non-Q-wave MI and the need for repeat revascularization<sup>[19]</sup>.

### Statistical analysis

Statistical analyses were performed with SPSS 12.0 software (SPSS, Inc, Chicago, IL, USA). Data were expressed as the mean $\pm$ SD or as the number of patients (percentage). Data were tested using the Pearson  $\chi^2$  test, Mann-Whitney U-test or Student's *t* test, as appropriate, to compare patients with HR<sub>reduced</sub> to patients with HR<sub>normal</sub>. Factors associated with HR<sub>reduced</sub> with a *P* value <0.05 in the univariate analysis were entered into a multivariate logistic regression analysis following a stepwise, forward model. To evaluate the relationship between the HSI and changes in cardiac enzyme levels

(highest postoperative cardiac enzyme level – preoperative cardiac enzyme level), linear regression analysis was performed. We determined that at least 148 patients would be required to detect a two-fold increase in the incidence of postoperative MI in patients with HR<sub>reduced</sub><sup>[7]</sup> at an alpha level of 0.05 with 80% power, considering the 20% incidence of HR<sub>reduced</sub><sup>[16, 20]</sup> in cardiac surgical patients and the 8% incidence of postoperative MI following OPCAB in our institute<sup>[21]</sup>.

## Results

A total of 199 patients were enrolled during this study period. Thirty-one (15.5%) of these 199 patients met the criteria for HR<sub>reduced</sub> (HSI range, 0.51 to 0.99). In the HR<sub>normal</sub> group, the HSI range was 1.00 to 4.04. The patient characteristics were not different between the two groups. Preoperative medications and the number of patients requiring continuous heparin use preoperatively were also similar between the groups (Table 1).

**Table 1.** Patients' characteristics. Data are expressed in numbers or mean±SD.

	HR <sub>normal</sub> (n=168)	HR <sub>reduced</sub> (n=31)	P value
Age (years)	64.0±8.5	65.5±9.6	0.361
Sex: male	120 (71%)	20 (65%)	0.439
Body surface area (m <sup>2</sup> )	1.72±0.17	1.68±0.19	0.199
MI within 1 week	6 (3.6%)	3 (9.7%)	0.149
MI within 1 month	12 (7.1%)	4 (12.9%)	0.224
Preoperative medications			
β-blockers	97 (57.7%)	14 (45.2%)	0.136
ACE inhibitors	57 (33.9%)	9 (29.0%)	0.379
ARB	48 (28.6%)	8 (25.8%)	0.470
Calcium channel blockers	72 (42.9%)	19 (61.3%)	0.058
α and β blockers	44 (26.2%)	8 (25.8%)	0.580
Sigmatart	102 (60.7%)	19 (61.3%)	0.559
Aspirin	138 (82.1%)	24 (77.4%)	0.779
Clopidogrel	129 (76.8%)	25 (80.6%)	0.490
Intravenous heparin	50 (29.8%)	11 (35.5%)	0.525
LVEF (%)	56±13	53±14	0.192
LVEDD (mm)	50±5	52±7	0.064
Grade of MR ≥2	7 (4.2%)	2 (6.5%)	0.633
NYHA ≤2	152 (90.5%)	29 (93.5%)	0.744
NYHA ≥3	16 (9.5%)	2 (6.5%)	0.744
Diseased vessel numbers	2.7±0.5	2.9±0.3	0.087

HR<sub>normal</sub>, normal heparin responsiveness; HR<sub>reduced</sub>, reduced heparin responsiveness; MI within 1 week, myocardial infarction within 1 week prior to the surgery; MI within 1 month, myocardial infarction within 1 month prior to the surgery; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; Intravenous heparin, preoperative intravenous heparin administration; LVEF, left ventricular ejection fraction; LVEDD, left ventricle end-diastolic diameter; MR, mitral regurgitation; NYHA, New York Heart Association Classification.

The preoperative laboratory results indicated that patients with HR<sub>reduced</sub> were more likely to have significantly lower

Hct, plasma total protein and plasma albumin concentrations; significantly higher neutrophil percentages, platelet counts, CRP and fibrinogen concentrations; and significantly shortened partial thromboplastin times compared to patients with HR<sub>normal</sub> (Table 2). In multivariate analysis, low plasma albumin concentrations ( $P=0.001$ , odds ratio 0.191, 95% confidence interval 0.073–0.498) and high platelet counts ( $P=0.033$ , odds ratio 1.006, 95% confidence interval 1.000–1.011) remained independent risk factors of HR<sub>reduced</sub>.

**Table 2.** Preoperative laboratory variables. Data are expressed in mean±SD.

	HR <sub>normal</sub> (n=168)	HR <sub>reduced</sub> (n=31)	P value
Age (years)	64.0±8.5	65.5±9.6	0.361
Hematocrit (%)	38±5	35±5	0.001
Protein (g/L)	7.0±0.7	6.5±0.8	0.005
Albumin (g/dL)	4.3±0.5	4.0±0.4	0.001
WBC count (/μL)	7325±2006	7825±2570	0.312
Neutrophil (%)	58.4±9.4	63.0±12.2	0.017
Platelet count (×10 <sup>3</sup> /μL)	239±68	275±88	0.011
CRP (mg/dL)	6.27±11.7	13.6±26.7	0.014
Fibrinogen (mg/dL)	361±92	432±124	0.001
Prothrombin time (s)	11.0±2.6	11.0±1.3	0.880
Partial thromboplastin time (s)	39.0±16.3	32.2±9.3	0.003
CK-MB (ng/mL)	3.5±2.5	4.2±3.9	0.390
Trponin T (ng/mL)	0.19±1.35	0.71±2.24	0.256
AT-III (%)	94.3±15.5	101.7±16.0	0.073
Baseline ACT (s)	142±16	148±19	0.101

HR<sub>normal</sub>, normal heparin responsiveness; HR<sub>reduced</sub>, reduced heparin responsiveness; WBC, white blood cell; CRP, C-reactive protein; CK-MB, creatine kinase-MB; AT-III, antithrombin-III; ACT, activated clotting time.

During surgery, patients with HR<sub>reduced</sub> received significantly larger amounts of heparin and transfused red blood cells (Table 3).

There was no significant relationship between the HSI and changes in the CK-MB and Tn-T levels ( $P=0.804$  and  $0.904$ , respectively). The HSI was also similar between the patients with and without postoperative myocardial infarction ( $1.5±0.5$  vs  $1.5±0.4$ ,  $P=0.939$ ). The incidence of perioperative MI within 7 d and the incidence of other postoperative complications were not significantly different between the two groups (Table 4). During the 6 month follow up period, none of the patients developed symptoms of ischemia except 1 patient in the HR<sub>normal</sub> group who developed a symptomatic arrhythmia caused by restenosis of the venous graft to the right coronary artery and underwent PCI with a stent procedure. CT angiography was performed in 105 patients and 16 patients of the HR<sub>normal</sub> and HR<sub>reduced</sub> groups, respectively. Sixteen patients in the HR<sub>normal</sub> group met the predefined criteria of restenosis, in contrast to none of the patients in the HR<sub>reduced</sub> group (Table 4).

## Discussion

In this prospective study evaluating the risk factors for

**Table 3.** Intraoperative and postoperative data. Data are expressed in numbers or mean±SD.

	HR <sub>normal</sub> (n=168)	HR <sub>reduced</sub> (n=31)	P value
<b>Intraoperative variables</b>			
Total heparin (units)	10 753±2124	12 590±1832	<0.001
Total protamine (mg)	42±11	43±15	0.836
Bleeding (mL)	236±177	279±145	0.210
pRBC (pack)	0.5±1.0	0.90±1.0	0.049
FFP (pack)	0.5±1.6	0.6±1.2	0.606
p-conc (pack)	0.3±1.5	0.1±0.7	0.543
<b>Postoperative variables</b>			
bleeding (mL)	1214±518	1291±453	0.440
pRBC (pack)	0.6±1.3	0.6±1.0	0.962
FFP (pack)	0.5±1.6	0.6±1.2	0.823
p-conc (pack)	0.3±1.5	0.1±0.7	0.483
<b>Graft numbers</b>			
Arterial grafts	3.3±0.7	3.5±0.6	0.051
Vein grafts	2.8±1.0	2.7±1.1	0.558
Both arterial and vein grafts	0.45±0.87	0.74±1.2	0.183
	42 (25%)	10 (32%)	0.398
Operation time (min)	249±50	266±36	0.067
Anesthesia time (min)	327±52	346±39	0.054

HR<sub>normal</sub>, normal heparin responsiveness; HR<sub>reduced</sub>, reduced heparin responsiveness; pRBC, packed red blood cells; FFP, fresh frozen plasma; p-conc, platelet concentrates.

**Table 4.** Postoperative outcome. Data are expressed in numbers or mean±SD.

	HR <sub>normal</sub> (n=168)	HR <sub>reduced</sub> (n=31)	P value
Highest CK-MB	13.4±17.1	11.2±8.7	0.511
Highest Tn-T	0.47±2.29	0.63±1.47	0.715
Postoperative MI	22 (13.1%)	2 (6.5%)	0.382
Stroke	2 (1.2%)	0	0.712
Renal failure	14 (10.1%)	2 (6.5%)	0.531
Reoperation	2 (1.2%)	0	0.712
Prolonged ventilation	1 (0.6%)	1 (3.2%)	0.288
A-fib development	40 (23.8%)	7 (22.6%)	0.544
<b>Six months follow up</b>			
cardiac morbidities	1 (0.6%)	0	1.000
restenosis	16/105 (15.2%)	0/16 (0%)	0.126

HR<sub>normal</sub>, normal heparin responsiveness; HR<sub>reduced</sub>, reduced heparin responsiveness; CK-MB, creatine kinase-MB; Tn-T, troponin-T; MI, myocardial infarction; A-fib, atrial fibrillation; restenosis, confirmed by computed tomographic angiography.

HR<sub>reduced</sub> and its association with MI and morbidity endpoints following OPCAB, low albumin concentrations and high platelet counts were identified as independent predictors of HR<sub>reduced</sub>. However, the incidences of postoperative MI and morbidity endpoints including cardiac morbidities were not

increased in patients with HR<sub>reduced</sub>.

The use of heparin during procedures involving coronary arteries requires particular attention to decrease perioperative thrombogenesis without increasing the risk of bleeding. During cardiopulmonary bypass (CPB), ACTs of less than 300 s caused coagulation in bypass circuits, and ACTs are recommended to be longer than 400–480 s<sup>[1, 22]</sup>. Accordingly, a single retrospective review evaluating the impact of heparin responsiveness on ischemic complications within the first postoperative 48 h revealed that HR<sub>reduced</sub> was an important risk factor for fatal MI after on-pump CABG<sup>[11]</sup>. Additionally, in patients undergoing coronary balloon angioplasty, there was an inverse relationship between heparin responsiveness and the incidence of abrupt vessel collapse during and after angioplasty<sup>[7, 8, 23]</sup>. On the contrary, other studies involving patients undergoing stent insertion reported no correlation between heparin responsiveness and ischemic complications<sup>[9, 10]</sup>, although there was a case of stent thrombosis associated with HR<sub>reduced</sub><sup>[6]</sup>.

OPCAB constitutes an important axis as a surgical revascularization technique of diseased coronary arteries, and by avoiding CPB, a reduced amount of heparin is required during surgery. Based on previous studies, ACTs between 250 and 300 s during OPCAB seem to be acceptable in many institutions<sup>[22, 24]</sup>, and the majority of hospitals administered 150 U/kg heparin at the beginning of graft anastomosis for a target ACT value of approximately 300 s<sup>[15]</sup>, which is similar to that for PCI. In view of the inflammation and coagulation statuses, OPCAB stands in a unique position because it is still associated with significant inflammatory responses and the activation of the coagulation and fibrinolytic systems following mid-sternotomy and cardiac manipulation, which are more pronounced in OPCAB patients than in patients undergoing PCI<sup>[2, 25]</sup>. Moreover, it has been demonstrated that OPCAB is associated with a postoperative procoagulant state related to increases in prothrombin factor and von Willebrand factor and to transient platelet dysfunction compared to on-pump CABG<sup>[13, 14]</sup>. In addition, unlike for PCI, all patients presenting for OPCAB have previous exposure to heparin during coronary angiography, which is a well-known risk factor for HR<sub>reduced</sub><sup>[4, 5, 12]</sup>, and yet, evidence is lacking with regard to heparin responsiveness and its clinical impact on OPCAB patients. Thus, we aimed to evaluate factors affecting HR<sub>reduced</sub> and the relationship between heparin responsiveness and postoperative MI and morbidity endpoints.

As our results indicate, patients with HSI<1.0 composed 16% of the study population, and low albumin concentrations and high platelet counts were identified as independent predictors of HR<sub>reduced</sub>. However, we did not observe any relationship between the HSI and changes in myocardial enzyme levels, and the HSI was also similar between patients with and without postoperative MI. Plausible causes for these results are as follows. Although previous studies found adverse ischemic outcomes in patients with HR<sub>reduced</sub>, these studies were either retrospective or did not prospectively manage the target ACT as in this study. In the current trial, the ACT was

closely monitored and maintained at >300 s prospectively by administering additive heparin if necessary during grafting. The ACT measured after the last heparin dose and before coronary anastomosis was above 300 s in all patients; this may be why HR<sub>reduced</sub> did not demonstrate any clinical relevance with respect to myocardial enzyme levels and MI during the perioperative period. This is in accordance with the results of previous studies in the PCI setting in which ACT was prospectively managed to be at least 225 s regardless of the presence of HR<sub>reduced</sub><sup>[9, 10]</sup>. Considering that patients with HR<sub>reduced</sub> seemed to be in a preoperatively hypercoagulable state and that the minimum ACT during surgery was significantly lower in patients with HR<sub>reduced</sub> (297±44 s vs 253±23 s,  $P<0.001$ ), it still might be important to acknowledge the risk in these patients and to perform additional and frequent ACT measurements to maintain an adequate ACT level and to titrate the heparin dosage during surgery. Inflammatory markers such as CRP and the neutrophil percentages were not independent risk factors for HR<sub>reduced</sub>. Perhaps the utilization of more distinct inflammatory markers such as interleukins could have resulted in a different outcome. Unlike previous studies of cardiac surgery, in our study, the AT-III levels were not lower in patients with HR<sub>reduced</sub>, and only a few patients exhibited AT-III levels below 60% (4 in the HR<sub>normal</sub> and 1 in the HR<sub>reduced</sub> group). Low AT-III activity has been reported to contribute to HR<sub>reduced</sub> and hypercoagulability<sup>[26, 27]</sup> and could result in major thrombotic complications after PCI and on-pump CABG<sup>[28, 29]</sup>. Considering the significant decrease in AT-III activity during on-pump CABG<sup>[30]</sup>, the different results compared to the previous study may also be partly attributable to the variable AT-III activity. Although, the HR<sub>reduced</sub> group received a significantly larger amount of heparin and transfused red blood cells during surgery, it is difficult to establish a direct relationship between them because the HR<sub>reduced</sub> group initially had a lower hematocrit level.

Heparin responsiveness potentially may influence not only the periprocedural morbidity but also the long term patency of grafted vessels. Heparin inhibits the activation of the mitogen-activated protein kinase in vascular smooth muscle cells, and thus, the relative resistance to the antiproliferative action of heparin could be associated with long term graft patency<sup>[31]</sup>. In an *in vitro* study, heparin resistance in cultured vascular smooth muscle cells was a highly significant predictor of subsequent vein graft stenosis<sup>[32]</sup>. Although there have been few studies evaluating whether a population clinically characterized by HR<sub>reduced</sub> during vascular procedures has concurrent hyperstenotic characteristics with an increased risk of graft stenosis, more careful follow-up is required in these patients. In this study, HR<sub>reduced</sub> was not associated with cardiac morbidities or restenosis of graft vessels during a six month follow-up period after OPCAB.

The limitations of this study are as follows. The anti-platelet therapy consisting of aspirin and clopidogrel was started empirically 24 h after surgery as appropriate, and the inter-individual variability of clopidogrel responsiveness was not assessed, which might have affected the ischemic outcomes of

the patients regardless of the HSI<sup>[33]</sup>.

In conclusion, low plasma albumin concentrations and high platelet counts were identified as independent predictors of HR<sub>reduced</sub>. Despite a strong theoretical possibility and a close relationship between HR<sub>reduced</sub> and postoperative MI in on-pump CABG patients, HR<sub>reduced</sub> was not associated with adverse ischemic outcomes during the postoperative period after OPCAB. A tight prospective protocol for obtaining a target ACT regardless of the presence of HR<sub>reduced</sub> seems to be of the highest importance while performing surgical revascularization.

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### Author contribution

Duk-hee CHUN, Seong-wan BAIK, and Young Lan KWAK designed the study; Duk-hee CHUN, So Yeon KIM, Jae Kwang SHIM, and Jong Chan KIM performed the research; Duk-hee CHUN, Seong-wan BAIK, and Jae Kwang SHIM analyzed the data; Young Lan KWAK wrote the manuscript.

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