Study of the factors related to atrial fibrillation after coronary artery bypass grafting: A search for a marker to predict the occurrence of atrial fibrillation before surgical intervention

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Objective: Atrial fibrillation after cardiac surgery is a frequent complication. In this study we studied various factors in addition to trying to identify a marker that would predict the potential for atrial fibrillation before surgical intervention to prevent its occurrence.

Methods: We targeted 234 cases in which isolated coronary artery bypass grafting had been performed. The items for study included age, EuroSCORE, and maximum values of creatine phosphokinase–MB, troponin I, and angiotensin II after surgical intervention and preoperative values of atrial natriuretic peptide, brain natriuretic peptide, and C-reactive protein. As fibrotic markers, we measured levels of the sialylated carbohydrate antigen KL-6 in the blood, hyaluronic acid, and pyridinoline cross-linked carboxyterminal telepeptide of type I collagen C. At the time of surgical intervention, a section of the right atrium was extracted, and atrial natriuretic peptide, the sialylated carbohydrate antigen KL-6, hyaluronic acid, and pyridinoline cross-linked telopeptide of type I collagen levels were measured.

Results: Atrial fibrillation was observed in 73 (31.2%) cases, and preoperative factors that showed statistically significant differences in the occurrence of atrial fibrillation included age, EuroSCORE, and preoperative values of atrial natriuretic peptide, angiotensin II, the sialylated carbohydrate antigen KL-6, hyaluronic acid, and pyridinoline cross-linked telopeptide of type I collagen in the blood. As for intraoperative and postoperative factors, statistically significant differences were observed in the postoperative maximum of angiotensin II, atrial natriuretic peptide of the right atrium, the sialylated carbohydrate antigen KL-6, hyaluronic acid, and pyridinoline cross-linked telopeptide of type I collagen levels.

Conclusion: The fibrosis of tissue associated with age is believed to be closely related to the occurrence of atrial fibrillation after coronary artery bypass grafting. This study suggests that the preoperative values of atrial natriuretic peptide, angiotensin II, the sialylated carbohydrate antigen KL-6, hyaluronic acid, and pyridinoline cross-linked telopeptide of type I collagen in the blood are useful as a new index for the occurrence of atrial fibrillation after coronary artery bypass grafting.

Atrial fibrillation (AF) after cardiac surgery is a frequent complication, with a rate of occurrence that has been reported to range from 18.3% to 33%.[1-4] Various studies regarding the causes of its occurrence have been conducted, including advanced age,[1-7] sex,[2] body mass index,[4,5] left atrial dimensions,[5] low cardiac function,[4,6] chronic respiratory failure,[4,7] and renal dysfunction,[6] but no definitive consensus has yet been reached. However, one fact that is common among the various reports in the past is that advanced age is believed to be one of the factors. The occurrence of postoperative AF also has an effect on a patient's prognosis, resulting in an increased hospital stay, and therefore prevention of its occurrence is important. In the elderly, in particular, it is important to predict and prevent postoperative AF before surgical intervention because complications occur in many cases as a result of a lengthy hospital stay, which strongly affects the patient prognosis.

In this study related to the occurrence of postoperative AF, we examined several factors. Many reports suggesting that age has a strong effect on the occurrence of postoperative AF have been presented in the past, and we measured levels of the sialylated carbohydrate antigen KL-6, hyaluronic acid, pyridinoline cross-linked telopeptide of type I collagen (I-CTP), and atrial natriuretic peptide (ANP) as indicators of the fibrosis of tissue to prevent the occurrence thereof. We thereafter examined whether any of these factors could be used as markers for predicting the occurrence of postoperative AF before surgical intervention.

MATERIALS AND METHODS

We targeted 234 consecutive cases in which isolated coronary artery bypass grafting (CABG) had been performed in our institute, but cases of acute myocardial infarction and patients who had a history of arrhythmia were excluded from this study. CABG with cardiopulmonary bypass (CPB) was

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Abbreviations and Acronyms

ACE-I = angiotensin-converting enzyme inhibitor
AF = atrial fibrillation
ANP = atrial natriuretic peptide
ARB = angiotensin II receptor blocker
BNP = brain natriuretic peptide
CABG = coronary artery bypass grafting
CI = confidence interval
CPB = cardiopulmonary bypass
CRP = C-reactive protein
I-CTP = pyridinoline cross-linked telopeptide of type I collagen
OR = odds ratio
RAAS = renin–angiotensin–aldosterone system

conducted in all cases by using the intermittent aortic crossclamp method, which does not use cardioplegia. The heart rate was monitored for a week after surgical intervention, and we studied its relationship to the occurrence of AF. In this study we defined AF as either cases that continued for more than 5 minutes or cases in which treatment was required due to the hemodynamic conditions. Regarding the treatment for AF, we administered 50 mg of pilsicainide hydrochloride (Sunrythm; AsubioPharma, Daiichi Sankyo, Tokyo, Japan) parenterally for 30 minutes, and then pilsicainide hydrochloride was administered internally as a first choice and amiodarone hydrochloride (Ancaron; Aventis Pharma, Tokyo, Japan) was administered internally for cases in which no effect was achieved.

The items for study included age, sex, incidence of emergency surgical intervention, body surface area, previous myocardial infarction, EuroSCORE, use of preoperative internal medicine (β-blockers, calcium antagonists, angiotensin II receptor blockers [ARBs], and angiotensin-converting enzyme inhibitors [ACE-Is]), diabetes mellitus, hypertension, hyperlipemia, history of smoking, use of hemodialysis, cerebrovascular disorders, cardiac function (left ventricular ejection fraction), and left atrial dimensions. We measured the ANP, brain natriuretic peptide (BNP), angiotensin II, and C-reactive protein (CRP) levels in the blood before surgical intervention. We also measured KL-6, hyaluronic acid, and I-CTP levels in the blood as markers of fibrosis. At the time of surgical intervention, a section of the right atrium was extracted, and we measured the levels of ANP (radioimmunoassay method; Shionogi, Co, Ltd, Tokyo, Japan), KL-6 (enzyme-linked immunosorbent assay method; Sanko Junyaku, Tokyo, Japan), hyaluronic acid (latex agglutination turbidimetric immunoassay; Mitsubishi Kagaku Latron, Inc, Tokyo, Japan), and I-CTP (radioimmunoassay method; TFB, Inc, Tokyo, Japan) therein. Regarding intraoperative and postoperative factors, aortic crossclamp time, CPB time, number of bypasses, operative mortality, complications (including cerebral infarction, respiratory failure, acute renal failure, acute cardiac failure, mediastinitis, and gastrointestinal complications), length of hospital stay, and, in a biochemical examination of the blood, creatinine phosphokinase–MB isoenzyme, troponin I, and CRP levels were measured immediately after surgical intervention, 3 hours after surgical intervention, and on the first, second, and third days after surgical intervention. ANP, BNP, and angiotensin II levels were measured immediately after surgical intervention and on the first and third days after surgical intervention. The maximum and minimum values of ANP were also measured and compared.

Results are expressed as the mean $\pm$ standard deviation. By using parametric and nonparametric data, statistically significant differences were determined by using the Student's t test and the Fisher's exact test, respectively. We compared patients with postoperative AF and those without AF regarding patient background, preoperative blood test findings, results during and after surgical intervention, and postoperative blood test findings by using the Fisher's univariate exact test or the unpaired Student's t test. Independent predictors for postoperative AF were examined by using a multivariate analysis with a logistic regression from the parameters detected by means of univariate analysis. All analyses were conducted with SPSS software (SPSS, Inc, Chicago, Ill).

TABLE 1. Postoperative complications

	AF (+)	AF (–)
Cerebral infarction	2	0
Acute cardiac failure	4	0
Mediastinitis	2	1
Acute renal failure	2	0
Respiratory failure	1	1
Gastrointestinal complication	1	1
Hemorrhage	1	0
Total	13	3

AF, Atrial fibrillation.

RESULTS

After CABG, AF was observed in 73 (31.2%) cases, and the time of occurrence averaged 2.42 $\pm$ 1.03 days (0–5 days). The sinus rhythm in all cases improved as a result of treatment. There were 2 cases of operative mortality, and both were cases of emergency surgical intervention for patients with unstable angina. These patients had perioperative myocardial infarction and died of cardiac failure. Postoperative AF was observed in both cases. The cases of postoperative complications were as follows: 2 cases of cerebral infarction, 4 cases of acute cardiac failure, 3 cases of mediastinitis, 2 cases of acute renal failure, 2 cases of respiratory failure, 2 cases of gastrointestinal complication, and 1 case of hemorrhage. Postoperative AF was observed in 2 cases of cerebral infarction, 4 cases of acute cardiac failure, 2 cases of mediastinitis, 2 cases of acute renal failure, 1 case of respiratory failure, 1 case of gastrointestinal complication, and 1 case of hemorrhage (Table 1).

The preoperative factors that showed statistically significant differences in the occurrence of AF included age, EuroSCORE, and preoperative values of ANP, angiotensin II, KL-6, hyaluronic acid, and I-CTP in the blood (Table 2). There were no differences in the risk factors, including sex, body surface area, hypertension, preoperative internal medicine treatment, previous incidence of myocardial infarction, incidence of emergency surgical intervention, preoperative ejection fraction, left atrial dimension, BNP, and CRP (Table 2).

Regarding intraoperative and postoperative factors, there were statistically significant differences observed in operative mortality, postoperative complications, length of hospital stay, maximum angiotensin II level after surgical intervention, ANP level in the right atrium, and KL-6, hyaluronic acid, and I-CTP levels. There were also no significant differences in the maximum postoperative value of

TABLE 2. Preoperative background of patients and preoperative data

	AF (+) (n = 73)	AF (–) (n = 161)	*P* value
Age (y)	72.1 ± 7.07	66.05 ± 9.54	<.001
Male sex	51	129	.084
BSA (m^2)	1.63 ± 0.16	1.64 ± 0.15	.765
Diabetes mellitus	38	83	.609
Hypertension	60	122	.274
Hyperlipidemia	40	91	.805
Hyperuricemia	13	26	.752
Smoking	18	60	.058
Previous MI	28	49	.232
Emergency	26	47	.326
Hemodialysis	3	13	.266
CVD	8	13	.475
Ejection fraction (%)	59.7 ± 11.9	60.4 ± 12.8	.723
Left atrial diameter (mm)	34.6 ± 7.1	32.1 ± 8.8	.095
BNP (pg/dL)	137.2 ± 215.7	149.7 ± 262.0	.751
EuroSCORE	6.15 ± 3.01	4.36 ± 3.49	.0002
KL-6 (U/mL)	281.0 ± 147.3	229.8 ± 111.1	.019
ANP (pg/dL)	38.8 ± 32.2	51.4 ± 49.8	.043
I-CTP (ng/mL)	10.47 ± 6.89	6.17 ± 7.36	.007
Hyaluronic acid (ng/mL)	80.9 ± 60.2	44.9 ± 43.8	<.001
CRP (mg/dL)	0.69 ± 1.74	1.19 ± 2.79	.230
Angiotensin II (pg/dL)	16.7 ± 29.1	9.1 ± 8.0	.0064
ARB use	26	51	.554
ACE-I use	13	60	.091
Ca antagonist use	23	48	.794
β-Blocker use	12	15	.114

AF, Atrial fibrillation; *BSA*, body surface area; *MI*, myocardial infarction; *CVD*, cerebrovascular disease; *BNP*, brain natriuretic peptide; *ANP*, atrial natriuretic peptide; *I-CTP*, hyaluronic acid, pyridinoline cross-linked telopeptide of type I collagen; *CRP*, C-reactive protein; *ARB*, angiotensin II receptor blocker; *ACE-I*, angiotensin-converting enzyme inhibitor; *Ca*, calcium.

TABLE 3. Intraoperative and postoperative data

	AF (+)	AF (–)	*P* value
ACCT (min)	28.7 ± 14.0	27.3 ± 13.2	.476
CPBT (min)	102.7 ± 23.5	99.4 ± 28.0	.373
Bypass	3.15 ± 0.86	3.18 ± 0.85	.761
Mortality	2 (2.7%)	0	.035
Complication	13	3	.023
Hospital stay (d)	25.3 ± 22.4	15.8 ± 7.90	<.001
ANP in RA (pg/wmg)	115.5 ± 106.1	208.5 ± 210.5	.007
I-CTP in RA (ng/wmg)	0.149 ± 0.086	0.114 ± 0.041	.0028
Hyaluronic acid in RA (ng/wmg)	268.6 ± 103.5	222.7 ± 76.4	<.001
Peak CK–MB (U/L)	76.2 ± 74.2	61.3 ± 42.3	.11
Maximum troponin I (ng/dL)	14.5 ± 15.0	13.7 ± 13.1	.722
Maximum angiotensin II (pg/dL)	30.7 ± 44.0	15.5 ± 20.7	.0014
Maximum BNP (pg/dL)	509.9 ± 405.3	496.6 ± 514.9	.859
Maximum CRP (mg/dL)	4.56 ± 2.92	4.71 ± 2.90	.768
Maximum ANP (pg/dL)	182.8 ± 352.8	157.6 ± 215.3	.542
Minimum ANP (pg/dL)	44.7 ± 26.3	68.2 ± 46.6	<.001

AF, Atrial fibrillation; *ACCT*, aortic crossclamp time; *CPBT*, cardiopulmonary bypass time; *ANP*, atrial natriuretic peptide; *RA*, right atrium; *I-CTP*, pyridinoline cross-linked telopeptide of type I; *CK–MB*, creatine kinase– MB isoenzyme; *BNP*, brain natriuretic peptide; *CRP*, C-reactive protein; *wmg*, weight of tissue/saline (2 mL).

ANP in the blood in both groups, but the number of cases in which AF did not occur was significantly lower than the number in which AF did occur at the minimum value. No significant differences were observed regarding the aortic crossclamp time, CPB time, postoperative peak of creatinine phosphokinase–MB isoenzyme, and troponin I and CRP values (Table 3). We were unable to obtain a measured value of KL-6 in the right atrium, and therefore we believe that it was not secreted from the right atrium.

The items that were categorized as risk factors for postoperative AF included a EuroSCORE of at least 8 points (odds ratio [OR], 6.37; 95% confidence interval (CI), 1.16–34.98; $P = .033$) in the logistic regression analysis, age of at least 70 years (OR, 5.89; 95% CI, 2.05–16.97; $P = .001$), a preoperative value of no more than 20 pg/mL of ANP in the blood (OR, 5.45; 95% CI, 1.0–30.02; $P = .045$), the occurrence of postoperative complications (OR, 5.09; 95% CI, 1.25–20.69; $P = .023$), at least 30 U/mL of KL-6 (OR, 4.61; 95% CI, 1.29–18.69; $P = .04$), at least 10 ng/mL I-CTP (OR, 2.99; 95% CI, 1.17–22.9; $P = .04$), and at least 80 ng/mL of hyaluronic acid (OR, 2.18; 95% CI, 1.15–13.33; $P = .03$).

When the correlation of the values was analyzed among the blood levels of ANP, hyaluronic acid, and I-CTP, for the levels in the right atrium, ANP resulted in an r value of 0.578 ($P < .001$) and hyaluronic acid resulted in an r value of 0.553 ($P < .001$), thus indicating a good correlation. On the other hand, I-CTP resulted in an r value of 0.091 ($P = .349$), and no correlation was found (Figure 1).

DISCUSSION

Studies related to the occurrence of AF after cardiac surgery have been conducted from various perspectives, and the factors of its occurrence were incorporated into a large-scale study conducted on more than 1000 cases, including advanced age, preoperative low cardiac function, renal dysfunction, cases of subsequent surgical intervention, use of a preoperative β-blocker, hypertension, hyperlipidemia, chronic cardiac failure, cerebrovascular disease, peripheral vessel disorder, history of chronic obstructive pulmonary disease, obesity, use of intra-aortic balloon pumping, use of CPB, history of arrhythmia, cases of left main coronary trunk, multivessel disease, use of ACE-I, digitalis, and a large left atrium.[3-7] However, no definitive consensus has yet been reached. Lo and coeorkers[8] reported that inflammation was associated with postoperative AF, and AF occurs less frequently in cases in which the preoperative CRP level is low. In recent years, reports that incidents of postoperative AF are fewer in patients undergoing off-pump CABG have been presented.[9] It has been reported that one cause is that CPB can induce inflammation.

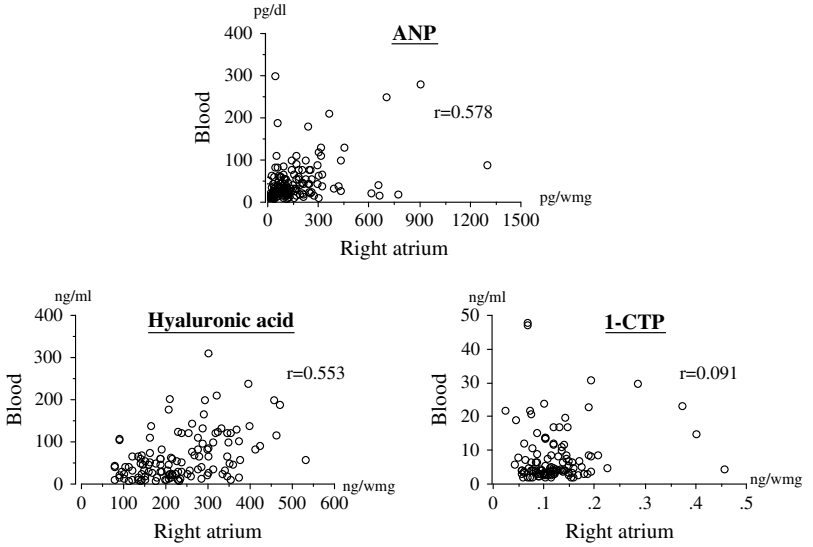

FIGURE 1. Correlation between the preoperative levels of atrial natriuretic peptide *(ANP)*, pyridinoline cross-linked telopeptide of type I collagen *(I-CTP)*, and hyaluronic acid in the blood and ANP, I-CTP, and hyaluronic acid in the right atrium.

However, there is a report of a randomized study that reported that neither off-pump CABG nor conventional CABG affected the occurrence of postoperative AF.[10,11] Therefore such factors as the age of a patient rather than factors associated with surgical intervention are believed to have a stronger effect on the occurrence of AF. It is clear in many reports that advanced age is closely associated with the occurrence of AF, and to the extent of our exhaustive research, no reports indicate that advanced age is not associated with the occurrence of AF. Amar and colleagues[3] reported that AF tends to occur in cases in which the P-wave duration is at least 100 ms in a preoperative electrocardiogram, whereas Zaman and associates[2] reported that AF tends to occur in cases in which the single averaged P-wave duration is at least 155 ms, and this duration tends to increase as patients increase in age. Nakai and associates[12] reported that postoperative AF commonly occurs in cases of advanced age and a history of AF, and a histologic study on the right atrium examined during surgical intervention suggests that the progression of fibrosis of the right atrium increases as the patients increase in age, which is associated with the occurrence of postoperative AF.

There is also a report that β-blockers and amiodarone are effective in preventing postoperative AF.[13] Conversely, some reports suggest that the preoperative use of β-blockers is not associated with AF.[7,12] In this study there were few cases in which a β-blocker was administered before surgical intervention, and therefore we are unable to verify this point, but statistically, it was not associated with the occurrence of postoperative AF.

We studied the fibrosis of tissue caused by aging in seeking an effective marker for the prevention of the occurrence of postoperative AF before surgical intervention. We examined KL-6, hyaluronic acid, I-CTP, and ANP as fibrotic markers in this study. KL-6 is a sialylated carbohydrate antigen that is present on mucin-1 and is said to be a biomarker with high specificity for pulmonary fibrosis.[14] Hyaluronic acid is said to be a mucous mucoperiosteum with a high molecular weight that is widely distributed throughout the connective tissues in a living body, and it is metabolized in the liver. It has also been shown to exhibit high values in cases of hepatic fibrosis.[15] Type I collagen is a protein that accounts for 90% of bone matrix. Type I collagen in bone tissues is degraded during bone absorption, thus causing I-CTP to be released into the blood from the C-terminus, and is selectively metabolized in the liver. It has been demonstrated to exhibit high values in cases of I-CTP osteoporosis and hepatic fibrosis.[16]

ANP is a hormone secreted in response to an extension of the atrium, and when fibrosis of the atrium progresses, secretion decreases.[17,18] There are few studies on the relationship between AF and I-CTP, hyaluronic acid, and KL-6, and we did not find any report related to cardiac surgery. Boldt and colleagues[19] reported that levels of collagen type III and I are significantly higher in patients with AF than in patients with a normal sinus rhythm, whereas Tziakas and associates[20] reported that serum levels of the carboxyterminal propeptide of collagen type I are significantly higher in patients with AF than in patients with a normal sinus rhythm. Luo and coworkers[21] reported that type I collagen volume fraction in the atria of patients with AF is significantly higher than that seen in patients with a normal sinus rhythm, thus playing a significant role in the fibrosis of the arterial muscle and suggesting that carboxyterminal propeptide of collagen type I might be a marker that could predict the occurrence of postoperative AF.

In this study there were significant differences in the occurrence of AF at all preoperative levels of KL-6, hyaluronic acid, I-CTP, and ANP in the blood. KL-6 levels were measured from the right atrium in this study; however, we were unable to obtain a measured value, and therefore it is believed that there is little possibility of such secretion in the atrium. However, it was measurable in the blood, and therefore this study suggests its effectiveness as a marker that might predict postoperative AF.

In terms of ANP, no report related to CABG has yet been published, but ANP is a hormone that is secreted from the atrial wall in response to the extension of the atrium. As age and fibrosis of the right atrium progress, ANP is believed to be poorly secreted because of poor extension of the atrial wall. ANP suppresses the renin–angiotensin–aldosterone system (RAAS), and angiotensin II is said to stimulate the development of fibroids. In a study on CABG, White and coworkers[22] presented a report in which the administration of ACE-I and ARB before surgical intervention reduces postoperative AF, whereas Guler and associates[23] published a report in which angiotensin II levels were shown to be significantly higher in cases in which AF occurred when angiotensin II was measured on day 2 after surgical intervention. Because angiotensin II causes electrophysiologic and structural remodeling,[24,25] ACE-I and ARB have been reported to prevent the occurrence of postoperative AF because it suppresses angiotensin II.[22] For the first time internationally, we therefore proposed a method of continuously administering low doses of hANP (Daiichi Pharmaceutical, Inc, Tokyo, Japan and Suntory, Inc, Osaka, Japan) from the initiation of extracorporeal circulation during cardiac surgery,[26] and we have verified that postoperative AF occurs less frequently in cases in which hANP is administered while incorporating it into a prospective randomized trial.[27] In this study we believe that the suppression of ischemic reperfusion disorder and the maintenance of potassium levels resulted in the less frequent occurrence of AF. However, according to the results of this study, namely that the minimum value of the postoperative ANP was significantly lower in cases in which AF occurred than in cases in which AF did not occur, the suppression of the decrease in ANP concentration during the preoperative period through the administration of hANP is therefore suggested to be associated with a lack of occurrence of AF. Furthermore, the postoperative suppression of angiotensin II with hANP is also believed to be one of the causes of AF. The RAAS becomes more active because of extracorporeal circulation. However, hANP was observed to suppress the RAAS, as was also proved in our previous studies. We thus believe that the AF of electrophysiologic and structural remodeling occurs when angiotensin II levels increase, thus resulting in the occurrence of AF. We would thus like to further study the method of administering postoperative low doses of hANP during cardiac surgery while focusing on postoperative AF in the future.

This study revealed that postoperative AF frequently occurs in cases in which the patients are at least 70 years old, the EuroSCORE is at least 8 points, and the postoperative value of ANP is no more than 20 pg/dL, KL-6 is at least 30 U/mL, I-CTP is at least 10 ng/mL, and hyaluronic acid is at least 80 ng/mL in the blood. This study suggests that the preoperative blood concentrations of ANP, angiotensin II, KL-6, hyaluronic acid, and I-CTP are effective as new indices for predicting the occurrence of AF after CABG. Therefore in such cases adjuvant therapies, such as those in which the level of ANP in the blood is kept high through the administration of a β-blocker or amiodarone before surgical intervention or in which hANP is administered during and after surgical intervention, might prevent postoperative AF, and we would like to elucidate these points in future studies.

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