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NT-pro-BNP, but not C-reactive protein, is predictive of atrial fibrillation in patients undergoing coronary artery bypass surgery

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Short title: NT-pro-BNP Predicts AF after CABG

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ABSTRACT

Objective: Atrial fibrillation (AF) remains the most commonly observed complication following myocardial revascularization surgery. We aimed to evaluate the clinical utility of NT-pro-BNP, troponin T, transcoronary lactate gradient (TCLG) and C-reactive protein as predictors of atrial fibrillation in patients undergoing isolated CABG.

Methods: Two hundred and fifteen consecutive patients in sinus rhythm (SR) undergoing elective CABG between May 2007 and May 2008 were included. Patients were grouped according to their respective postoperative rhythm into SR and AF groups. The data are presented as mean values ± standard deviation, or medians with quartiles.

Results: Fifty five patients developed AF (26%). The preoperative NT-pro-BNP values were 273 ± 347 and 469 ± 629 pg/ml in the SR and AF groups, respectively ($p < 0.0001$). The postoperative NT-pro-BNP values were 3110 ± 3600 in the SR and 4625 ± 5640 pg/ml in the AF group ($p = 0.027$). The transcoronary lactate gradient rose from the pre-cardiopulmonary bypass (CPB) values to those observed 5 minutes after revascularization in both groups (-0.05 ± 0.37 to 0.39 ± 0.46 mmol/l ($p < 0.0001$) in the SR group and -0.01 ± 0.27 to 0.43 ± 0.46 mmol/l ($p < 0.0001$) in the AF group). The CRP values increased from 6 ± 13 to 163 ± 88 mg/L ($p < 0.0001$) in the SR group, and from 6 ± 16 to 163 ± 104 mg/l ($p < 0.0001$) in the AF group. The dynamics of TCLG and CRP did not differ between the groups ($p = 0.71$, $p = 0.44$, respectively). The troponin T values on postoperative day one were significantly higher in the AF than the SR group (0.86 [0.49-2.1] ng/ml vs. 0.67 [0.37-1.16] ng/ml, $p = 0.046$). The duration of cardiopulmonary bypass (CPB) was 85 ± 24 in the SR and 93 ± 30 min in the AF group ($p = 0.05$). Patients who developed AF were older (66 ± 7 vs 60 ± 9 years, $p < 0.0001$) and had a higher EuroSCORE (3.9 ± 2.7 vs 2.9 ± 2.2, $p = 0.009$). Multivariate analysis identified age ($p = 0.0043$), preoperative NT-pro-BNP ($p = 0.019$) and duration of cardiopulmonary bypass ($p = 0.035$) as independent predictors of AF.

Conclusions: Preoperative and postoperative NT-pro-BNP, as well as, TnT values were significantly higher in patients that subsequently developed AF. TCLG and CRP were not useful in identifying patients at higher risk for AF. Multivariate analysis identified age, preoperative NT-pro-BNP and duration of CPB as independent correlates of AF.

Key words: atrial fibrillation, coronary artery bypass

INTRODUCTION

Atrial fibrillation (AF) remains a frequent complication after coronary artery bypass surgery (CABG), occurring in 10-40% of patients (1,2,3). Notably, the recruitment of older patients into the contemporary cardiac surgical referral pattern is reflected by an increasing incidence of postoperative AF (1,4). Atrial fibrillation may present as a benign and self limiting disorder. Conversely, it may have a significant adverse impact on patient recovery because of its association with hemodynamic compromise, renal insufficiency, prolonged requirement for ventilatory support and stroke (3,5). It is also responsible for a longer hospital length of stay and, predictably, cost of care (2, 6). The clinical sequelae of AF combined with the increased utilization of resources have motivated the definition of various algorithms aimed to identify patients at higher risk for developing this complication. Uncompromising AF prophylaxis in the higher risk subpopulation of CABG patients could reduce cost and improve the postoperative patient recovery.

The pathogenesis of postoperative AF is multifactorial and may be linked to age, intraoperative manipulation with the heart, ischemia, atrial distension, inflammation and structural heart disease (2,7). C-reactive protein (CRP) is an acute-phase protein which has been effective in defining the degree of inflammation, and was used for that purpose in this study (7). Increased CRP levels have been linked to the severity of atherosclerosis, risk of coronary events and even long term outcome after CABG (8,9). The mechanism of its arrhythmogenesis has been postulated to be related to sodium and calcium exchange disturbances following its linkage to phosphocoline (7). A sympathovagal imbalance coupled with beta blocker withdrawal has also been postulated to be associated with new onset AF (2,3).

Ischemia may be responsible for an inhomogeneous distribution of local atrial refractoriness (10). This dispersion of refractory periods within adjacent atrial regions provides a suitable milieu for the development of reentry arrhythmias (10). In the present study we aimed to

quantify the extent of myocardial ischemia by documenting the transcoronary lactate gradient in addition to measuring troponin T values. The non-physiologic metabolism of the heart during aortic cross clamping may lead to myocardial injury manifested by impaired ventricular function and delayed recovery (11). Lactic acid concentrations have been extensively studied as markers of anaerobic metabolism and hypoperfusion (12,13,14,15). Selective sampling of coronary sinus blood may offer insight into the regional metabolic state of the heart which may be more profoundly affected by its dramatic alteration of normal blood flow than would be reflected by the systemic lactate concentration. Coronary sinus lactate has been used as an adjunct in the diagnosis of perioperative myocardial ischemia (11).

Troponin T is the structural component of the troponin complex that binds to tropomyosin. The elevation of the serum concentration of troponin T begins as early as three hours after myocardial injury, and may persist for up to 10-14 days (16).

Brain natriuretic peptide is predominantly released from the ventricles in response to myocardial stretch. and as such has been found to be instrumental in determining structural heart disease (9, 17). It promotes diuresis, natriuresis, arterial vasodilatation and attenuates the activity of the renin-angiotensin-aldosterone system (9). The frequent co-existence of structural heart disease and atrial fibrillation prompted us to explore the correlation between the N-terminal fragment of the brain natriuretic peptide (NT-pro-BNP) and AF in the patient population undergoing CABG. NT-pro-BNP is released when the inactive prohormone is split into the active brain natriuretic peptide and the inactive NT-pro-BNP.

We hypothesized that myocardial ischemia, the inflammatory response and the presence of structural heart disease may influence the development of postoperative atrial fibrillation. The aim of our study, therefore, was to test the hypothesis that CRP, transcoronary lactate gradient, troponin T and NT-pro-BNP are predictors of postoperative AF.

MATERIALS AND METHODS

Following the approval from our institutional ethics committee, 215 consecutive patients found to be in sinus rhythm undergoing coronary artery bypass grafting using cardiopulmonary bypass (CPB) were included into our study from May 2007 to May 2008. Informed consent was obtained from all patients. The study was conducted in a prospective observational fashion. Exclusion criteria were concomitant valvular pathology requiring surgery, reoperative surgical myocardial revascularization and prior history of atrial fibrillation. Patients that developed atrial fibrillation during the postoperative period comprised the AF group, while the remaining patients formed the SR group. Episodes of AF lasting for more than 10 minutes were defined as sustained AF (2, 18). Only patients in whom sustained AF was noted were included in the AF group.

Perioperative management

Patients receiving preoperative beta blockers were given their normal dose on the morning of surgery. The patients received diazepam and morphine 30 minutes prior to induction of anesthesia. Endotracheal tube, urinary catheter, as well as radial artery and pulmonary artery catheters were inserted. The anesthetic regime included induction and maintenance of anesthesia with midazolam, fentanyl and pancuronium bromide. This was coupled with sevoflurane inhalation. The initial ventilator settings included a tidal volume of 8 ml/kg, and a respiratory rate of 12 breaths per minute. Typically, the FiO_2 was set at 50%. The critical components of the employed cardiopulmonary circuit were the Medtronic Affinity Trillium membrane oxygenator, venous reservoir and PVC tubing (Medtronic, Minneapolis, USA) and a Stoeckert III roller pump (Stoeckert, Munich, Germany). The ascending aorta and right atrium were cannulated for cardiopulmonary bypass. Myocardial protection consisted of both antegrade and retrograde cardioplegia. Systemic heparinization aiming at an ACT > 480 seconds was used, followed by full reversal with protamine after decannulation. Tepid CPB was employed, targeting the flow at 2.2 L/min/m^2. The target mean arterial pressure during

CPB was 60 mmHg. If necessary, norepinephrine was employed to reach the aimed blood pressure. The distal coronary anastomoses were performed on an arrested heart, during a single period of aortic cross-clamping. The lungs were open to atmosphere during CPB. Weaning from CPB was initiated once the patient's rhythm had stabilized and normothermia had been achieved. Inotropic support was initiated in order to maintain a cardiac index greater than 2.2 L/min/m^2. The preferred inotropic agent was dobutamine. Norepinephrine was used if dobutamine produced excessive vasodilatation. Epinephrine was used if the hemodynamic performance remained inadequate with the previously mentioned catecholamines. An intraaortic balloon pump was inserted if further support was required.

Measurement and Calculations

The study protocol consisted of obtaining arterial blood gas samples from the radial artery and venous blood samples from the coronary sinus. The samples were drawn simultaneously by members of the surgical and anesthesiological teams. The first samples were drawn prior to the institution of cardiopulmonary bypass (CPB). The second and third samples were drawn five and ten minutes after completing the revascularization procedure, respectively. These raw data were then processed to obtain the transcoronary lactate gradient by subtracting the radial artery lactate content from the coronary sinus lactate content. Lactate levels were obtained using the IL Gem Premier 3000 auto-analyzer (Instrumentation Laboratory, Lexington, MA, USA). This analyzer uses amperometry to determine lactate concentration levels. It measures the current level of the analyzed blood sample after applying electrolytic potential, which is proportional to the analyte concentration. The initial NT-pro-BNP values were drawn preoperatively, as an adjunct to the standard preoperative laboratory assessment. The postoperative NT-pro-BNP values were drawn on the first postoperative day. NT-pro-BNP levels were obtained using the Elecsys 2010 analyzer (Roche, Basel, Switzerland). C-reactive protein serum concentrations were measured preoperatively, and then daily for the next three consecutive days. CRP levels were obtained using the Olympus AU 2700 clinical

chemistry platform (Olympus, Tokyo, Japan). An immunoassay method, using a general latex-enhanced immunoturbidimetry measurement kit was used to determine the analyte quantity. Troponin T levels were obtained using the Elecsys 2010 analyzer (Roche, Basel, Switzerland).

Atrial fibrillation detection, prophylaxis and management

All patients were continuously monitored with telemetry (Nihon Kohden WEP-4208, Tokyo, Japan) until postoperative day 5. A 12 lead EKG was obtained on the day prior to discharge. Any clinical suspicion of arrhythmia was followed by a 12 lead EKG and reinstitution of telemetry monitoring. Patients were routinely started on beta blockers on postoperative day 1 or once inotropic support has been suspended. Throughout their hospital stay magnesium and potassium supplements were administered in order to maintain high normal levels of these electrolytes. Atrial fibrillation was treated with amiodarone, sometimes in conjunction with electrical cardioversion.

Statistical analysis

The continuous data are presented as mean values ± standard deviation or medians with the interquartile range. Categorical variables are presented as absolute numbers and percentages. Longitudinal comparisons between samples of the same subject were analyzed using the Wilcoxon matched pairs test. Analyses of continuous data between different groups of patients were performed using the Mann-Whitney U test. Differences between categorical variables in patients who developed AF and those that remained in sinus rhythm were evaluated using Fisher's exact test. A two tailed p value was used. A multivariate analysis of variables found to be significant on univariate analysis was performed using multiple linear regression in order to assess the independent correlates for AF. A $p < 0.05$ was considered to be of statistical significance for all deployed statistical calculations. The data were processed using the Statistica software package (StatSoft Inc., Tulsa, USA).

RESULTS

Perioperative summary

Two hundred and fifteen consecutive patients undergoing coronary artery bypass grafting were included into our study. The demographic data and the list of comorbidities are presented in Table 1.

Fifty-five patients developed AF for an incidence of 26%. The mean time to develop AF was 2.9 ± 2.1 days. The mean duration of AF was 15.3 ± 12.1 hours. There were no differences in the preoperative ejection fraction, body mass index, incidence of hypertension or severity of coronary artery disease between the two groups. Preoperative serum creatinine values, as well as, left atrial dimensions were similar between the groups. There was no difference in the incidence of mild valvular disease, nor was the preoperative use of antiarrhythmics, statins or angiotensin converting enzyme inhibitors different among the groups. Notably, the group of patients that developed atrial fibrillation was older (66 ± 7 vs. 60 ± 9 years, $p < 0.0001$), more symptomatic (NYHA class 2.8 ± 0.8 vs. 2.5 ± 0.8, $p = 0.03$) and had a higher risk profile (EUROScore 3.9 ± 2.7 vs. 2.9 ± 2.2, $p = 0.009$). The SR group of patients had a higher incidence of hyperlipidemia.

We found no difference in the duration of mechanical ventilation or the incidence of any major complications (Table 2). The mortality in the SR group was 1.3% (2/160), while one patient died in the AF group for a mortality of 1.8% ($p = 1.0$). The length of stay in the intensive care unit (ICU) was longer in the AF than the SR group (3 [3-5] vs. 2 [2-3] days, $p < 0.0001$). There were no strokes with permanent neurologic sequelae in either cohort of patients. One patient in the SR group had a transient ischemic event which was followed by prompt and complete neurologic recovery. The duration of cardiopulmonary bypass was longer in the AF group of patients (93 ± 30 vs. 85 ± 24 min, $p = 0.05$).

Biomarker comparisons between the two groups are presented in Table 3. The mean values of the transcoronary lactate gradient increased from the pre-intervention value of -0.05 ± 0.37 to 0.39 ± 0.46 mmol/L ($p < 0.0001$) calculated at 5 minutes after completion of the

revascularization procedure in the group of patients that maintained stable sinus rhythm. A similar increase was observed in the subgroup of patients that later developed atrial fibrillation where the preoperative TCLG value rose from -0.01 ± 0.27 to 0.43 ± 0.46 mmol/L at 5 minutes after the revascularization was complete ($p < 0.0001$). In both groups a trend towards normalizing the TCLG was seen at 10 minutes after the completion of bypass grafting. While the trend in longitudinal comparisons within each group was highly statistically significant, we found no difference between the two groups. The C-reactive protein serum concentration increased steadily in both groups, and peaked on postoperative day two. The values increased from 6 ± 13 to 163 ± 88 mg/L ($p < 0.0001$) and from 6 ± 16 to 163 ± 104 mg/L ($p < 0.0001$) in the SR and AF groups, respectively. No difference in the trends of CRP was noted between the two groups. The preoperative NT-pro-BNP concentration was significantly lower in the subset of patients that maintained stable sinus rhythm in comparison to those that went on to develop AF during the immediate postoperative period (273 ± 347 pg/ml in the SR group vs. 469 ± 629 pg/ml in the AF group, $p < 0.0001$). A similar relationship was observed for the postoperative NT-pro-BNP values as well (3111 ± 3600 pg/ml in the SR group vs. 4625 ± 5640 pg/ml in the AF group, $p = 0.027$). The longitudinal increase in the observed pre and postoperative values was highly significant in both groups ($p < 0.0001$ for both groups). The SR group of patients had a less pronounced enzyme leak in comparison to the AF group of patients as quantified by the serum troponin T values (0.67 [0.37-1.16] vs. 0.86 [0.49-2.1], $p = 0.046$).

Multiple linear regression analysis

Variables found to be significantly different between the AF and SR groups on univariate analysis were further scrutinized using the multiple linear regression analysis. The variables included were age, preoperative and postoperative NT-pro-BNP, troponin T, NYHA class, duration of CPB and EuroSCORE. We found age ($p = 0.0043$), preoperative NT-pro-BNP ($p = 0.019$) and duration of cardiopulmonary bypass ($p = 0.035$) to be significant independent correlates for atrial fibrillation in our population of patients on multivariate analysis. Troponin

T (p = 0.076), NYHA class (p = 0.058), EuroSCORE (p = 0.77) and postoperative NT-pro-BNP (p = 0.79) were not found to be statistically significant predictors of AF.

DISCUSSION

The pathogenesis of AF is multifactorial and may be linked to intraoperative manipulation with the heart, ischemia, atrial distension, inflammation and structural heart disease. Atrial fibrillation remains the most commonly observed arrhythmia following cardiac surgery. It may have profound implications on the patient's hemodynamic status as well as contribute to the development of thromboembolic complications inherent to the stagnation of blood within the dysfunctional atria. The bleeding burden brought on by the requirement for anticoagulation should also not be neglected. While atrial fibrillation may have a plethora of negative repercussions upon patient recovery, it is often self limiting and benign in its course. Different treatment strategies have been devised and tested in the clinical setting with the aim of reducing the incidence of postoperative atrial fibrillation in the cardiac surgical patient population. These include the administration of beta blockers, amiodarone, statins and ACE inhibitors (2,4,19,20,21,22). The main origin of brain natriuretic peptide is the ventricular myocardium, although the atria may be responsible for some of its production (23). The relationship between BNP and AF remains elusive. The irregularity of the rhythm may be responsible for uneven filling periods of the ventricle and intermittently provoke ventricular distention thus stimulating BNP production (23). Lactate is a sensitive marker of tissue acidosis. The transcoronary lactate gradient may offer more insight into the regional myocardial perfusion. Poor correlation of the intraoperative coronary sinus lactate and the postoperative serum lactate has been previously documented (11) and may indicate that the latter lacks sufficient sensitivity to detect subtle myocardial metabolic derangement. Whether there exists a relationship between CRP and atrial fibrillation is controversial (7,24).

The aim of our study was to identify biomarkers which could prove to be useful in discriminating between patient populations that would develop atrial fibrillation after surgical coronary revascularization and those that would maintain stable sinus rhythm. We have demonstrated a short lived lactate washout from the heart following the revascularization procedure. This acute and statistically significant increase in the transcoronary lactate

gradient was seen in both the SR and AF group of patients. There was no significant variability in the TCLG between the patients that maintained sinus rhythm in comparison to those that developed AF. The hypothesis that the magnitude of the inflammatory response would influence the incidence of postoperative AF was not corroborated by the results of our study. While Ahlsson et al had already found that the CRP concentration measured on postoperative day three had no correlation with the incidence of atrial fibrillation, we extended our evaluation to incorporate CRP levels at three different time points.

The serum concentration of CRP increased by a factor of 27 in both groups which was highly significant in a longitudinal analysis at different time points. However, there was no variability between the SR and AF groups at any of the studied time points. In contrast, the preoperative NT-pro-BNP values were very dissimilar between the patient subpopulations that developed AF and those that did not. The preoperative NT-pro-BNP concentration was significantly lower, indicating perhaps less pronounced cardiac structural abnormality, in the group of patients that did not develop atrial dysrhythmia. A dramatic accentuation of the NT-pro-BNP serum concentration was observed in both groups in response to surgery. The postoperative values on univariate analysis were, however, significantly higher among patients that went on to develop AF later in their postoperative course. Our univariate analysis further suggested that myocardial ischemia may also play a role in the genesis of postoperative AF, as the AF group of patients had higher troponin T values measured on postoperative day one. However, multivariate analysis identified only age, preoperative NT-pro-BNP and duration of cardiopulmonary bypass as independent predictors of AF.

The present study has certain limitations that warrant mentioning. The patients were monitored up to the seventh postoperative day. Any episode of atrial fibrillation occurring after that day would not have been recorded and therefore not be reflected by the results of our study. Furthermore, the variability of the coronary sinus anatomy coupled with the fact that not all venous drainage from the heart enters the coronary sinus signifies that the lactate sample from it may not reflect all areas of the myocardium.

In summary, we believe that definition of algorithms that would aim to identify patients at higher risk for developing atrial fibrillation could select those who would benefit from more vigilant AF prophylaxis. The findings of our study suggest that preoperative NT-pro-BNP should be included into such algorithms as it was an important discriminating biomarker between the patient populations undergoing CABG that developed atrial fibrillation and those that did not.

Table 1. Preoperative patient characteristics

	SR group	AF group	*p* value
N	160	55	
Age (yrs)	60±9	66±7	< 0.0001
Gender (n/%)			0.49
Male	117 (73)	37 (67)	
Female	43 (27)	18 (33)	
EUROScore	2.9±2.2	3.9±2.7	0.009
Ejection fraction (%)	58±10	58±12	0.81
Creatinine	96±48	96±29	0.91
NYHA class	2.5±0.8	2.8±0.8	0.03
Left atrial diameter (mm)	39±5	38±7	0.07
Body mass index	29±4.9	28.1±4.1	0.08
Hypelipidemia (n/%)	113 (70)	29 (53)	0.02
Hypertension (n/%)	136 (85)	49 (89)	0.51
Diabetes mellitus (n/%)	35 (22)	18 (33)	0.15
Smoking history (n/%)	85 (53)	21 (38)	0.06
Preop. AMI (n/%)	81 (51)	28 (51)	1.0
Left main stenosis (n/%)	53 (33)	18 (33)	1.0
Three vessel disease (n/%)	117 (73)	44 (80)	0.37
Mild mitral regurgitation (n/%)	47 (29)	19 (35)	0.5
Mild aortic stenosis (n/%)	21 (13)	6 (11)	0.82
Preoperative medications			
B-blockers	130 (81)	41 (75)	0.33
Amiodarone	9 (6)	2 (4)	0.73
Ca-blockers	52 (33)	24 (44)	0.14
ACE-I	118 (74)	36 (65)	0.3
Statins	141 (88)	46 (84)	0.49
Digoxin	2 (1)	0 (0)	1.0

NYHA: New York Heart Association class; Preop. AMI: preoperative acute myocardial infarction; ACE-I: angiotensin converting enzyme inhibitors; Ca-blockers: calcium channel blockers

Table 2. Perioperative data summary

	SR group	AF group	*p* value
No. of grafts	2.8±0.7	2.8 ±0.6	0.58
Thrombendarterectomy (n/%)	6 (4)	4 (7)	0.28
Ischemia (minutes)	59±19	63±21	0.17
CPB time (minutes)	85±24	93±30	0.05
Inotropic support (n/%)	34 (21)	18 (33)	0.1
ICU (days)*	2 [2-3]	3 [3-5]	< 0.0001
Mechanical ventilation (hours)*	9 [8-12]	10 [8-15]	0.28
Creatinine	103±25	114±36	0.12
Complications (n/%)			
Permanent stroke	0 (0)	0 (0)	NS
TIA	1 (1)	0 (0)	1.0
Periop. myocardial ischemia	6 (4)	3 (5)	0.7
Reexploration for bleeding	8 (5)	3 (5)	1.0
Acute renal failure	1 (1)	1 (2)	0.45
Sternal wound infection	1 (1)	0 (0)	1.0
IABP requirement (n/%)	9 (6)	4 (7)	0.74
Mortality (n/%)	2 (1.3)	1 (1.8)	1.0

* Data as medians and quartiles
CPB: cardiopulmonary bypass; ICU: intensive care unit stay; TIA: transient ischemic attack; IABP: intraaortic balloon pump

Table 3. Comparison of biomarkers between the SR and AF groups

	SR group	AF group	*p* value
TCLG [a]	-0.05±0.37	-0.01±0.27	0.93
TCLG [b]	0.39±0.46	0.43±0.46	0.71
TCLG [c]	0.14±0.30	0.17±0.39	0.29
CRP [d]	6±13	6±16	0.22
CRP [e]	88±51	87±41	0.55
CRP [f]	163±88	163±104	0.44
CRP [g]	137±72	149±82	0.18
NT-pro-BNP [h]	273±347	469±629	<0.0001
NT-pro-BNP [i]	3111±3600	4625±5640	0.027
TnT *	0.67 [0.37-1.16]	0.86 [0.49-2.1]	0.046

* Data as medians and quartiles
TCLG: transcoronary lactate gradient ([a] prior to cardiopulmonary bypass, [b] 5 and [c] 10 minutes after cross-clamp removal); CRP: C-reactive protein ([d] preoperative, [e] postoperative day 1, [f] postoperative day 2, [g] postoperative day 3); NT-pro-BNP: N-terminal fragment of the brain natriuretic peptide ([h] preoperative, [i] postoperative day 1), TnT: troponin T

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