Nodal vessels disease as a risk factor for atrial fibrillation after coronary artery bypass graft surgery

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Abstract

Objective: Atrial fibrillation (AF) is common after coronary artery bypass graft (CABG) surgery. Atrial ischaemia due to diseased atrioventricular (AV) and sinoatrial (SA) arteries has been proposed as a cause of AF post-CABG. We examined if the presence of diseased nodal arteries was a significant predictor of the development of AF post-CABG.

Methods: 100 consecutive cases (AF post-CABG) were compared to 100 consecutive controls (No AF post-CABG) with respect to pre-operative angiographic evidence of diseased nodal arteries. Cases and controls identified from the Society of Thoracic Surgeons database underwent detailed chart reviews to obtain data on potential risk factors. Patients were excluded if they were undergoing anything but a routine CABG procedure, were older than 65 years, or had previous AF. All angiograms were reviewed by a single radiologist blinded to outcome. The effect of grafting diseased nodal arteries on the development of AF post-CABG was also measured. A multiple logistic regression model was utilized to measure the effect of disease in each artery on the development of AF post-CABG.

Results: Cases and controls were comparable regarding potential risk factors, with the exception that the AF group was older than the non-AF group. Significant AV artery disease was detected in 78 cases compared to 74 controls (adjusted odds ratio (OR) OR 0.4, CI, 0.51–2.12, P = 0.82). Significant SA artery disease was detected in 34 cases compared to 21 controls (adjusted OR = 2.093, CI: 1.06–4.09, P = 0.03). Six of ten patients having revascularization of their SA nodal artery developed AF versus 28 of 45 of those who did not (OR = 0.91, CI: 0.18–5.06, P = 0.58). Forty-eight of 87 patients having revascularization of their AV nodal artery developed AF versus 30 of 65 of those who did not (OR = 1.44, CI: 0.72–2.88, P = 0.27). Conclusion: The presence of a diseased SA artery is significantly associated with AF post-CABG. Such association may be used to identify a subset of patients who might be targeted with prophylaxis.

Keywords: Atrial Fibrillation; Coronary Artery; Bypass Grafting; Arrhythmia

1. Introduction

Coronary artery bypass graft surgery (CABG) is widely used in the treatment of patients with coronary artery disease [1–3]. CABG provides significant relief of anginal symptoms, enhances cardiac function, and improves survival. Although the procedure is very successful and usually well-tolerated [4], there are many potential post-operative complications [5,6]. Atrial fibrillation (AF) is one of the most common post-operative complications after CABG surgery [7–10]. The incidence of AF in patients after CABG surgery ranges from 25 to 50% [11]. Although it has been suggested that this arrhythmia does not influence the long-term outcome of surgery [12,13], it has become evident that post-operative AF is associated with increased post-operative morbidity and mortality. AF may cause hypotension, congestive heart failure, subjective discomfort, and anxiety [13,14]. In addition, it may necessitate the use of medications post-operatively both during and post-hospitalization, which can also increase the cost of care and introduce other complications [13,14]. Patients who have AF post-operatively have higher rates of readmission to the intensive care unit, and the rate of reintubation is almost tripled [15]. Stroke and thromboembolic events, although not common, are serious complications of AF post-CABG [16,17].

Studies have suggested that some patients are more vulnerable to the development of AF post-CABG, and that a triggering factor is needed to induce its occurrence.
Among the most strongly proposed triggers is intraoperative atrial ischaemia.

Recently, occluded sinoatrial (SA) and atrioventricular (AV) nodal arteries were proposed as mechanisms for intraoperative atrial ischaemia [11].

The purpose of this study was to determine if there is a relationship between atrial ischaemia as indicated by occluded SA and/or AV nodal arteries, detected preoperatively by angiography, and the occurrence of postoperative AF. If such a relation exists, this will define a group of patients at high risk of AF post-CABG who can be identified by preoperative angiogram.

A secondary objective was to determine if the surgical revascularization of the diseased SA and/or AV nodal vessels is associated with AF post-CABG.

2. Methodology

A case-control study design was utilized. Cases with AF post-CABG were compared with controls who had no AF post-CABG with regard to the presence of pre-operative diseased SA and/or AV nodal arteries.

One hundred cases and 100 controls were identified consecutively from the Society of Thoracic Surgeons (STS) database of the cardiovascular surgery department at the Queen Elizabeth II hospital in Halifax, Nova Scotia. The first 100 controls were identified over the period March 1–August 31 1995, while the first 100 cases were identified over the period March 1 1995–August 1 1997. Cases needed a longer period to be identified since the prevalence of AF post-CABG is only about 25–30%.

Cases were those patients who developed AF within 5 days after CABG surgery. Patients were considered to have AF if it was documented in the physician’s progress notes, and the patient had been started on a pharmacological agent for heart rate control or possible conversion to sinus rhythm. Controls were those patients who did not develop AF within 5 days after CABG surgery, and remained in sinus rhythm. In order to confirm the diagnosis of AF after CABG surgery as recorded in the STS database, the medical records of all patients (cases and controls) were reviewed retrospectively. Progress notes completed by physicians, electrocardiogram strips and sheets, and the order sheets for pharmacological treatment of AF were checked for that purpose. Patients were excluded if they were older than 65 years of age, if they had previous CABG, previous AF, emergency CABG, or other procedures with CABG.

Exposure in the study is defined as the preoperative presence of significant anatomical disease (critically stenosed (>75% narrowing) or occluded), involving SA nodal or AV nodal arteries, which was ascertained for all patients (cases and controls) by examining coronary angiograms performed preoperatively. A single cardiac radiologist blinded to the outcome reviewed the 200 angiograms with respect to the blood supply of the SA and AV nodal arteries. They were reported as diseased when critically stenosed (>75% of the lumen occluded) or totally occluded; otherwise, they were reported as normal. In addition, the same cardiac radiologist suggested the artery (or arteries) that needed to be grafted that may indirectly revascularize the diseased SA and/or AV nodal arteries.

Information about demographic data, cardiac risk factors, preoperative medications, risk factors of AF post-CABG, and operative details were also retrieved from hospital records. Variables which have been shown consistently to be risk factors for the development of AF post-CABG were collected.

The Epi-info 6.4 system was used to calculate sample size for unmatched case-control study based on 80% power and alpha value of 0.05 to detect a 20% absolute difference between the groups.

2.1. Statistical analysis

Descriptive statistics were calculated for potential confounders in each group and compared between cases and controls. χ² test and Fisher’s exact test were used to compare proportions, and Mann–Whitney test was used to compare medians. The analysis of patients’ data was done for each artery separately, odds ratios (OR) and 95% confidence intervals (CI) were calculated using multivariate logistic regression. Potential confounding variables were subtracted in successive stages to determine which variable significantly affected the regression coefficient of the exposure variable (diseased SA or AV nodal arteries). Variables which affected the regression coefficient of the exposure variable by 5% or more, were included in the final model. These methods are described and justified by Greenland and Rothman [18,19]. Possible interactions between the exposure variable (diseased vessels) with age, sex, chronic obstructive pulmonary disease (COPD) status, and the cross clamp time were assessed. The likelihood ratio test was used to assess if the interaction terms had a significant effect on the model.

Due to the difference in the length of the interval over which the cases and controls were selected, sensitivity analysis was conducted to check if time of surgery had any effect on the results of the study. Cases (33 patients), who had surgery during the same interval (March 1–August 31 1995) as the controls (100 patients), were included in the sensitivity analysis. Adjusted odds ratios and confidence intervals were obtained from this subset of cases and controls.

As an exploratory analysis, patients with occluded SA and/or AV nodal arteries, and who had not had them revascularized (based on the recommendation of the cardiac radiologist) were compared to patients who had occluded SA and/or AV nodal arteries, and who had them revascularized (based on the recommendation of the cardiac radiologist) regarding the development of the AF post-CABG. Odds
ratios and 95% confidence intervals were calculated for each artery.

All the statistical analyses were conducted using SAS package, version 6.12.

### 3. Results

#### 3.1. Descriptive statistics

The two groups were comparable with regard to the clinical and demographic variables except age (Tables 1 and 2). The median age of the AF group was 58 years, while the median age of the control group was 55 years. This difference was significant ($P = 0.001$). There were no missing values for any variable.

#### 3.2. AV artery

As shown in Table 1, there were 78 patients with diseased (critically stenosed or occluded) AV arteries in the AF group compared to 74 patients in the control group ($P = 0.51$). Age, sex, clamp time, preoperative B-blocker use, preoperative digoxin use, preoperative left ventricular ejection fraction (LVEF), hypertension (HTN), diabetes mellitus (DM), smoking status, and number of vessels grafted affected the relation between AV nodal artery status and the occurrence of AF postoperatively in the multiple logistic regression model (Table 3). The adjusted OR was 1.05 (95% CI 0.51–2.12, $P = 0.82$) which suggests that the two groups were not significantly different with regard to the presence of AV artery disease. None of the interaction terms was found to affect the model significantly.

#### 3.3. SA artery

As shown in Table 1, there were 34 patients with diseased (critically stenosed or occluded) SA nodal artery in the AF group compared to 21 patients in the control group ($P = 0.04$). Age, history of stroke, and grafting three vessels affected the relation between SA nodal artery status and the occurrence of AF postoperatively in the multiple logistic regression model (Table 4). The adjusted OR was 2.09 (95% CI 1.07–4.1, $P = 0.03$) which suggests that the two groups were significantly different with regard to the presence of SA artery disease. None of the interaction terms was found to affect the model significantly.

#### 3.4. Sensitivity analysis

There were 33 patients with AF who were selected over the same interval over which the controls (100 patients) were selected; the sensitivity analysis was restricted to these 133 patients.

There were 19 patients with diseased (critically stenosed or occluded) AV artery in the AF group compared to 74 patients in the control group. The adjusted OR was 0.42 (95% CI: 0.16–1.06, $P = 0.07$) which suggests that the

### Table 1

Comparison of cases and controls for the exposure variable and for the presence of potential confounding factors (categorical variables)

<table>
<thead>
<tr>
<th>Categorical variable</th>
<th>AF group 100 patients (%)</th>
<th>Control group 100 patients (%)</th>
<th>$P$ value ($\chi^2$ test or Fisher’s exact test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of diseased SA artery</td>
<td>34</td>
<td>21</td>
<td>0.04*</td>
</tr>
<tr>
<td>Presence of diseased AV artery</td>
<td>78</td>
<td>74</td>
<td>0.51</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>86</td>
<td>85</td>
<td>0.84</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>9</td>
<td>7</td>
<td>0.60</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>14</td>
<td>12</td>
<td>0.67</td>
</tr>
<tr>
<td>History of stroke</td>
<td>1</td>
<td>6</td>
<td>0.054</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>47</td>
<td>46</td>
<td>0.89</td>
</tr>
<tr>
<td>History of diabetes mellitus</td>
<td>24</td>
<td>19</td>
<td>0.39</td>
</tr>
<tr>
<td>Smoker</td>
<td>70</td>
<td>72</td>
<td>0.76</td>
</tr>
<tr>
<td>Preoperative digoxin use</td>
<td>3</td>
<td>1</td>
<td>0.31</td>
</tr>
<tr>
<td>Preoperative B-blocker use</td>
<td>79</td>
<td>76</td>
<td>0.61</td>
</tr>
<tr>
<td>Mammary artery use</td>
<td>91</td>
<td>91</td>
<td>1.00</td>
</tr>
</tbody>
</table>

* Significant.
odds ratio of AF post-CABG was reduced in the presence of AV artery disease, but was not statistically significant. There were 12 patients with diseased (critically stenosed or occluded) SA nodal artery in the AF group compared to 21 patients in the control group. The adjusted OR was 2.55 (95% CI: 1.03–6.28, P = 0.04) which suggests that the two groups were significantly different with regard to the presence of SA artery disease.

3.5. The exploratory analysis

Exploratory analysis was performed to determine if the surgical revascularization of the diseased AV and/or SA nodal vessels had any impact on the occurrence of AF post-CABG. Six of ten patients having revascularization of their SA nodal artery developed AF versus 28 of 45 of those who did not (OR = 0.91, 95% CI: 0.18–5.06, P = 0.58). Forty-eight of 87 patients having revascularization of their AV nodal artery developed AF versus 30 of 65 of those who did not (OR = 1.44, 95% CI: 0.72–2.88, P = 0.27).

4. Discussion

Despite the major advances in cardiac surgery generally, and coronary artery surgery in particular, the incidence of AF post-CABG remains high. On the contrary, such advances may have paradoxically contributed to an increase in the incidence of AF seen in recent years [13]. Improvements in surgical technique, myocardial protection, cardiopulmonary bypass and care of critically ill patients in the operating room and the intensive care unit, coupled with evolution of technology have led to broadening of the indications for CABG. This has led to the consideration of older patients for such procedures. Older patients are at higher risk for increased morbidity and mortality [20]. In addition, advances in continuous monitoring technology have led to more frequent diagnosis of AF, which remains the most common cause of morbidity after coronary surgery [21].

Although, in the long run, the effect of AF on the outcome of CABG surgery is modest compared to other more serious complications, the relative high incidence of this complication makes its impact on patients outcome as well as hospital resource utilization far more significant. Identifying patients at risk of AF post-CABG and targeting them with more intensive prophylactic measures may result in a reduction in its incidence.

Although the classification of patients according to their vulnerability to AF postoperatively as supported by the experimental work [22] seems to be valid, it does not clarify the trigger factors that can induce AF post-CABG, technically difficult, and impractical.

Many studies have identified risk factors that may be associated with the occurrence of AF post-CABG. Age is the most commonly identified risk factor [9]. Although age is an easily available demographic feature that can predict the occurrence of AF post-CABG, its clinical usefulness and its impact on the incidence of AF are limited. This is due to the fact that available prophylactic measures are not totally safe, especially in older population [23], and they are less effective in older compared with younger populations [24]. In this study, patients older than 65 years of age were excluded in order to minimize the effect of age on the occurrence of AF post-CABG. Also, due to the fact that older patients are less amenable to prophylaxis and since the ultimate goal of this study was the identification of a group of patients who might benefit from such prophylaxis, we wished to examine younger patients. Despite the exclusion of patients older than 65 years, the AF group was still significantly older than the control group, denoting the importance of age as a predictor factor for AF post-CABG.

Intra-operative atrial ischaemia caused by inadequacy of the preservation of atrial myocardium compared to the ventricular myocardium during the cardiopulmonary bypass, as shown in experimental studies [25], has been proposed as a trigger factor of AF post-CABG. Recently, the presence of diseased SA and/or AV nodal arteries (vascular critical stenosis or occlusion) was proposed as the mechanism by which this ischaemia occurs [11]. Since this can be detected preoperatively on routinely performed coronary artery angiograms, it is a practical and simple
method by which a high-risk group may potentially be identified and targeted to ultimately reduce the incidence of AF post-CABG.

Although the direct ischaemic insult to the atria as indicated by the presence of diseased SA and/or AV nodal arteries is biologically plausible, many issues need to be addressed concerning it. Initially, it must be determined whether these diseased vessels are the cause of the dispersion of refractoriness that makes patients vulnerable to the development of AF post-CABG, or the trigger factor, or both. The mechanism by which the AF happens on the 2nd or 3rd day post-operatively rather than immediately after the surgery (which might be expected if AF is due to direct intra-operative ischaemia) must also be determined. Finally, if there is an association between the presence of diseased nodal vessels and development of AF post-CABG, the question of whether the revascularization of the diseased SA and/or AV nodal arteries decrease the incidence of AF post-CABG remains.

In a small study (n = 50), it was shown that there was a strong association between the development of AF post-CABG and the presence of diseased SA (OR = 6.90, 95% CI 1.15–71.47) and AV (OR = 14.25, 95% CI 2.92–77.11) nodal vessels [11]. In the current larger study, this association was only found with diseased SA nodal vessels, and that to a lesser degree. These different findings could be due to a difference in the populations studied. Patients in this study were all younger than 65 years of age, while 40% of the patients included in the previous study were older than 65 years [11]. Due to the small sample size, results from that study for patients older and younger than 65 years could not be stratified. There was more detectable disease radiologically in this study’s population (28% had SA disease, and 76% had AV disease) compared to the population examined in the previous study (22% had SA disease, and 47% had AV disease). It can not be determined whether this reflects a true difference in the nature of the disease between the two populations, or if a difference was created during the selection of the patients. A matching procedure was used to select the control group in the previous study, which seems to be appropriate due to the small sample size. However, the procedure for selection of cases was not clarified, a fact that may throw some doubts around the representativeness of this group of patients to the rest of the population. Given the retrospective nature of the study, the selection of cases and controls is an important aspect, around which issues of validity are centered. Although the interpretation of the angiograms seems to be standard, this could also explain the different results. Since no inter-rater reliability or intra-rater reliability tests were performed in either study, misclassification could be a factor here. Moreover, possible differences in the methods by which the patients were monitored post-operatively can explain different results. In the previous study the monitoring process was not described. In the current study, non-sustained AF that did not cause any symptoms or hemodynamic instability could have been missed, especially after the discharge of patients from the intensive care unit, which was converted spontaneously to sinus rhythm. This type of AF was not included in the case definition because it is less likely to cause any morbidity or increased costs.

Our results showed no impact of revascularization of the diseased SA and AV nodal arteries on the development of AF post-CABG. There was a suggestion of increased risk associated with the revascularization of AV artery, while the revascularization of SA artery was protective (decreased the risk of AF post-CABG), but neither were clinically significant. The sample that was analyzed was small, but the fact that the effects of revascularization of AV and SA arteries were in the opposite directions suggests that its impact on the development of AF post-CABG is probably weak. On the other hand, revascularization of the diseased vessels in this study is arbitrary, and since we have not performed postoperative coronary angiograms, an effective revascularization can not be assumed, and conclusions can not be made.

This study has several limitations. The study is retrospective, and due to limitations inherent in its design, bias can be introduced during the selection of the cases and controls (especially controls), and during the collection of the data. Although, our exposure data were collected objectively and blindly, we have not performed any inter-rater reliability or intra-rater reliability tests, and this could introduce misclassification bias.

4.1. Conclusion

The presence of SA nodal artery disease as detected by preoperative coronary angiogram is a risk factor which can predict the occurrence of AF post-CABG, and can identify a subgroup of patients who might be targeted with prophylaxis. More studies are needed to support this hypothesis, preferably larger prospective studies.

References

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