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Genetic Variants Associated With Atrial Fibrillation and PR Interval Following Cardiac Surgery

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Abstract

Objective—The authors hypothesized that genetic association between atrial fibrillation (AF)-associated and PR-associated genetic loci was biologically mediated through slower conduction velocities for some or all of these loci.

Design—Prospectively collected cohort study.

Setting—Single tertiary care university hospital.

Participants—A total of 1227 Caucasian patients who underwent coronary artery bypass grafting (CABG).

Interventions—A total of 677 single nucleotide polymorphisms previously associated with ambulatory AF or PR interval were tested for association with postoperative atrial fibrillation (poAF) and preoperative PR interval, maximum PR interval, maximum change in PR interval, and maximum change in PR interval from preoperative PR interval.

Measurements and Main Results—The incidence of new-onset poAF was 31%. All of the PR interval variables were longer in the poAF cohort. Two variants on 1q21 and 12 on 4q25 were associated with poAF after adjustment for false discovery rate (FDR), but no variants were associated with PR interval variables after adjustment for FDR. Several variants were associated with both poAF and PR interval variables at $p < 0.05$, but none of them remained significant after adjusting for FDR.

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APPENDIX A. SUPPORTING INFORMATION

Supplementary material cited in this article is available online at doi:10.1053/j.jvca.2014.10.028.

Conclusion—It was found that patients with poAF have significantly longer PR interval. Genetic variants in both the 1q21 and 4q25 regions associate with poAF after CABG surgery, but the authors were unable to find association between these variants and PR interval after adjusting for FDR.

Keywords

atrial fibrillation; genomics; PR interval; cardiac surgery; 4q25; 1q21

Postoperative atrial fibrillation (poAF) occurs after approximately 30% of cardiac surgeries. It is associated with increased postoperative morbidity, mortality, longer hospital stay, and increased use of healthcare resources.¹ Several clinical predictors of poAF have been identified, including advanced age, male sex, concomitant valve surgery, prior history of atrial fibrillation (AF), hypertension, and chronic obstructive pulmonary disease.¹

Prolonged electrocardiogram (ECG) PR interval has been observed in patients with paroxysmal AF^{2,3} and with poAF in cardiac surgery cohorts.^{4,5} The observed reduction in atrial conduction velocity present with prolonged PR interval, is presumed to be a mechanism for re-entry of atrial excitation foci and development of AF.⁶

Multiple studies have examined the genetic risk factors for AF in ambulatory populations by comparing the frequency of single nucleotide polymorphisms (SNPs) between patients with and without AF. This has either been done using a candidate gene approach in which the SNPs are chosen from preselected genes based on biologic plausibility or in a genome-wide manner in which the entire genome is scanned for variants associated with AF. Using the latter approach, several genetic loci have been discovered. The most significantly associated genomic location found thus far is the 4q25 locus, close to the *PITX2* gene.⁷ This gene is responsible for embryonic development of the pulmonary venous vasculature that is known to be the origin of electrical foci causing AF.⁸ Several SNPs within the 4q25 locus also have been associated with poAF⁷ after coronary artery bypass graft (CABG) surgery.⁹ Among other genome locations associated with AF in ambulatory cohorts are the 1q21 locus near the *KCNN3* gene^{10,11} and the 16q22 locus near the *ZFHX3* gene.^{10,12}

Several groups have studied the genetic variants associated with ECG durations and have identified SNPs associated with PR interval in ambulatory cohorts.^{13–19} This includes SNPs within the 3q22 locus that includes 2 genes, *SCN10A* and *SCN5A*, which code for sodium channels involved in the cardiac action potential.^{15,17} Interestingly, several genetic loci associated with PR interval also are associated with the ambulatory AF, including the aforementioned 3q22 locus.^{10,15,17} This relationship is understood poorly and some associations are counterintuitive, as exemplified by the associations for the rs6795970 SNP within the *SCN10A* gene. This SNP is associated with prolonged PR interval while being protective for AF.¹⁷ Importantly, these associations between the genetic variants associated with AF and PR interval have not been studied concurrently in the same population.

This study used a prospectively collected cohort of Caucasian patients undergoing CABG surgery (with or without additional valve surgery) to assess whether genetic variants associated with poAF also were associated with increased PR interval following CABG

surgery. The authors hypothesized that genetic association between AF-associated and PR-associated genetic loci was biologically mediated through slower conduction velocities for some or all of these loci.

METHODS

Patient Cohort and Clinical Data

A subset of patients enrolled from August 2001 to April 2013 were chosen from the prospectively collected CABG Genomics study (<http://clinicaltrials.gov/show/NCT00281164>) that has both genetic and clinical data on more than 2,600 adults undergoing CABG surgery or combined CABG and valve surgery at 2 study sites (Brigham and Women's Hospital, Boston, MA and Texas Heart Institute, St. Luke's Hospital, Houston, TX) were used. For the current study, a subset of 1,224 patients was used who were selected based on self-reporting Caucasian ancestry and enrolled by 1 of the study centers (Brigham and Women's Hospital) that routinely stored electronic perioperative ECG data and were not in AF during their preoperative evaluation. The study was approved by the Institutional Review Boards of both study sites, and all patients provided written informed consent. Potential clinical confounders were collected, including age at surgery, sex, body mass index, prior medical history and medications, the prior occurrence of AF, type of surgery, and cardiopulmonary bypass time.

PR interval and cardiac rhythm were obtained from stored ECGs using the MUSE system (GE Healthcare, Waukesha, WI) at Brigham and Women's Hospital. ECGs with a reported PR interval of > 500 msec (24 out of 7038 ECGs analyzed) were reviewed manually and excluded. ECGs with an uninterpretable PR interval due to motion artifact, second-or third-degree atrioventricular block, junctional rhythm, bundle-branch block, or cardiac pacing also were excluded.

The authors prospectively defined 4 PR-interval outcome variables from ECGs performed during primary surgical hospitalization: 1) PR interval closest to the date of cardiac surgery within the prior 30 days (preoperative PR interval); 2) maximum PR interval from the entire period (maximum PR interval); 3) maximum postoperative change in PR interval, defined as the difference between the maximum postoperative PR interval and minimum PR interval (delta PR interval); 4) maximum change in PR interval from the preoperative value (delta postoperative PR interval). These variables were chosen to represent both a static (preoperative and maximum PR interval) and dynamic (delta PR interval and delta postoperative PR interval) estimate of atrial conduction.

The authors defined the poAF outcome as AF of any duration occurring postoperatively (for patients not in atrial fibrillation on the preoperative ECG) that lead to a change in treatment (such as drug administration or cardioversion). The poAF could be identified by the physician or nursing staff from using ECG recording obtained at any time during the postoperative course of the primary surgical hospitalization.

Genotyping

The authors genotyped 677 SNPs from 40 loci within 1 Mbps distance of SNPs with previously known association with either AF^{7,10,12,20–22} or PR interval^{13–19} in nonsurgical populations. These SNPs were chosen from the originally reported SNP, which described linkage disequilibrium structure of the locus, and SNPs with potentially functional importance such as coding, promoter, and splice junction variants. SNPs with a minor allele frequency < 2.5% and with significant deviations from Hardy-Weinberg equilibrium ($p < 0.001$) after genotyping were excluded. Supplementary Tables S1 and S2 show the regions assessed. DNA was extracted from white blood cells by standard methods. Genotyping was performed using the Illumina Golden Gate assay (Illumina, San Diego, CA) or the Sequenom iPLEX assay (Sequenom, San Diego, CA), using standard procedure described by the manufacturers. Raw genotyping data then were analyzed by Illumina Genome Studio (Golden Gate) and SpectroTyper 4 software (Sequenom).

Statistical Analysis

All statistics and image processing were performed in R, version 2.14 (The R Foundation, Austria)²³ and PLINK.²⁴ Categorical variables between groups with and without poAF with the chi-square test, and continuous variables using t-test were compared. *SNPassoc* and PLINK were used for uni- and multivariate regression modeling of clinical phenotypes.²⁵ As each autosomal chromosome is present in duplicate, each individual can have either 0, 1, or 2 copies of each risk allele. The odds ratios for associations between SNPs and either poAF were determined using dominant (having 1 risk allele out of 2 available being sufficient to modify risk of phenotype), recessive (2 risk alleles are needed to modify risk of phenotype), and additive (risk increases with each risk allele present) genetic models using logistic regression.²⁶ Similarly, the authors tested for association between these SNPs and the 4PR interval variables using linear regression methods. To adjust for multiple testing, the authors estimated false discovery rate (FDR) adjusted p value (q value) using the Benjamini and Hochberg FDR correction. SNPs with a q value of 0.05 were considered significant.

RESULTS

Patient Demographics and Properties of the PR Interval

Of 1,224 patients, 377 (31%) developed new-onset poAF. The incidence of atrial fibrillation did not change significantly over the study duration (data not shown). The population demographics and perioperative variables are shown in Table 1. Patients with poAF were older, and a higher ratio of them had history of AF, hypertension, or were taking an antiarrhythmic medication. A higher percentage of patients who underwent concurrent valve surgery experienced poAF (Table 1). PoAF was most often diagnosed on the second postoperative day (33% of patients with poAF) and only 7% of patients with poAF experienced poAF on postoperative day 7 or later. Hospital stay did not change significantly during the study period (data not shown) but patients with poAF had a significantly longer hospital stay than patients not diagnosed with poAF (10.1 v 6.7 days, $p < 0.001$).

Preoperative PR interval, maximum PR interval, delta PR interval and delta postoperative PR interval were all significantly longer in patients who subsequently experienced poAF (Table 1).

Association of SNPs With poAF and PR Interval

Figure 1 shows the analytic steps performed to find SNPs associated with both poAF and PR interval. Of the 677 genotyped SNPs, 43 had a minor allele frequency of <2.5% and 4 had a significant deviation from Hardy-Weinberg equilibrium, leaving 630 SNPs for analysis. Figure 2 shows associations between these SNPs and the poAF and the 4 PR interval outcomes. The authors did not find a significant association between SNPs and poAF for rs3825214 (near *TBX5*) or rs3807989 (near *CAVI*) previously associated with AF.^{17,20} Associations were found between SNPs on chromosomes 1q21.3 (rs13376333), 1q24.2 (rs3903239), and 7q36.1 (rs1805123) and poAF, which previously have been associated with ambulatory AF (Supplementary Table S1). These SNPs did not associate with PR interval in the current study. Several SNPs were observed that previously had been associated with PR interval in ambulatory cohorts also were associated with preoperative PR interval in this cohort, but were not associated with poAF (Supplementary Table 2).

Without adjustment for false discovery rate by multiple testing, at $p < 0.05$, it was found 185 SNPs associated with poAF and 168 SNPs associated with any of the 4 PR interval variables in any of the 3 genetic models (Figs 2 and 3). Of the PR interval variables, most of the SNPs with any significant associations were associated with the preoperative PR interval (Fig 3). All SNPs associated with both poAF and preoperative PR interval at $p < 0.05$ were on chromosome 4q25, both for additive and dominant models (Fig 3, data not shown).

After adjustment for multiple testing, ($q = 0.05$), 14 SNPs on chromosomes 1q21 and 4q25 were associated significantly with poAF in either additive or dominant models (Table 2). All of these remained significant in a multivariate model correcting for age group, sex, prior history of atrial fibrillation, cardiopulmonary bypass time, and valve surgery. No SNPs were associated with poAF in a recessive model after adjustment for multiple comparisons. No SNPs were associated with any PR interval after adjusting for multiple comparisons (data not shown).

DISCUSSION

Genetic variants associated with PR interval and poAF in a prospectively collected cohort of cardiac surgery patients were studied. The authors' hypothesis was based on previous observation that several variants associated with AF also were associated with PR interval. It is known that prolonged PR interval is a risk factor for AF⁵ and several genomic regions associated with PR interval also are associated with AF in ambulatory cohorts.^{15,17} In this study, PR interval outcomes were observed to be significantly prolonged in patients who subsequently developed poAF. Variants in 1q21 and 4q25 that were associated with poAF were observed. However, after adjusting for multiple comparisons, the authors did not observe any variants associated with both poAF and PR interval.

Of 630 SNPs selected for the study based on prior literature in ambulatory and surgical cohorts, several variants within 4q25 were associated with both poAF and PR interval outcomes at $p < 0.05$. However, none of these was associated with poAF and PR interval outcomes after adjustment for false discovery rate.

After adjustment for multiple comparisons, it was observed that several SNPs within 1q21 and 4q25 region were significantly associated with poAF. Of the 10 poAF-associated SNPs on chromosome 4q25, all but 1 (rs3853445) are in close proximity and are very likely to be inherited as a whole block (belong to the same haplotype block). This block of SNPs previously has been identified in ambulatory and surgical populations.^{7,9,10} The SNPs within 4q25 included some SNPs found in earlier analysis by the authors in a smaller subset of the patients.⁹ To the authors' knowledge, the association between variants within 1q21 and poAF has not been described.

Other ambulatory studies that have found SNPs associated with increased risk of AF have found these variants to be associated with longer or shorter PR intervals.^{15,17} This phenomenon is poorly understood, and the authors hoped that studying both the poAF and PR phenotypes in the same patient cohort would clarify the issue. The authors were, however, unable to identify any variants associated with both poAF and PR interval after adjusting for false discovery rate.

The current study confirmed that some of the SNPs affecting the risk of AF in ambulatory cohorts also affect the risk of poAF. This suggests that the pathogenesis of poAF is at least partially similar to the pathogenesis of AF in nonoperative cohorts. The higher incidence of poAF in patients with prior AF, who were not in AF at preoperative evaluation and thus included in the study, also supports this. Perhaps atrial fibrillation is the final common phenotype when genetically susceptible individuals are exposed to environmental factors by cardiac surgery (such as massive inflammation response) or other stimuli in nonoperative cohorts (such as atrial stretching). However, there might be alternative pathways in pathogenesis of poAF and ambulatory AF. This is supported by a number of SNPs associated with AF in ambulatory cohorts that have not been replicated in surgical cohorts who develop poAF.

This study had several important limitations. The current study was limited by the relatively small cohort size and could thus be underpowered to demonstrate association between several genetic regions (such as those described on chromosomes 1 and 3) and either poAF or PR variables. There is a chance that self-terminated AF of short duration was missed, however, the authors are unsure of the clinical importance of these episodes. Although the authors confirmed previously associated AF loci in ambulatory patients and included all loci previously associated with poAF, the results stem from a surgical cohort complicated by surgical trauma and cardiopulmonary bypass, which is not directly comparable to ambulatory AF. The PR-interval data was added to the database after the primary data entry so the authors were not able to perform ECG signal averaging. This limits comparisons with other studies using signal averaging for their phenotypes, which can estimate the PR interval over hundreds of cardiac cycles and apply noise reduction algorithms. The authors were also

unable to measure derived parameters suggested as surrogate markers of atrial conduction, such as p-wave diversity.

In conclusion, it was found that patients with poAF have significantly longer PR interval. Genetic variants in both the 1q21 and 4q25 regions associate with poAF after CABG surgery, but the authors were unable to find association between these variants and PR interval after adjusting for false discovery rate.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig 1.

Flow diagram of association analysis. The figure shows the steps to find SNPs associated with both atrial fibrillation and PR interval from the initial SNPs chosen for this study. Originally, 677 SNPs from 40 genetic regions were selected. Numbers shown are unique SNPs associated with either AF or any of the PR interval variables. Some SNPs had association in multiple genetic models (additive, dominant, recessive).

Fig 2.

Association between genetic markers, poAF and PR variables. The figure shows the result for the dominant model for all variables. The y-axis shows the negative natural logarithm of the p values measuring the association between selected SNPs on several chromosomes (chromosomes 1, 2-3, 4, 5-14, 16-21) and either atrial fibrillation (poAF) or different PR interval variables. The red dotted line marks $p = 0.05$ for

Fig 3.

Venn diagram showing the SNPs associated both with poAF and any of the 4 PR interval variables. Shown are associations with an uncorrected p value less than 0.05 for A, additive, B, dominant and C, recessive model. When FDR corrected values were used, no SNPs were associated both with poAF and any of the PR variables (data not shown).

Table 1**Patient Demographics and Properties of the PR Interval**

Parameter	No poAF (847)	poAF (377)	p Value
Age, yr			
<50	74 (9)	12 (3)	
50–59	240 (28)	53 (14)	
60–69	286 (34)	127 (34)	
70–79	196 (23)	137 (36)	
> 85	51 (6)	48 (13)	< 0.001
Female	192 (23)	77 (20)	0.42
BMI, kg/m²	29 ± 5	29 ± 6	0.56
Medical History			
Prior Atrial Fibrillation	27 (3)	38 (10)	< 0.001
Hypertension	607 (72)	301 (80)	0.003
Insulin-Dependent Diabetes	81 (10)	31 (8)	0.52
Noninsulin-Dependent Diabetes	194 (23)	83 (22)	0.79
Myocardial Infarction	331 (39)	154 (41)	0.60
Creatinine > 1.5 mg/dL	54 (6)	27 (7)	0.70
LVEF < 40%	86 (11)	46 (13)	0.42
Preoperative Medications			
ACE-inhibitors	354 (47)	182 (48)	0.61
Anti-arrhythmic	4 (0.4)	13 (3.4)	0.001
ASA	681 (80)	298 (79)	0.30
β-blocker	666 (78)	301 (80)	0.68
Ca-blocker	117 (14)	56 (15)	0.69
Diuretic	201 (24)	106 (28)	0.12
Statin	660 (78)	277 (73)	0.10
Operative Characteristics			
CPB duration, min	108 ± 44	126 ± 63	< 0.001
CABG only	751 (89)	300 (80)	
CABG/Valve	96 (11)	77 (20)	< 0.001
PR-interval Properties			
Preoperative PR, ms	172 ± 30	177 ± 31	< 0.001
Maximum PR, ms	187 ± 39	198 ± 45	< 0.001
Delta PR Interval, ms	36 ± 32	45 ± 39	< 0.001
Delta Postoperative PR Interval, ms	15 ± 28	21 ± 34	0.001

NOTE. The table compares the properties of the patient population with and without post operative atrial fibrillation (poAF) after CABG. Data are shown as n (%) or mean ± standard deviation. The table provides the number of patients with percentages in brackets.

Abbreviations: ACE, angiotensin-converting enzyme; ASA, acetylsalicylic acid; BMI, body mass index; CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; LVEF, left ventricular ejection fraction; poAF, post operative atrial fibrillation.

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Abbreviations: CI, confidence interval; OR, odds ratio; poAF, post operative atrial fibrillation; SNP, single nucleotide polymorphisms.

* Shown are both the p value and the false discovery rate adjusted p value (q value) for the association between the SNP and either poAF or preoperative PR interval for dominant and log-additive models. No associations were found for recessive models.