Published in final edited form as:

Am J Cardiol. 2012 November 1; 110(9): 1315–1321. doi:10.1016/j.amjcard.2012.06.037.

Risk Factors For Bradycardia Requiring Pacemaker Implantation In Patients With Atrial Fibrillation

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Abstract

Symptomatic bradycardia may complicate atrial fibrillation (AF) and necessitate a permanent pacemaker. Identifying patients at increased risk for symptomatic bradycardia may reduce associated morbidities and healthcare costs. We investigated predictors for developing bradycardia requiring a permanent pacemaker among AF patients. We reviewed records of all patients treated for AF/flutter in an academic hospital's emergency department from 8/1/2005 to 8/30/2008. We determined survival and presence of a pacemaker as of 11/1/2011. Cases were defined as patients with pacemakers placed for bradycardia after their AF diagnoses. Patients without a pacemaker who were followed at our hospital comprised the controls. We identified *a priori* variables for the logistic regression analysis. We fit a post-hoc model adjusting for AF type and atrioventricular nodal blocker (AVN) use. Of the 362 patients in our cohort, 119 cases had permanent pacemakers implanted for bradycardia subsequent to AF diagnosis and 243 controls were alive without a pacemaker. Median and interquartile range follow-up time was 4.5 (3.8 – 5.4) years. Odds ratios and 95% confidence intervals were determined for age at time of AF diagnosis (1.02 [1, 1.04]), female (1.58 [0.95, 2.63]), prior heart failure (2.72 [1.47, 5.01]), and African-American (0.33 [0.12, 0.94]). Post-hoc model identified permanent AF (2.99 [1.61, 5.57]) and AVN use (1.43 [0.85, 2.4]). In conclusion, among AF patients, heart failure and permanent AF each nearly triple the odds of developing bradycardia requiring a permanent pacemaker; while not statistically significant, our results suggest that women are more likely and African-Americans less likely to develop bradycardia requiring pacemaker implantation.

Keywords

atrial fibrillation; bradycardia; sinus node dysfunction; pacemaker

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CONFLICTS OF INTERESTS

None

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Symptomatic bradycardia, often due to sinus node dysfunction, complicates atrial fibrillation (AF) management, often requiring permanent pacemaker implantation. [1–5] Bradycardia may be a manifestation of general conduction system disease or iatrogenic due to medications used for AF rate control. [6] Studies examining outcomes in patients who received permanent pacemakers for sinus node dysfunction report that 36–76% had preexisting paroxysmal or persistent AF. [1–3] Previous investigations have focused on the prevention of incident AF in patients with pacemakers for previously diagnosed sinus node dysfunction. [3, 7–13] The identification of patients at increased risk for symptomatic bradycardia is important for preventing associated morbidity and the related high health care costs. Improved risk stratification for symptomatic bradycardia may lead to earlier placement of a permanent pacemaker to avert associated complications such as syncope and traumatic hemorrhage in anticoagulated patients. Preventing bradycardia-related syncope in AF patients is increasingly important given the escalating use of new oral anticoagulants without validated reversal agents and whose therapeutic levels are less easily measured in the acute setting. We investigated potential predictors for developing symptomatic bradycardia requiring a permanent pacemaker among individuals with preexisting AF. We hypothesized that specific patient characteristics predispose individuals with AF to the development of symptomatic bradycardia and the need for a permanent pacemaker.

Methods

We performed a secondary analysis of a retrospective, observational cohort comprised of consecutive patients >18 years of age with a primary or supporting International Classification of Diseases, Ninth Revision (ICD-9) emergency department discharge diagnosis of AF between August 1, 2005 and July 31, 2008. Our hospital is a university-affiliated, regional cardiac referral center that implanted 412 permanent pacemakers in 2011. The detailed methodology for the original investigation has been previously reported. [14] Briefly, 2 investigators systematically reviewed the electronic medical record for corresponding data adhering to strict chart review methodology guidelines. [15] In November 2011, we reexamined the cohort's medical records and documented additional data pertinent to this investigation, including patient survival status and presence or absence of a pacemaker as of November 1, 2011. Patients whose pacemaker status could not be determined and those individuals who died without undergoing the implantation of a permanent pacemaker prior to November 1, 2011 were excluded. We classified patients as cases if, subsequent to their AF diagnosis, they experienced symptomatic bradycardia that required an implantable permanent pacemaker. Patients without a pacemaker who were still followed at our hospital comprised the control group for the primary multivariable analysis. Our medical center's institutional review board approved this study.

The primary outcome measure was the occurrence of symptomatic bradycardia necessitating placement of an implantable permanent pacemaker subsequent to the patient's AF diagnosis. We defined symptomatic bradycardia as the primary cause if the reported indication for pacemaker implantation was one of the following: sinus node dysfunction, sick sinus syndrome or tachycardia-bradycardia syndrome. Patients whose pacemakers were placed for alternative indications including pacemaker/internal cardiac defibrillator following sudden cardiac death and biventricular pacemakers for heart failure were excluded. We reviewed supporting clinical documentation, including cardiology and arrhythmia inpatient and outpatient consultations, electrocardiograms, cardiology clinic notes, emergency department records and hospital admission and discharge summaries to determine the acute symptoms resulting in evaluation for permanent pacemaker placement. We determined whether symptomatic bradycardia was the primary indication for permanent pacemaker implantation by reviewing the operative procedure note.

We recorded demographics, medical history, presence of pacemaker, operative note indication for pacemaker, symptoms prompting evaluation for pacemaker therapy, and emergent or scheduled procedure. Medical history and medication use classification was based upon available information in the medical record at the time of the patient's visit to the emergency department for symptomatic AF. Death certificates and patient death summaries were examined to determine the cause of death in those individuals who had died without a pacemaker implantation prior to November 1, 2011. For the multivariable logistic regression model, we selected *a priori* candidate predictors based on clinical relevance and previously published associations with incident sinus node dysfunction. [1–5, 7–13] We included the following candidate predictors in the multivariable logistic regression: age at time of AF diagnosis, sex, prior heart failure, reported race/ethnicity, prior coronary artery disease, documented hypertension, renal insufficiency, and diabetes. Data were entered directly into IBM SPSS Statistical database. (Version 20.0, Chicago, IL).

To ensure a reliable and valid regression analysis, we adhered to the accepted formula that there must be 15 events per predictor degree of freedom (i.e. per regression coefficient estimated). [16, 17] We selected 8 candidate variables for our primary multivariable logistic regression analysis in accordance with these standards. We did not match the cases and controls. We adjusted for important baseline characteristics in the multivariable analysis. Descriptive statistics on baseline variables are presented as median (interquartile range [IQR]) or number of non-missing values (%) as appropriate. We analyzed the association of the *a priori* selected variables with the primary outcome using multivariable logistic regression. We also fit a second post-hoc model that included 2 additional variables: AF type (defined as permanent versus persistent/ paroxysmal/newly diagnosed) and home use of atrioventricular nodal blocking medications (e.g., beta-adrenergic blocking medications and non-dihydropyridine calcium channel blockers) at the time of index emergency department visit. All analyses were done using the statistical programming language R, version 2.14.2 (R Development Core Team, Vienna, Austria).

Results

There were 831 patients in the original cohort and of these 619 patients met this study's inclusion criteria. Figure 1 provides a detailed description of patients included in the analysis. The final cohort included 119 cases that developed symptomatic bradycardia requiring permanent pacemakers. Among the 424 patients without an implanted permanent pacemaker, 243 (44%) were alive without a pacemaker and comprised the control group. The remaining 181 (34%) were deceased without a pacemaker. Documented cause of death among these 181 patients included: metastatic cancer (19%), acute decompensated heart failure (17%), sepsis (16%), acute cardiac arrest (12%) and ischemic or hemorrhagic stroke (12%). Table 1 reports the baseline cohort characteristics and symptoms necessitating pacemaker therapy. Nearly half (49%) of pacemakers were implanted during an unplanned hospitalization.

Table 2 reports the multivariable analysis (odds ratios [OR] and 95% confidence intervals [CI]) for risk factors associated with bradycardia compared to the 243 control patients who were alive and still followed at our hospital. Among patients with AF, a history of heart failure nearly triples the odds of developing symptomatic bradycardia that requires a permanent pacemaker. While not reaching statistical significance, our data suggested that women are at increased risk, and that African-Americans are at decreased risk, of symptomatic bradycardia requiring pacemaker implantation.

Table 3 presents the results of the post-hoc multivariable analysis with the inclusion of AF type and home atrioventricular nodal blocking agent medication use. Heart failure remains a

significant predictor with a slightly reduced OR of 2. Compared to paroxysmal and persistent AF, permanent AF triples the odds of developing symptomatic bradycardia requiring a pacemaker. Home atrioventricular nodal blocking agent medications did not meet statistical significance.

Discussion

This study is the first to evaluate risk factors for incident symptomatic bradycardia requiring a pacemaker in patients with AF. Prior studies have focused primarily on the epidemiology and prevention of AF in patients with sinus node dysfunction requiring pacemaker placement. [1–3, 5, 7–12] Investigators have hypothesized that sinus node dysfunction represents an exaggerated age-related decline in sinus node function. [18, 19] The incidence of AF also increases with age. [20] A review of prior studies evaluating patients with sinus node dysfunction shows that the baseline AF prevalence increases in older patient cohorts; [1–3] therefore, one might assume that sinus node dysfunction is more prevalent in older patients with AF. We found that AF patients who developed symptomatic bradycardia requiring a permanent pacemaker were on average 4 years older. There was also a weak association between the need for pacemaker treatment and age at the time of AF diagnosis. The age-related decline in sinus node function and AF-associated electrophysiologic remodeling may render these patients more susceptible to symptomatic bradycardia due to rate control agents such as atrioventricular nodal blockers. [4, 18, 19, 21] Permanent AF has been shown to result in sinus node damage. [22] We found that permanent AF was associated with three-fold increased odds of needing a pacemaker to treat symptomatic bradycardia.

Heart failure nearly triples the odds of a patient with AF needing a pacemaker to treat symptomatic bradycardia. Heart failure has been associated with significant sinus node remodeling, a decrease in the intrinsic heart rate, and conduction system disease characterized by impaired action potential propagation from the sinus node to the distal conduction system. [16, 17, 21, 22] Atrioventricular nodal blocking agents indicated for the treatment of heart failure may directly cause or exacerbate symptomatic bradycardia. Home use of these medications was not a statistically significant predictor in our cohort. Patients with heart failure are likely at heightened risk for syncope related to sinus node dysfunction, and its associated trauma, due to their inability to adequately compensate for decreases in cardiac output. [23, 24]

A National Heart, Lung and Blood Institute expert panel on AF recommended that research enhance our understanding of the epidemiology of AF specifically in ethnic/racial minorities. [25] This study found that African-Americans had a 67% decreased odds of symptomatic bradycardia requiring a pacemaker compared to Caucasian patients. Individuals identified as not Caucasian and not African-American had more than twice the odds of symptomatic bradycardia requiring a pacemaker compared to Caucasian patients, although this conclusion is limited by the small number of non-African-American underrepresented minorities in the original cohort. We hope that our ongoing prospective AF studies will further our understanding regarding the impact of race and ethnicity on the development of symptomatic bradycardia in non-Caucasian AF populations. [26, 27]

The study was a retrospective cohort analysis and therefore is subject to the inherent limitations of such studies. We did not prospectively collect data on predictors or outcomes, and there is the potential that missing data might bias our results. Patients might have experienced symptomatic bradycardia prior to the AF diagnosis that was not recorded in the EMR. We closely examined both inpatient and outpatient records for mention of possible arrhythmia, syncope or related symptoms both preceding and following their AF diagnosis.

The reporting of sinus node dysfunction as the indication for pacemaker placement in the setting of permanent AF may be a misdiagnosis. Sick sinus syndrome and tachycardia-bradycardia syndrome are used interchangeably, yet only the former implies some knowledge of sinus node function. We specifically avoided drawing conclusions based on these stated indications for pacemaker placement and instead focused on the broader, and more reliable, indication of symptomatic bradycardia. This term describes the end result of sick sinus syndrome and tachycardia-bradycardia syndrome as well as high-grade atrioventricular block, which is probably a more common cause of symptomatic bradycardia yet is difficult to characterize non-invasively in the setting of ongoing AF. There is the potential for classification bias as patients designated as controls in this study might ultimately develop symptomatic bradycardia requiring pacemaker therapy subsequent to our November 1, 2011 endpoint. This study was conducted at a single tertiary referral center ED that might introduce selection and referral bias and limit applicability to patients treated in other settings.

More than 20% of patients with AF in our cohort required pacemaker placement for symptomatic bradycardia, most within 5 years of their AF diagnosis. Half of these pacemakers were placed during unscheduled hospitalizations following symptomatic bradycardia. As more patients with AF use novel oral anticoagulants that lack reversal treatments and whose coagulation status is not easily quantified acutely, it is important to identify at risk patients and intervene before they incur serious injury due to bradycardia-related trauma. Among patients with AF, a history of heart failure and permanent AF are each associated with three-fold increased odds of developing symptomatic bradycardia that requires a permanent pacemaker. Nearing statistical significance, women have 58% greater odds and African-Americans have 67% lower odds of developing symptomatic bradycardia requiring pacemaker placement.

Acknowledgments

FUNDING

No industry financial support or compensation has been or will be received for conducting this study. Dr. Barrett and this study are funded by NIH grant K23 HL102069 from the National Heart, Lung and Blood Institute. Dr. Storrow is supported in part by NIH grant R01 HL088459. Dr. Darbar is supported in part by NIH grants U01 HL65962 and R01 HL092217. The study was also supported in part by Vanderbilt CTSA grant 1 UL1 RR024975 from NCRR/NIH.

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Figure 1.
Detailed Description of Selection of Cohort and Classification of Patients as Cases and Controls.

Table 1

Baseline Characteristics Of Patients With Documented Atrial Fibrillation Stratified By Pacemaker Placement For Symptomatic Bradycardia.

Variable	N	Cases: Patients With Pacemaker Placed For Sinus Node Dysfunction Subsequent To Atrial Fibrillation Diagnosis (N=119)	Controls: Atrial Fibrillation Patients Still Alive Without A Pacemaker (N=243)	Combined (N=362)
Age (Years)	362	71 (64, 80)	62 (51, 71)	65 (54, 76)
Women	362	60 (50%)	93 (38%)	153 (42%)
Caucasian		110 (93%)	206 (85%)	316 (88%)
African-American		5 (4%)	32 (13%)	37 (10%)
Latino		2 (2%)	3 (1%)	5 (1%)
Asian		1 (1%)	0	1 (0%)
Native American		0	1 (0%)	1 (0%)
Other		0	1 (0%)	1 (0%)
Weight (kg)	344	82 (70, 96)	84 (73, 103)	84 (72, 100)
Body mass index (kg/m ²)	195	27 (24, 32)	28 (24, 33)	28 (24, 32)
Current smoker *	361	7 (6%)	27 (11%)	34 (9%)
Current alcohol drinker *	361	4 (3%)	32 (13%)	36 (10%)
Prior cocaine use *	361	0	7 (3%)	7 (2%)
Atrial fibrillation type at index emergency department visit	362			
New diagnosis		13 (11%)	113 (47%)	126 (35%)
Paroxysmal/Persistent		67 (56%)	103 (42%)	170 (47%)
Permanent		39 (33%)	27 (11%)	66 (18%)
Lone atrial fibrillation	362	0	45 (19%)	45 (12%)
Prior pacemaker	362	119 (100%)	0	119 (33%)
Patient status as of 11/1/11	362			
Alive with pacemaker		83 (70%)	0	83 (23%)
Deceased with pacemaker		36 (30%)	0	36 (10%)
Alive without pacemaker		0	243 (100%)	243 (67%)
Age when pacemaker implanted (Years)	119	71 (64, 79)	N/A	71 (64, 79)
Age when atrial fibrillation diagnosed (Years)	354	66 (59, 75)	58 (48, 68)	61 (50, 71)
Interval between pacemaker implantation and atrial fibrillation diagnosis (Years)	119	4.2 (1.1, 7.7)		4.2 (1.1, 7.7)
Time from index emergency department visit to 11/1/11 follow-up (Years)	362	4.8 (3.8, 5.4)	4.4 (3.8, 5.3)	4.5 (3.8, 5.4)
Time from index emergency department visit to pacemaker implantation (Days)	119	3 (-504, 394)		3 (-504, 394)
Reported operative note indication for pacemaker	119			
Sinus node dysfunction		94 (79%)		94 (79%)
Tachycardia-bradycardia syndrome		25 (21%)		25 (21%)

Variable	N	Cases: Patients With Pacemaker Placed For Sinus Node Dysfunction Subsequent To Atrial Fibrillation Diagnosis (N=119)	Controls: Atrial Fibrillation Patients Still Alive Without A Pacemaker (N=243)	Combined (N=362)
Clinical symptoms requiring pacemaker evaluation and placement	119			
Symptomatic bradycardia		48 (40%)		48 (40%)
Near syncope		26 (22%)		26 (22%)
Syncope		16 (13%)		16 (13%)
General weakness		9 (8%)		9 (8%)
Failed medical rate control management		5 (4%)		5 (4%)
Worsening heart failure		1 (1%)		1 (1%)
Status post cardiac arrest/critical arrhythmia		1 (1%)		1 (1%)
Following ablation		5 (4%)		5 (4%)
Indication not documented		8 (7%)		8 (7%)
Condition under which pacemaker placed	119			
Unscheduled emergent/inpatient procedure		58 (49%)		58 (49%)
Scheduled procedure		45 (38%)		45 (38%)
Undetermined		16 (13%)		16 (13%)
Prior myocardial infarction *	361	21 (18%)	36 (15%)	57 (16%)
Coronary artery disease *	362	46 (39%)	63 (26%)	109 (30%)
Diabetes, insulin dependent *	362	10 (8%)	13 (5%)	23 (6%)
Diabetes, non-insulin dependent *	362	19 (16%)	31 (13%)	50 (14%)
Chronic obstructive pulmonary disease *	359	10 (8%)	25 (10%)	35 (10%)
Hypertension *	362	87 (73%)	149 (61%)	236 (65%)
Valvular heart disease *	362	38 (32%)	35 (14%)	73 (20%)
Heart failure *	362	34 (29%)	29 (12%)	63 (17%)
Left atrial diameter (mm) *	295	45 (40,53)	41 (36, 47)	43 (37, 49)
Left ventricular ejection fraction (percentage) *	311	55 (50, 55)	55 (55, 55)	55 (52.5, 55)
Prior cerebrovascular accident *	362	14 (12%)	25 (10%)	39 (11%)
Prior transient ischemic attack *	362	7 (6%)	6 (2%)	13 (4%)
Renal insufficiency *	362	13 (11%)	15 (6%)	28 (8%)
Prior cardiac surgery *	362	35 (29%)	38 (16%)	73 (20%)
Prior electrical cardioversion *	358	26 (22%)	36 (15%)	62 (17%)
Family history of atrial fibrillation	360	8 (7%)	22 (9%)	30 (8%)
Beta blocker drug use [§]	362	65 (55%)	93 (38%)	158 (44%)
Diltiazem/verapamil use [§]	362	19 (16%)	31 (13%)	50 (14%)
Digoxin use [§]	362	28 (24%)	24 (10%)	52 (14%)

Variable	N	Cases: Patients With Pacemaker Placed For Sinus Node Dysfunction Subsequent To Atrial Fibrillation Diagnosis (N=119)	Controls: Atrial Fibrillation Patients Still Alive Without A Pacemaker (N=243)	Combined (N=362)
Warfarin use [§]	362	64 (54%)	63 (26%)	127 (35%)
Statin use [§]	362	51 (43%)	84 (35%)	135 (37%)

N is the number of non-missing values. Data is reported as Frequencies and percentages or median with interquartile range in parentheses, respectively.

* Patient had reported history of characteristic at their index emergency department visit.

[§] Patient was taking these medication classes at their index emergency department visit.

Table 2

Predictors For Developing Bradycardia Requiring An Implantable Permanent Pacemaker

Covariate	Odds Ratio (95% CI)	P Value
Age at time of atrial fibrillation diagnosis	1.02 (1, 1.04)	0.04
Women	1.58 (0.95, 2.63)	0.08
Heart failure	2.72 (1.47, 5.01)	0.001
Race		0.06
Race, African-American	0.33 (0.12, 0.94)	
Race, non-Caucasian/non-African- American	2.29 (0.45, 11.82)	
Coronary artery disease	1.32 (0.76, 2.31)	0.33
Hypertension	1.27 (0.74, 2.18)	0.39
Renal insufficiency	1.36 (0.57, 3.22)	0.48
Diabetes	1.1 (0.6, 2.02)	0.77

95% CI: 95% Confidence Interval

Table 3

Secondary Prediction Model For Developing Bradycardia Requiring An Implantable Permanent Pacemaker

Covariate	Odds Ratio (95% CI)	P Value
Age at time of atrial fibrillation diagnosis	1.02 (1, 1.04)	0.05
Women	1.51 (0.90, 2.55)	0.12
Heart failure	2.00 (1.05, 3.82)	0.03
Race		0.07
Race, African-American	0.36 (0.13, 1.04)	
Race, non-Caucasian/non-African-American	2.50 (0.48, 13.11)	
Coronary artery disease	1.12 (0.62, 2.02)	0.71
Hypertension	1.06(0.60, 1.87)	0.85
Renal insufficiency	1.31 (0.54, 3.22)	0.55
Diabetes	1.10 (0.58, 2.07)	0.77
Home atrioventricular nodal blocking medication use	1.43 (0.85, 2.40)	0.17
Permanent atrial fibrillation	2.99 (1.61, 5.57)	0.0005

95% CI: 95% Confidence Interval