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Original Article

A nationwide cohort analysis to determine the prevalence of sinus node dysfunction and rates of pacemaker implantation in systemic lupus erythematosus

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Abstract: Systemic lupus erythematosus (SLE) has been known to have various degrees of cardiac involvement. However, limited evidence exists on prevalence of heart rhythm disorders in patients with SLE who have subsequent pacemaker (PM) implantation. The purpose of this study was to examine the prevalence of sinus node dysfunction (SND) in patients with SLE. The data was retrospectively analysed from the National Inpatient Sample database for the years 2010 to 2014 using the International Classification of Disease-9 diagnosis codes for SLE and SND in patients 18 years or older. We analysed data of 158,368 patients with SLE that were admitted from 2010 to 2014. The sample of patients ranged between 18 and 101 years of age (M = 52.13 ± 17.61), were primarily female (88.2%), and were Caucasian (50.6%). The prevalence of SND was 4.3%. In patients with both SLE and SND, the prevalence of PM implantation over the five-year period of analysis was 3.6% and the majority of these patients had a dual-chamber PM (85.6%). Prevalence rates of SND in patients with SLE increased for females over this five-year period (p = 0.023). Prevalence estimates of complications associated with PM in patients with SLE and SND were venous thromboembolism (2.1%), cardiac tamponade (0.4%), sepsis and severe sepsis (0.4%), septic shock (0%), pneumothorax (0%) and PM site hematoma (1.7%). The findings of this study revealed that the prevalence of SND and the prevalence of PM in patients with both SLE and SND have remained relatively consistent over the five years that our study analysed.

Keywords: SLE, pacemaker, sinus node dysfunction, NIS

Introduction

Autoimmune rheumatic diseases have long been demonstrated to display varying degrees of cardiac involvement. Coronary artery disease, conduction abnormalities, and sudden cardiac death have been observed to have an overall higher incidence in patients with rheumatic diseases as compared to the general population [1]. Systemic lupus erythematosus (SLE) is an autoimmune disease that affects multiple systems including the joints, skin, kidneys, nervous system, and heart. Cardiac involvement has been reported in up to 50% of patients with lupus [2, 3]. While the most frequently reported cardiac manifestations of SLE include pericarditis, coronary artery disease, and valvular disease, conduction system abnormalities have also been observed in these patients [4]. The most commonly reported conduction system abnormalities in patients with SLE include atrial fibrillation, QT interval prolongation, atrial ectopic beats, and sinus tachycardia [5, 6].

Sinus node dysfunction (SND) in SLE is rare [2, 3]. SND is the result of the inability of the sinoatrial node (SA) to produce a physiologically adequate heart rate. This dysfunction may be caused by either abnormal automaticity of the SA node or abnormal conduction, which may stem from underlying complex mechanisms including infiltrative, inflammatory, fibrotic, or medication-induced pathology [2, 7]. Although the pathophysiology of sinus node dysfunction in SLE is not well understood, it is reasonable to postulate that the cause may be due to underlying immune-mediated damage to the sinoatrial node or its surrounding tissue. Despite the availability of literature on sinus bradycardia and sick sinus syndrome in patients with SLE, there is limited data available to assess the prevalence of sinus node conduction abnormality and pacemaker implantation in cases of SLE. Additionally, there are no studies available to date to assess the prevalence of pacemaker complications in patients with SLE.

Methodology

Data source

The data was obtained and analyzed for the years 2010 to 2014 from the National Inpatient Sample (NIS) database, which forms part of the Healthcare Cost and Utilization Project (HCUP). The database was created by the agency for healthcare research and quality. It contains data regarding 5-8 million hospital stays from approximately 1,000 hospitals. It was designed to incorporate data from a 20% sample of discharges from all participating hospitals, which helps deliver stable, precise estimations and also reduces the margin of error. All states that participate in the HCUP provide data to the NIS, which covers > 95% of the US population. The database includes data from all nonfederal, short-term, general, and other specialty hospitals in the US (excluding rehabilitation and long-term acute care hospitals) in the form of de-identified patient information containing demographics, discharge diagnoses, comorbidities, procedures, outcomes, and hospitalization costs. Because the NIS database is publicly available and contains de-identified patient information, no approval from the local Institutional Review Board was required.

Study population and patient characteristics

We performed a five-year population-based retrospective cross-sectional analysis from 2010-2014 using NIS and the International Classification of Disease-9 (ICD-9) diagnosis codes and procedure codes in patients 18 years or older. We used ICD-9 codes diagnosis code of 710.0 for SLE. We looked at the prevalence of SND in patients who were 18 years of age or older with diagnosis code of 427.8 and 427.6. We identified patients who had pacemaker implantation using procedure codes 00.51, 37.73, 37.81, 37.82, 37.83. In this dataset, we also used specific ICD-9 diagnosis codes for complications associated with pacemakers [8]. We excluded patients with incomplete data for gender and mortality. We also excluded patients with any indication of transfer to another acute-care facility to reduce the chance of data duplication. **Table 1** shows baseline patient characteristics which include age, sex, race, insurance, and hospital region, specific types of pacemakers, SND, in-hospital mortality, length of stay (LOS), total hospitalization charges, complications associated with pacemakers.

Statistical analysis

Statistical analyses were done using One-way ANOVA (analysis of variance) to compare means of two or more samples, Chi-square test of independence, and Fisher's exact test for categorical variables as mentioned in **Table 1**. National estimates were calculated without applying discharge weights to the discharge data. SPSS Statistics 25.0 (IBM Corp., Armonk, New York) software was used to perform the statistical analysis. All statistical analyses were performed with the Type I error rate set to .05. Categorical variables were expressed as percentages and continuous variables as mean ± SD for normally distributed data or median with interquartile range for skewed data.

Results

We performed a retrospective cross-sectional analysis of 158,368 hospitalizations with SLE that were admitted from 2010 to 2014 in patients 18 years or older. Among these patients with SLE, the prevalence rate of SND was 6768 (4.3%). In the sample that consisted of both SLE and SND, the age-group ranged between 18 and 101 years (Mean = 52.13 ± 17.61 years), and patients were primarily female (88.2%), Caucasian (50.6%), and had been admitted to hospitals located in the South region (43.8%). Prevalence rates of SND in

Table 1. Characteristics of patients with systemic lupus erythematosus and bradycardia for index admission by year

Variable	Year					*P*-value	Total
	2010	2011	2012	2013	2014		
SLE	30,655	34,386	30,744	30,794	31,789		158,368
Bradycardia, *n* (%)	1,244 (4.06%)	1,397 (4.06%)	1,292 (4.20%)	1,356 (4.40%)	1,479 (4.65%)		6,768 (4.27%)
Any pacemaker, *n* (%)	50 (4.02%)	51 (3.65%)	47 (3.64%)	48 (3.54%)	47 (3.18%)	.841[b]	243 (3.59%)
Biventricular pacemaker, *n* (%)	#	#	#	#	#	.323[c]	14 (0.21%)
Dual chamber pacemaker, *n* (%)	44 (3.54%)	43 (3.08%)	37 (2.86%)	44 (3.24%)	40 (2.70%)	.755[b]	208 (3.07%)
Single chamber pacemaker, *n* (%)	#	#	#	#	#	.629[c]	21 (0.31%)
Mortality, *n* (%)	44 (3.54%)	52 (3.72%)	51 (3.95%)	62 (4.57%)	63 (4.26%)	.666[b]	272 (4.02%)
Age, *n* (%)						.844[b]	
18-34	246 (19.77%)	263 (18.83%)	250 (19.35%)	283 (20.87%)	296 (20.01%)		1338 (19.77%)
35-49	313 (25.16%)	355 (25.41%)	297 (22.99%)	316 23.30%)	375 (25.35%)		1656 (24.47%)
50-64	363 (29.18%)	410 (29.35%)	396 (30.65%)	391 (28.83%)	439 (29.68%)		1999 (29.54%)
≥ 65	322 (25.88%)	369 (26.41%)	349 (27.01%)	366 (26.99%)	369 (24.95%)		1775 (26.23%)
Male, *n* (%)	178 (14.31%)	172 (12.31%)	146 (11.30%)	154 (11.36%)	153 (10.34%)	.023[b]	803 (11.86%)
Race, *n* (%)						.866[b]	
White	587 (52.13%)	619 (47.80%)	651 (51.91%)	667 (51.47%)	704 (49.86%)		3228 (50.57%)
Black	367 (32.59%)	442 (34.13%)	393 (31.34%)	408 (31.48%)	467 (33.07%)		2077 (32.54%)
Hispanic	117 (10.39%)	162 (12.51%)	142 (11.32%)	145 (11.19%)	159 (11.26%)		725 (11.36%)
Other	55 (5%)	72 (6%)	68 (6%)	76 (6%)	72 (6%)		353 (6%)
Insurance, *n* (%)						.019[b]	
Medicare	575 (46.41%)	671 (48.10%)	639 (49.50%)	659 (48.60%)	693 (46.89%)		3237 (47.89%)
Medicaid	231 (18.64%)	242 (17.35%)	226 (17.51%)	236 (17.40%)	335 (22.67%)		1270 (18.79%)
Private	354 (28.57%)	371 (26.59%)	333 (25.79%)	354 (26.11%)	359 (24.29%)		1771 (26.20%)
Self-pay	43 (3.47%)	73 (5.23%)	59 (4.57%)	73 (5.38%)	64 (4.33%)		312 (4.62%)
No charge	#	#	#	#	#		35 (0.52%)
Other	30 (2.42%)	29 (2.08%)	29 (2.25%)	25 (1.84%)	21 (1.42%)		134 (1.98%)
Hospital region, *n* (%)						.003[b]	
Northeast	161 (12.94%)	277 (19.83%)	208 (16.10%)	230 (16.96%)	252 (17.04%)		1128 (16.67%)
Midwest	283 (22.75%)	295 (21.12%)	272 (21.05%)	309 (22.79%)	320 (21.64%)		1479 (21.85%)
South	545 (43.81%)	594 (42.52%)	589 (45.59%)	585 (43.14%)	648 (43.81%)		2961 (43.75%)
West	255 (20.50%)	231 (16.54%)	223 (17.26%)	232 (17.11%)	259 (17.51%)		1200 (17.73%)
Length of stay (days), *M* ± *SD*	5.85 ± 6.53	5.91 ± 6.43	5.71 ± 6.05	5.53 ± 5.99	5.95 ± 7.24	.423[a]	5.79 ± 6.48
Total charges (dollars), *M* ± *SD*	50,510.87 ± 68,853.46	56,712.90 ± 74,559.84	54,449.21 ± 69,876.42	57,139.87 ± 83,100.15	61,603.59 ± 89,475.43	.006[a]	56,280.84 ± 78,033.73
Complications							
Venous thromboembolism, *n* (%)	47 (3.78%)	44 (3.15%)	49 (3.79%)	49 (3.61%)	54 (3.65%)	.897[b]	243 (3.59%)
Cardiac tamponade, *n* (%)	#	#	#	#	#	.360[c]	26 (0.38%)
Sepsis and severe sepsis, *n* (%)	77 (6.19%)	105 (7.52%)	79 (6.11%)	127 (9.37%)	137 (9.26%)	< .001[b]	525 (7.76%)
Septic shock, *n* (%)	22 (1.77%)	37 (2.65%)	24 (1.86%)	39 (2.88%)	39 (2.64%)	.214[b]	161 (2.38%)
Pneumothorax, *n* (%)	#	#	#	#	#	.910[c]	18 (0.27%)
Hematoma, *n* (%)	28 (2.25%)	29 (2.08%)	16 (1.24%)	20 (1.47%)	23 (1.56%)	.229[b]	116 (1.71%)

Note: a, One-way ANOVA, b, Chi-square test of independence, c, Fisher's exact test. #indicates Cell sizes less than or equal to 10.

Table 2. Multivariate binary logistic regression model of pacemaker

Determinant	Pacemaker (0 = No, 1 = Yes)	
	Estimate (*SE*)	AOR (95% CI)
Block 1		
Age (reference 18-34)		
35-49	1.27* (0.64)	
50-64	2.58** (0.59)	
≥ 65	3.51** (0.59)	
Sex		
Female	0.04 (0.20)	
Race (reference White)		
Black	-0.37* (0.18)	
Hispanic	-0.93* (0.35)	
Other	0.08 (0.40)	
Model χ^2 (*df*)	373.29 (9)**	
Nagelkere R^2	.20	
Block 2		
Venous thromboembolism	-0.28 (0.47)	
Cardiac tamponade	0.93 (1.08)	
Sepsis and severe sepsis	-2.48* (1.01)	
Septic shock	-13.15 (470.39)	
Pneumothorax	-15.74 (1495.06)	
Hematoma	-0.13 (0.60)	
Model χ^2 (*df*)	404.06 (15)**	
Nagelkere ΔR^2	.22**	

Note: *P < .05, **P < .001. AOR, adjusted odds ratio; DM, Diabetes without chronic complications; BMI, Body Mass Index; COPD, Chronic obstructive pulmonary disease.

patients with SLE increased for females over the five-year span (p = 0.023). In patients with both SLE and SND, prevalence of Pacemaker (PM) implantation over the five years was 3.6%, and rates of Dual-chamber pacemaker, single chamber pacemaker, and Biventricular pacemaker were 3.1%, 0.3%, and 0.21%, respectively. Prevalence estimates of complications associated with PM in patients with SLE and SND were venous thromboembolism (2.1%), cardiac tamponade (0.4%), sepsis and severe sepsis (0.4%), septic shock (0%), pneumothorax (0%), and PM site hematoma (1.7%). LOS was (M ± SD) 5.79 ± 6.48 days.

Total charges related to hospitalizations were 56,280.84 ± 78,033.73 ($). Over the five years period, in-hospital mortality was 4%, the mean length of stay was 5.79 ± 6.48 days, and the mean total charges for hospitalization was 56,280.84 ± 78,033.73$. Although the mean length of stay (p = 0.423), and in-hospital mortality (P = 0.666), did not vary over the five-year time period that we analyzed, there was a significant increase in mean hospital charges (P < 0.006). Overall pacemaker implantation did not differ significantly from the year 2010 to 2014 (P = 0.841). The hierarchical binary logistic regression analysis revealed a significant improvement in model fit for Step 2 compared to Step 1, ΔX 2 (6) = 30.77, Nagelkerke ΔR 2 = 0.02, P < 0.001. After statistically controlling for effects of age, sex, and race, complications that emerged as significant predictors of in-hospital mortality were sepsis and severe sepsis. All other comorbidities included in the model were not significantly associated with in-hospital mortality (P > 0.05) (**Table 2**).

Discussion

This study was geared towards the assessment of the prevalence of sinus node dysfunction in SLE patients and the prevalence and complications of pacemaker implantation. Our study revealed a SND prevalence of 4.3% in this patient population. This is a relatively higher rate when compared to other studies such as the Cardiovascular Health Study (CHS) and Atherosclerosis Risk in Communities (ARIC) which report an incidence rate of 0.8 cases per 1000 person-years of SND in the general population [9].

The mean age of SND in the SLE patient population in this study was found to be 52 years. This observation reveals that SND occurs at a relatively younger age in SLE patients as compared to other studies that report a mean age of 73 to 76 years of age in the general population [10-12]. Studies demonstrate no clear gender involvement in the occurrence of SND with equal incidence rates reported in males and females. One such study that analyzed gender differences is the MOST selection trial which reported a 49% incidence of SND in women [13]. Our data revealed a higher incidence in females of 88.2%. This may be attributed to an overall higher incidence of SLE in females as compared to the male population [14].

The prevalence of pacemaker implantation over the five-year study period was observed to be 3.6%. Due to limited data on pacemaker implantation in patients with SLE, it is difficult to comment on this rate. However, the overall prevalence of pacemaker implantation in the general population has been reported to be about 0.4 in 1000 people between the ages of 18 to 64 and 26 in 1000 people at the age of 75 and above in a large population-based survey [8]. The observation that prevalence rates of both SND and pacemaker implantation increase with age in this study were consistent with observations made in other studies [8]. The Caucasian population comprised a total of 50.57% of the pacemaker recipient population. Other studies have also commented on pacemaker implantation rates being higher in the white population as compared to black, Hispanic, and other races [8, 15]. This finding raises concerns for racial disparities in access to health care resources.

In a large multicenter study, Udo et al reported a prevalence of 2.9% of hematoma following pacemaker implantation which is greater than the 1.71% prevalence observed in this study [16]. Similarly, the rates of pneumothorax reported by other studies are higher than that observed in this study [16, 17]. Regarding infectious complications such as sepsis and severe sepsis as well as septic shock, previous studies have reported a relatively lower rate of infection-related complications following pacemaker implantation [16]. It can be postulated that this observation may partly be due to an overall higher risk of infections in SLE patients due to immune dysfunction or as a result of immunosuppressive medications often used to manage this condition.

Cardiac tamponade was reported in 0.38% of cases in this study. This is a relatively rare complication and other studies such as the FOLLOWPACE trial report a similarly low rate [16]. On the other hand, venous thromboembolism was observed to have a prevalence of 3.59% following pacemaker implantation in this study. Venous thromboembolic events were reported to occur with an incidence of as high as 23% in a study conducted by Cornelis et al on 145 patients following implantation of pacemaker leads. However, it is pertinent to note that only 3 patients developed overt symptoms while in the remaining 31 patients the clots were discovered incidentally [18]. Although the rates of pacemaker complications are comparable, it is crucial to acknowledge that the complications following pacemaker implantation are largely determined by patient characteristics, risk factors, and surgery techniques [19].

Even though the NIS is a large database that includes > 95% of the US population, it has certain limitations that need to be addressed. The NIS is an administrative database and there could be coding errors and accuracy depends on the proficiency of the coders. It is a cross-sectional database, so we were not able to estimate the long-term events. We were also not able to determine the time of onset, duration, type or severity of co-morbidities, complications occurring during the recorded hospitalization, the temporal relation between pacemaker placement, and the time of occurrence of complications. This database also does not provide information about the severity of the disease. It is limited to in-hospital events and thus, does not provide outpatient/out-of-hospital events.

Our study revealed that the prevalence of SND and PM in patients with both SLE and SND has remained relatively consistent over a five-year period of analysis but appears to be higher than PM implantation rates in the general population. Future, prospective studies are needed to validate and assess the trends found in our study.

Disclosure of conflict of interest

None.

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