ORIGINAL RESEARCH

Intermediate Pause at Daytime Is Associated With Increased Cardiovascular Risk and Mortality: An 8-Year Cohort Study

Chih-Min Liu, MD; Chin-Yu Lin, MD; Shih-Lin Chang, MD, PhD; Yenn-Jiang Lin, MD, PhD; Li-Wei Lo, MD, PhD; Yu-Feng Hu, MD, PhD; Tze-Fan Chao, MD, PhD; Fa-Po Chung, MD, PhD; Ta-Chuan Tuan, MD; Jo-Nan Liao, MD, PhD; Yun-Yu Chen, MPH; Abigail Louise D. Te, MD; Shinya Yamada, MD; Ling Kuo, MD; Hsing-Yuan Li, MD, PhD; Ting-Yung Chang, MD; Hoang Quang Minh, MD; Simon Salim, MD; Vu Van Ba, MD; Jennifer Jeanne B. Vicera, MD; Cheng-I Wu, MD; Chieh-Mao Chuang, MD; Ting-Chung Huang, MD; Yu-Cheng Hsieh, MD, PhD; Shih-Ann Chen, MD

***Background*—**Long-term cardiovascular risk in patients with intermediate pauses remains unclear. Whether asymptomatic patients with intermediate pauses have increased future cardiovascular events remains unknown. We hypothesize that intermediate pause is associated with increased cardiovascular risk and mortality.

***Methods and Results*—**We retrospectively analyzed 5291 patients who have pauses of <3 seconds on 24-hour Holter monitoring. Patients with pauses of 2 to 3 seconds constitute the intermediate pause patients, who are further divided into daytime pause (8:00 AM–8:00 PM), nighttime pause (8:00 PM–8:00 AM), and daytime plus nighttime pause groups depending on the occurring time of the pauses. The rest of the patients (pause <2 seconds) are the no pause group. The multivariate Cox hazards regression model was used to assess the hazard ratio for mortality (primary outcome) and adverse cardiovascular events (secondary outcome). There were 4859 (91.8%) patients in no pause, 248 (4.7%) in nighttime pause, 103 (1.9%) in daytime pause, and 81 (1.5%) in daytime plus nighttime pause groups. After a follow-up of 8.8±1.7 years' follow-up, 343 (6.5%) patients died. The risk for adverse cardiovascular events, including all-cause hospitalization, cardiovascular-cause hospitalization, pacemaker implantation, new-onset atrial fibrillation/heart failure, and transient ischemic attack, were higher in daytime pause and nighttime pause patients than those in the no pause group. Daytime pause (hazard ratio, 2.35; P=0.008) and daytime plus nighttime pause (hazard ratio, 2.26; P=0.016) patients have a higher mortality rate than that in nighttime pause.

***Conclusions*—**Patients with intermediate pause are associated with increased cardiovascular risk. Intermediate pauses occurring at daytime have a higher mortality rate than that at nighttime during long-term follow-up. **(*J Am Heart Assoc*. 2018;7:e009034. DOI: 10.1161/JAHA.118.009034.)**

Key Words: 24-hour Holter monitoring • intermediate pause • mortality

Symptomatic bradycardia is the most common indication for permanent pacemaker implantation, which can result in cerebral hypoperfusion and subsequent syncope.[1,2] In symptomatic patients with a ventricular pause of more than 3 seconds, the European Society of Cardiology and American Heart Association guidelines recommend pacemaker implantation in these patients to prevent further adverse events, except for patients who were asleep or on medication.[1–4] However, the current 3-second criterion is an arbitrary clinical observation with a low specificity.[3] Most patients with intermediate pauses (2–3 seconds in duration) are asymptomatic and not candidates for pacemaker implantation by current practical guidelines.[1,2,5] However, some patients with intermediate pauses (ie, sinus pause of 2–3 seconds in

From the Division of Cardiology, Department of Medicine (C.-M.L., C.-Y.L., S.-L.C., Y.-J.L., L.-W.L., Y.-F.H., T.-F.C., F.-P.C., T.-C.T., J.-N.L., Y.-Y.C., A.L.D.T., S.Y., L.K., H.-Y.L., T.-Y.C., H.Q.M., S.S., V.V.B., J.J.B.V., C.-I.W., C.-M.C., T.-C.H., Y.-C.H., S.-A.C.), and Department of Internal Medicine, Yuan-Shan Branch (C.-Y.L.), Taipei Veterans General Hospital, Taipei, Taiwan; Institute of Clinical Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan (C.-Y.L., S.-L.C., Y.-J.L., L.-W.L., Y.-F.H., T.-F.C., F.-P.C., T.-C.T., J.-N.L., L.K., T.-Y.C., C.-I.W., Y.-C.H., S.-A.C.); Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan (Y.-Y.C.); Cardiovascular Center (Y.-C.H.), and Department of Internal Medicine, Chiayi Branch (Y.-C.H.), Taichung Veterans General Hospital, Taichung, Taiwan.

Correspondence to: Yu-Cheng Hsieh, MD, PhD, Cardiovascular Center, Taichung Veterans General Hospital, 1650 Taiwan Boulevard Sect 4, Taichung 40705, Taiwan. E-mail: ychsieh@vghtc.gov.tw

Received February 28, 2018; accepted May 15, 2018.

Clinical Perspective

What Is New?

- In our study, patients with pauses 2 to 3 seconds in length (intermediate pauses) occurring during the day or night increased the risk of adverse cardiovascular events (including all-cause hospitalization, cardiovascular hospitalization, pacemaker implantation, new-onset atrial fibrillation, new-onset heart failure, and transient ischemic attack) compared with patients without pauses.
- Intermediate pauses occurring during the day, either alone or in combination with intermediate pauses at night, were associated with increased mortality rate compared with pauses present that solely occurred at night; this was especially notable in those with a sick sinus syndrome pause pattern and a high frequency of pauses.

What Are the Clinical Implications?

- In daily clinical practice, physicians should pay attention to patients with intermediate pause and intensively follow them for the development of atrial fibrillation and heart failure.
- Early and adequate treatment of underlying comorbidities might help to reduce future cardiovascular risk in intermediate pause patients.
- An electrophysiology study might be considered to uncover sinus or atrioventricular nodal dysfunction in patients with intermediate pauses who present with presyncope or syncope.

duration) did develop syncope that eventually leads to pacemaker implantation.[1,2,6,7] There were no long-term follow-up data regarding patients with intermediate pauses and future cardiovascular events and mortality. Whether these asymptomatic patients with intermediate pauses have a benign clinical course for future cardiovascular events remains unclear.

In this study, using the 24-hour Holter monitoring database in a patient population that was followed up for 8 years, we will be able to explore the long-term risk of cardiovascular events and mortality in patients with intermediate pauses. Pauses at nighttime have been considered to be a physiological rather than pathological response attributed to autonomic regulation and might spare intensive intervention. Therefore, intermediate pauses occurring at daytime or nighttime may have a different impact on cardiovascular risks. Furthermore, the patterns (ie, atrioventricular block [AVB] or sinus arrest) and frequency of these intermediate pauses might also differently contribute to cardiovascular events with respect to their occurring time. We hypothesize that intermediate pauses occurring at daytime is associated with higher cardiovascular risk and mortality rate than those at nighttime.

Methods

This study was approved by the Institutional Review Board at Taipei Veterans General Hospital, Taipei, Taiwan (VGH-IRB Number: 2013-08-002AC#1). Because the patient records/information was anonymous and de-identified before analysis, there was no need for obtaining patients' informed consent. The data, analytical methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure because this was not part of our original Institutional Review Board approval.

Study Population

This retrospective, observational study was performed by analyzing the "Registry of 24-hour ECG monitoring at Taipei Veterans General Hospital" database. Taipei Veterans General Hospital is a large integrated healthcare delivery system and provides comprehensive medical services to more than 3 million people in Taiwan. The study database included 5903 consecutive patients who were aged >18 years and who underwent clinically indicated 24-hour Holter monitoring between January 1, 2002 and December 31, 2004. Indications for Holter monitoring were palpitation, syncope, suspected arrhythmia, and clinical follow-up by the physicians' discretion. Clinical variables, including past medical histories, risk factors, comorbidities, and medications, were obtained from the medical records of the primary/secondary referral hospitals, outpatient visits, emergency visits, the Collaboration Center of Health Information Application (CCHIA), and the Ministry of Health and Welfare in Taiwan. *The International Classification of Diseases - Ninth Revision* (*ICD-9*) codes were also used for identifying underlying diseases, including diabetes mellitus, hypertension, coronary artery disease, heart failure, chronic kidney disease, liver disease, myocardial infarction, and valvular heart disease. The New York Heart Association functional classifications of patients were determined from the medical and nursing records.

Clinical diagnoses of interests were confirmed to be valid only if they have been recorded at least twice in outpatient records or once in hospitalization records. Patients were excluded if they have atrial flutter/AF, high-degree AVB, symptomatic bradycardia, or the longest R-R interval is ≥3 seconds by the 12-lead ECG or 24-hour Holter monitoring. Patients were also excluded if they had a pacemaker implanted before this study or had a history of catheter ablation for arrhythmia. After excluding the above-mentioned patients, the final sample size was 5291 patients.

Cardiovascular Outcomes

The primary outcome in this study is mortality. Secondary outcomes include hospitalization for any reason (all-cause

hospitalization), hospitalization for cardiovascular causes, the occurrence of new-onset AF, new-onset heart failure (HF), permanent pacemaker (PPM) implantation, transient ischemic attack (TIA) and ischemic stroke. Patients taking regular medication were regularly followed up at an interval of 1 to 3 months. Those with a new cardiovascular event were followed up every 2 weeks for the first month and at an interval of 1 to 3 months thereafter. Patients who did not take regular medication were followed up annually or at the discretion of the physicians. Medical records retrieved from the Taipei Veterans General Hospital were used for outcome survey as in our previous study.[8] New cardiovascular events, inpatient admissions, and deaths were identified through the *ICD* diagnostic codes, mention of an end point on the face sheet of the medical record, previous discharge summary, and outpatient clinic reports. Mortality was defined as passing away during hospitalization or discharge under critical condition. Hospitalization was defined as an overnight stay in a hospital ward, excluding emergency department visit. New-onset HF and AF were identified by physician report, echocardiography data, ECG tracing, and mention of the events in the medical record. The observation period was from the date of patient registration until February 28, 2013. Multivariate analysis with the Cox hazards regression model was used to assess the hazard ratio (HR) for mortality (primary outcome) and adverse cardiovascular events (secondary outcome).

Patient Groups and Definition of Pauses

The 24-hour Holter monitoring data were reviewed by electrophysiological experts as in our previous work.[8] Patients with intermediate pauses (the longest R-R interval of ≥2 and <3 seconds) constituted the study group. Intermediate pause patients whose pause occurred solely at daytime (8:00 AM–8:00 PM) were classified into the daytime pause (DTP) group, whereas those whose pause occurred only at nighttime (8:00 PM–8:00 AM) were the nighttime pause (NTP) group. Patients whose intermediate pause occurred at both daytime and nighttime constituted the daytime plus nighttime pause (DNTP) group. Control group patients were those whose R-R interval was <2 seconds in duration and constituted the no pause (NOP) group.

Patterns of intermediate pauses were classified into sick sinus (ISS), AVB (intermediate pause of atrioventricular block pattern), and combined (both ISS and intermediate pause of atrioventricular block pattern) patterns. The ISS pattern was defined as sinus arrest, sinus exit block, or sinus pause proceeded by an atrial/ventricular premature contraction, whereas the intermediate pause of atrioventricular block pattern was intermediate pauses caused by Mobitz type 1 second-degree AVB. Frequency of intermediate pauses was divided into high and low frequencies. High-frequency patients were those whose pause occurrence frequency was equal or higher than the median frequency in each group. The rest of the patients in each group constituted the low-frequency patients.

Statistical Analysis

Statistical analyses were performed by SPSS statistical software (version 20.0; SPSS, Inc., Chicago, IL). Patient characteristics are expressed as mean±SD for continuous variables and percentages for categorical variables. Continuous and categorical variables were compared using the Student *t* test and Pearson's chi-square test with Yates' correction, respectively. An alpha error of less than 5% was considered statistically significant. Kaplan–Meier survival curves with log-rank tests were used to analyze survival data (time to adverse event). A Cox regression hazards model was applied to estimate the HR of the time to adverse events.

Results

Baseline Characteristics

A total of 5291 patients were enrolled in this study: 4859 (91.8%) were in the NOP (control) group, whereas 248 (4.7%), 103 (1.9%), and 81 (1.5%) patients were in the NTP, DTP, and DNTP groups, respectively. Table 1 shows the baseline characteristics of the patients. Patients in the NTP, DTP and DNTP groups were older ($P<0.001$), had a higher percentage of male patients ($P<0.001$), and with a higher incidence of hypertension ($P<0.001$) compared with the NOP group. The incidence of coronary artery disease in the DTP group (26.2%) was lower than that of the NOP (28.9%), NTP (37.1%), and DNTP (32.1%) groups ($P=0.039$). Therefore, the percentage of patients who used cardiovascular medications were lower in the DTP group (7.8%) than the other groups ($P=0.020$). There was no statistical difference among these 4 groups of patients on baseline ECG characteristics, including first-degree AVB ($P=0.228$), Mobitz type I AVB ($P=0.405$), left bundle branch block ($P=0.501$), and right bundle branch block ($P=0.366$).

Intermediate Pause and Cardiovascular Outcomes

During the follow-up period of 8.8±1.7 years, a total of 343 (6.5%) patients died. In the 5291 patients, 3061 (57.9%) were hospitalized for any reasons, 1129 (21.3%) were hospitalized for cardiovascular causes, 108 (2.0%) had PPM implantation, 399 (7.5%) developed new-onset AF, 524 (9.9%) had new-onset HF, 493 (9.3%) had TIA, and 480 (9.1%) had ischemic stroke episodes.

Table 2 shows the composite cardiovascular outcomes during the follow-up period. Comparing with the NOP group,

Table 1. Baseline Characteristics of the Patients

Baseline Characteristics	NOP (N=4859)	NTP (N=248)	DTP (N=103)	DNTP (N=81)	*P* Value
Age, y	60.9±18.6	69.5±17.2	69.1±16.3	71.0±13.4	<0.001
Men, n (%)	2844 (58.5)	184 (74.2)	72 (69.9)	62 (76.5)	<0.001
Previous MI, n (%)	27 (0.6)	2 (0.8)	0 (0.0)	1 (1.2)	0.684
Valvular heart disease, n (%)	95 (2.0)	7 (2.8)	1 (1.0)	0 (0.0)	0.373
Hypothyroidism, n (%)	23 (0.5)	2 (0.8)	0 (0.0)	1 (1.2)	0.581
Malignancy, n (%)	142 (2.9)	6 (2.4)	7 (6.8)	4 (4.9)	0.089
Cirrhosis, n (%)	25 (0.5)	0 (0.0)	1 (1.0)	1 (1.2)	0.468
Cardiovascular risk factors					
Diabetes mellitus, n (%)	464 (9.5)	30 (12.1)	11 (10.7)	12 (14.8)	0.238
Hypertension, n (%)	1666 (34.3)	114 (46.0)	43 (41.7)	46 (56.8)	<0.001
Dyslipidemia, n (%)	180 (3.7)	11 (4.4)	2 (1.9)	5 (6.2)	0.457
Heart failure, n (%)	229 (4.7)	13 (5.2)	3 (2.9)	0 (0.0)	0.179
LVEF, %	64.0±5.3	64.2±4.1	64.2±4.5	64.7±1.2	0.664
NYHA Fc I, n (%)	119 (2.4)	10 (4.0)	3 (2.9)	0 (0.0)	0.204
NYHA Fc II, n (%)	55 (1.1)	1 (0.4)	1 (1.0)	0 (0.0)	0.555
NYHA Fc III, n (%)	53 (1.1)	2 (0.8)	1 (1.0)	0 (0.0)	0.784
NYHA Fc IV, n (%)	2 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.981
CAD, n (%)	1406 (28.9)	92 (37.1)	27 (26.2)	26 (32.1)	0.039
CKD, n (%)	50 (1.0)	2 (0.8)	2 (1.9)	2 (2.5)	0.476
Medication, n (%)	921 (19.0)	39 (15.7)	8 (7.8)	16 (19.8)	0.020
Antiarrhythmia*	34 (0.7)	2 (0.8)	0 (0.0)	2 (2.5)	0.233
Antihypertensives	895 (18.4)	38 (15.3)	8 (7.8)	15 (18.5)	0.028
Beta-blocker	135 (2.8)	5 (2.0)	3 (2.9)	0 (0.0)	0.421
Dihydropyrimidine CCB	388 (8.0)	14 (5.6)	5 (4.9)	6 (7.4)	0.378
Nondihydropyrimidine CCB	187 (3.8)	10 (4.0)	1 (1.0)	2 (2.5)	0.436
ACEI/ARB	246 (5.1)	9 (3.6)	5 (4.9)	6 (7.4)	0.573
Diuretics	370 (7.6)	16 (6.5)	4 (3.9)	7 (8.6)	0.461
Alpha-blocker	53 (1.1)	1 (0.4)	0 (0.0)	3 (3.7)	0.059
Statins	173 (3.6)	10 (4.0)	2 (1.9)	5 (6.2)	0.471
ECG parameters					
First-degree atrioventricular block	405 (8.3%)	26 (10.5%)	13 (12.6%)	9 (11.1%)	0.228
Mobitz type I atrioventricular block	91 (1.9%)	7 (2.8%)	3 (2.9%)	3 (3.7%)	0.405
LBBB	32 (0.7%)	3 (1.2%)	0 (0.0%)	0 (0.0%)	0.501
RBBB	341 (7.0%)	23 (9.3%)	9 (8.7%)	8 (9.9%)	0.366

Values are number and percentage (%) of the variables±SD. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CCB, calcium channel blocker; CKD, chronic kidney disease; DNTP, daytime plus nighttime pause; DTP, daytime pause; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NOP, no pause; NTP, nighttime pause; NYHA Fc, New York Heart Association Functional Classification; RBBB, right bundle branch block.
*Class I or III antiarrhythmic drugs.

NTP patients showed a higher rate of the composite cardiovascular events, including all-cause of hospitalization (HR, 1.19; *P*=0.030), cardiovascular-cause hospitalization (HR, 1.83; *P*<0.001), PPM implantation (HR, 4.28; *P*<0.001), new-onset of AF (HR, 2.13; *P*<0.001), new-onset of HF (HR, 1.63; *P*=0.001), and TIA (HR, 2.52; *P*<0.001; Table 2). Similarly, DTP and DNTP patients had a higher rate of composite cardiovascular events, including all-cause hospitalization (DTP versus NOP: HR, 1.28, *P*=0.039; DNTP versus NOP: HR, 1.47, *P*=0.003), cardiovascular-cause hospitalization (HR, 1.71, *P*=0.003; HR, 2.15, *P*<0.001,

Table 2. Cardiovascular Event Rates in Patients With Intermediate Pauses

	NOP	NTP	DTP	DNTP	NTP vs NOP*		DTP vs NOP*		DTP vs NTP*		DNTP vs NTP*	
	N=4859	N=248	N=103	N=81	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
All-cause hospitalization, n (%)	2756 (56.7)	171 (69.0)	73 (70.9)	61 (75.3)	1.19 (1.02–1.39)	0.030	1.28 (1.01–1.62)	0.039	1.08 (0.81–1.42)	0.611	1.22 (0.91–1.64)	0.191
Cardiovascular-cause hospitalization, n (%)	964 (19.8)	97 (39.1)	33 (32.0)	35 (43.2)	1.83 (1.48–2.26)	<0.001	1.71 (1.21–2.43)	0.003	0.93 (0.62–1.39)	0.706	1.13 (0.77–1.67)	0.535
PPM implantation, n (%)	67 (1.4)	19 (7.7)	7 (6.8)	15 (18.5)	4.28 (2.54–7.20)	<0.001	3.97 (1.80–8.74)	0.001	0.84 (0.35–2.02)	0.700	2.48 (1.24–4.95)	0.010
New-onset AF, n (%)	329 (6.8)	39 (15.7)	14 (13.6)	17 (21.0)	2.13 (1.52–2.98)	<0.001	1.90 (1.11–3.26)	0.020	0.80 (0.43–1.50)	0.494	1.29 (0.72–2.30)	0.389
New-onset HF, n (%)	438 (9.5)	49 (20.9)	19 (19.0)	18 (22.2)	1.63 (1.21–2.20)	0.001	1.70 (1.07–2.70)	0.025	0.92 (0.53–1.58)	0.749	1.05 (0.61–1.81)	0.857
TIA, n (%)	399 (8.2)	54 (21.8)	18 (17.5)	22 (27.2)	2.52 (1.89–3.36)	<0.001	2.08 (1.29–3.35)	0.003	0.76 (0.44–1.31)	0.317	1.23 (0.75–2.04)	0.414
Ischemic stroke, n (%)	433 (8.9)	27 (10.9)	11 (10.7)	9 (11.1)	1.12 (0.75–1.65)	0.584	1.07 (0.59–1.95)	0.831	0.92 (0.45–1.88)	0.822	1.07 (0.50–2.27)	0.871
Mortality, n (%)	286 (5.9)	23 (9.3)	19 (18.4)	15 (18.5)	1.00 (0.65–1.54)	0.997	2.26 (1.41–3.61)	0.001	2.35 (1.25–4.41)	0.008	2.26 (1.16–4.40)	0.016

Values are number and percentage (%) of events. AF indicates atrial fibrillation; CI, confidence interval; DNTP, daytime plus nighttime pause; DTP, daytime pause; HF, heart failure; HR, hazard ratio; NOP, No pause; NTP, nighttime pause; TIA, transient ischemic attack.

*Multivariate analysis for HRs was adjusted for patient age, sex, hypertension, diabetes mellitus, coronary artery disease, valvular heart disease, malignancy, and medication used.

respectively), PPM implantation (HR, 3.97, *P*=0.001; HR, 10.92, *P*<0.001, respectively), new-onset AF (HR, 1.90, *P*=0.020; HR, 2.72, *P*<0.001, respectively), new-onset HF (HR, 1.70, *P*=0.025; HR, 1.70, *P*=0.028, respectively), and TIA (HR, 2.08, *P*=0.003; HR, 2.98, *P*<0.001, respectively) than those of NOP patients (Tables 2 and 3). The above-mentioned cardiovascular event rates were similar among NTP, DTP and DNTP patients, except for PPM implantation rates. PPM implantation rate was higher in the DNTP than that in the NTP (HR, 2.48; *P*=0.010; Table 2) and DTP (HR, 2.64; *P*=0.041) groups (Table 3). Ischemic stroke rate was indifferent among the 4 groups of patients (*P*=ns for any 2 of the 4 groups; Table 2).

The mortality rate in DTP patients is higher than that of the NOP (HR, 2.26; *P*=0.001) and NTP (HR, 2.35; *P*=0.008) patients (Table 2). DNTP patients also have a higher mortality rate than that of the NTP (HR, 2.26; *P*=0.016; Table 2) and NOP (HR, 2.04; *P*=0.008; Table 3) patients. Mortality rates were similar between NTP and NOP patients (HR, 1.00; *P*=0.997) and between DNTP and DTP patients (HR, 1.04; *P*=0.910; Tables 2 and 3).

Figure 1 shows Kaplan–Meier survival curves with log-rank test in all-cause hospitalization (Figure 1A; *P*<0.001), cardiovascular causes of hospitalization (Figure 1B; *P*<0.001), PPM implantation (Figure 1C; *P*<0.001), new-onset AF (Figure 1D; *P*<0.001), new-onset HF (Figure 1E; *P*<0.001), TIA (Figure 1F; *P*<0.001), ischemic stroke (Figure 1G; *P*=0.609), and all-cause mortality (Figure 1H; *P*<0.001) among the 4 groups of patients. Log-rank *P* values between different groups are shown in Table 4.

Intermediate Pause Patterns and Frequencies on Mortality

Mortality rates were similar among different patterns within the NTP (*P*=0.304), DTP (*P*=0.710), and DNTP (*P*=0.440) groups (Table 5). Kaplan–Meier survival curves showed no differences in mortality rate among different pause patterns within the 3 groups of patients (Figure 2). ISS patients in the DNTP groups had a higher mortality rate than that of ISS patients in the NTP groups (HR, 2.37; *P*=0.032; Table 6). Patients presenting with ISS pattern in the DTP (HR, 1.88; *P*=0.028) and DNTP (HR, 1.94; *P*=0.032) groups showed a higher mortality rate than that in the NOP group (Table 6). Compared with the NOP group, DTP patients with intermediate pause of atrioventricular block pattern also have an increased mortality rate (HR, 4.24; *P*=0.005; Table 6).

Median frequencies of the intermediate pauses were 3, 3, and 23 times/day in the NTP, DTP, and DNTP patients, respectively (Table 7). Mortality rates were indifferent between high- and low-frequency patients within the NTP (*P*=0.325), DTP (*P*=0.221), and DNTP (*P*=0.484) groups (Table 7). Kaplan–Meier survival curves showed no difference

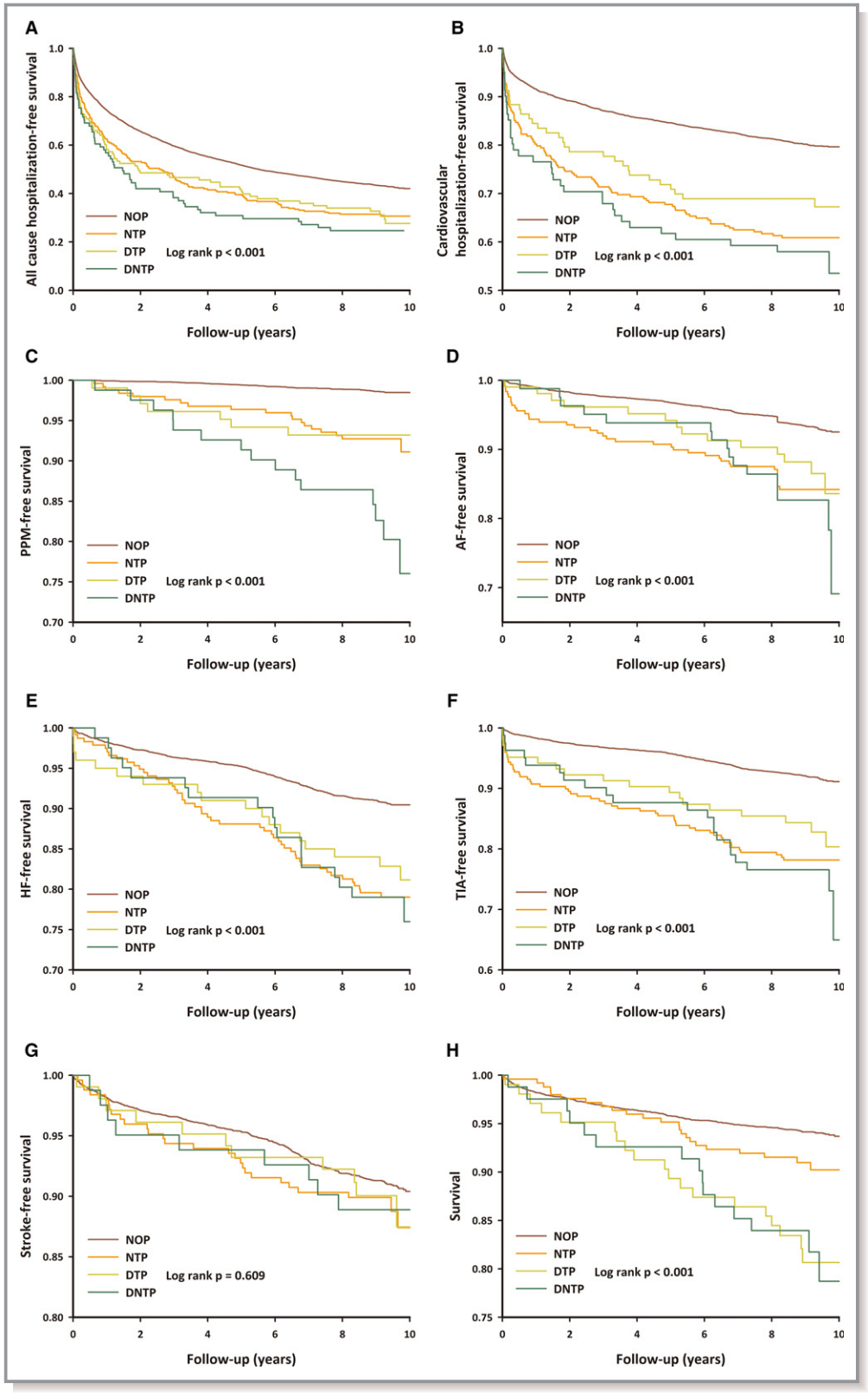

Figure 1. Kaplan–Meier survival curves of cardiovascular outcomes and mortality in the 4 groups of patients. A, All-cause hospitalization; B, cardiovascular cause of hospitalization; C, permanent pacemaker (PPM) implantation; D, new-onset atrial fibrillation (AF); E, new-onset heart failure (HF); F, transient ischemic attack (TIA); G, ischemic stroke; and H, all-cause mortality. *P* values were calculated with the log-rank test. DNTP indicates daytime plus nighttime pause; DTP, daytime pause; NOP, no pause; NTP, nighttime pause.

Table 3. Cardiovascular Event Rate in Patients With Intermediate Pauses

	DNTP vs NOP*		DNTP vs DTP*	
Cardiovascular Event	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
All-cause hospitalization	1.47 (1.14–1.90)	0.003	1.20 (0.84–1.70)	0.321
Cardiovascular-cause hospitalization	2.15 (1.53–3.02)	<0.001	1.27 (0.77–2.10)	0.341
PPM implantation	10.92 (6.14–19.41)	<0.001	2.64 (1.04–6.71)	0.041
New-onset AF	2.72 (1.66–4.45)	<0.001	1.23 (0.58–2.60)	0.585
New-onset HF	1.70 (1.06–2.74)	0.028	1.08 (0.54–2.14)	0.831
TIA	2.98 (1.93–4.60)	<0.001	1.34 (0.70–2.57)	0.376
Ischemic stroke	1.12 (0.58–2.17)	0.743	1.07 (0.43–2.64)	0.886
Mortality	2.04 (1.21–3.44)	0.008	1.04 (0.50–2.17)	0.910

AF indicates atrial fibrillation; CI, confidence interval; DTP, daytime pause; DNTP, daytime plus nighttime pause; HF, heart failure; HR, hazard ratio; NOP, no pause; NTP, nighttime pause; TIA, transient ischemic attack.
*Multivariate analysis for HR was adjusted for patient age, sex, hypertension, diabetes mellitus, coronary artery disease, valvular heart disease, malignancy, and medication used.

in mortality rate between the high- and low-pause-frequency patients within the 3 groups of patients (Figure 3). High-pause-frequency patients in the DTP (HR, 3.42; *P*=0.006) and DNTP (HR, 1.72; *P*=0.023) groups had a higher mortality rate than that in NTP patients with high pause frequency (Table 8). Similarly, DTP (HR, 2.64; *P*=0.001) and DNTP (HR, 2.35; *P*=0.012) patients with high pause frequency showed increased mortality rate compared with the high-pause-frequency patients in the NOP groups (Table 8).

Figure 4 shows the percentage of patients in different pause groups according to the causes of death. The leading causes of death in intermediate pause patients are infection and malignancy. DTP and DNTP patients had a higher rate of infection-related mortality than that of the NOP patients (DTP versus NOP, *P*=0.002; DNTP versus NOP, *P*=0.002; Table 9). Similarly, DTP and DNTP patients also had a higher rate of malignancy-related death compared with that of NOP patients (DTP versus NOP, *P*<0.001; DNTP versus NOP, *P*=0.004; Table 9). Cardiovascular (myocardial infarction, HF, and sudden cardiac death; *P*=0.084) and other (gastrointestinal bleeding, stroke, chronic obstructive pulmonary diseases, and uremia; *P*=0.785) causes of mortality rate were similar among these 4 groups of patients.

Percentage and causes of PPM implantation in different pause groups are shown in Figure 5. Compared with NOP patients, DNTP, DTP, and NTP patients had a higher rate of sick sinus syndrome (DNTP versus NOP, *P*<0.001; DTP versus NOP, *P*=0.018; NTP versus NOP, *P*<0.001) and AVB (DNTP versus NOP, *P*<0.001; DTP versus NOP, *P*<0.001; NTP versus NOP, *P*<0.001) related PPM implantation (Table 10).

Discussion

Main Finding

This study has the following major findings: (1) Intermediate pause occurring at daytime or nighttime increased the risk of

Table 4. Log-Rank *P* Values of Kaplan–Meier Curves for Adverse Cardiovascular Events in Patients With Intermediate Pauses

	NTP vs NOP	DTP vs NOP	DNTP vs NOP	DTP vs NTP	DNTP vs NTP	DNTP vs DTP
Kaplan–Meier Curve	Log-Rank *P* Value	Log-Rank *P* Value	Log-Rank *P* Value	Log-Rank *P* Value	Log-Rank *P* Value	Log-Rank *P* Value
All-cause hospitalization	<0.001	0.001	<0.001	0.846	0.181	0.309
Cardiovascular-cause hospitalization	<0.001	0.001	<0.001	0.223	0.476	0.106
PPM implantation	<0.001	<0.001	<0.001	0.780	0.005	0.015
New-onset AF	<0.001	0.010	<0.001	0.550	0.390	0.205
New-onset HF	<0.001	0.001	<0.001	0.671	0.843	0.579
TIA	<0.001	0.001	<0.001	0.339	0.454	0.141
Ischemic stroke	0.270	0.605	0.505	0.902	0.975	0.905
Mortality	0.033	<0.001	<0.001	0.016	0.026	0.989

AF indicates atrial fibrillation; DNTP, daytime plus nighttime pause; DTP, daytime pause; HF, heart failure; NOP, no pause; NTP, nighttime pause; PPM, permanent pacemaker; TIA, transient ischemic attack.

Table 5. Patterns of Intermediate Pause on Mortality Rate

	NTP (N=248)			DTP (N=103)			DNTP (N=81)		
Pause Patterns	N	Death	Mortality (%)	N	Death	Mortality (%)	N	Death	Mortality (%)
Sick sinus	189	17	9.0	78	13	16.7	66	11	16.7
Atrioventricular block	44	3	6.8	17	4	23.5	13	3	23.1
Combined	15	3	20.0	8	2	25.0	2	1	50.0
P value within group*	0.304			0.710			0.440		

Values are number and percentage (%) of the variables. Sick sinus patterns include pauses caused by postatrial premature contraction block, postventricular premature contraction block, sinus pause, sinus arrest, and sinus exist block. Atrioventricular block pattern is intermediate pauses caused by Mobitz type I atrioventricular block. Combined patterns are intermediate pauses caused by both sick sinus and atrioventricular block patterns. DNTP indicates daytime plus nighttime pause; DTP, daytime pause; NTP, nighttime pause.
*The *P* value was obtained by Pearson's chi-square test.

adverse cardiovascular events, including all-cause hospitalization, cardiovascular cause of hospitalization, pacemaker implantation, new-onset AF, new-onset HF, and TIA, compared with those without pause; (2) intermediate pause occurring at daytime, either daytime only or day plus nighttime, was associated with increased mortality rate than those whose

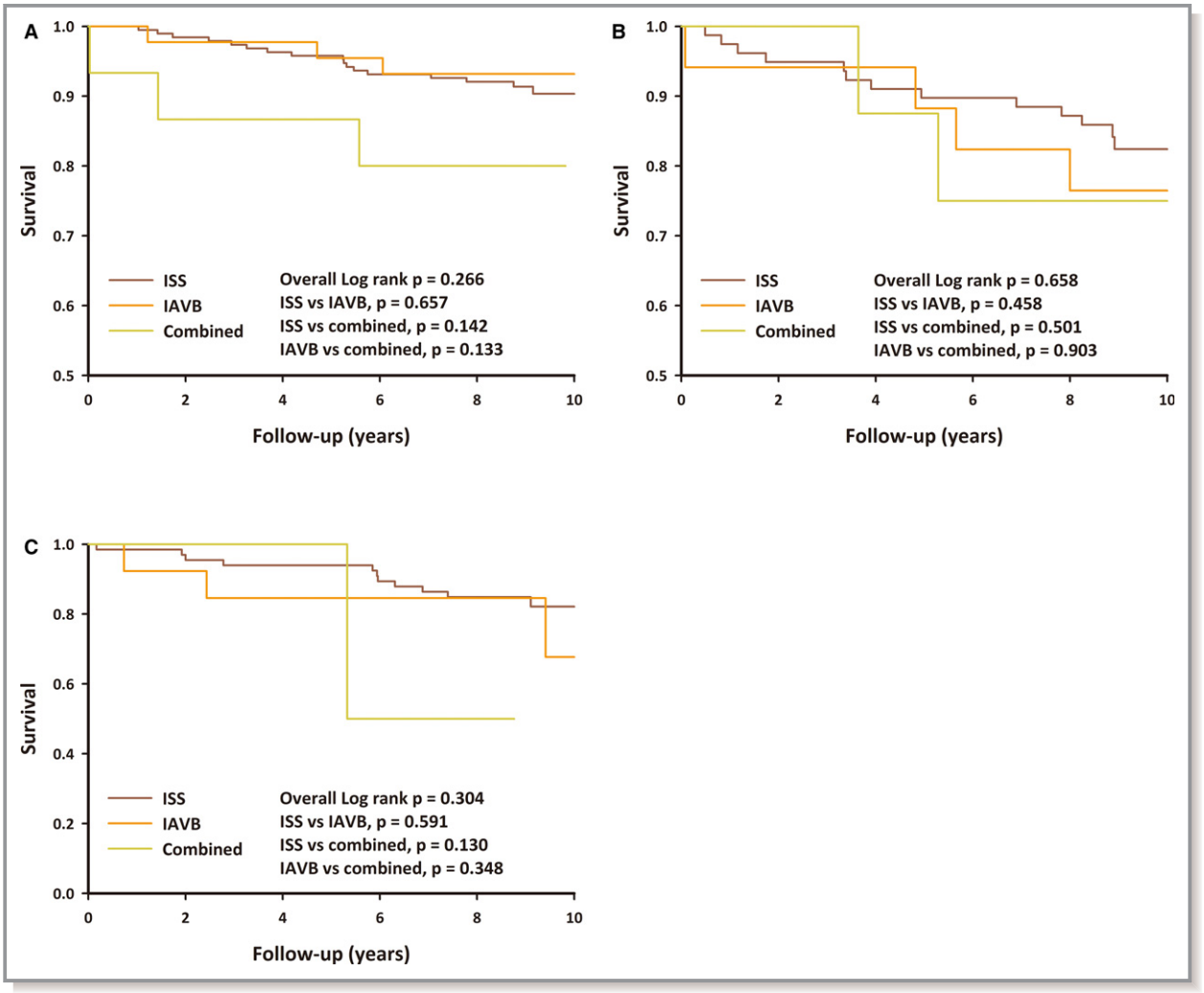

Figure 2. Intermediate pause pattern on mortality rates within the NTP (A), DTP (B), and DNTP (C) groups. *P* values were calculated with the log-rank test in the Kaplan–Meier survival curves. DNTP indicates daytime plus nighttime pause; DTP, daytime pause; IAVB, intermediate pause of atrioventricular block pattern; combined, combined ISS, and IAVB; ISS, intermediate pause of sick sinus pattern; NTP, nighttime pause.

Table 6. Patterns of Intermediate Pause on Mortality Rate Between Different Pause Groups

Pause Pattern	DTP vs NTP*		DNTP vs NTP*		DNTP vs DTP*		NTP vs NOP*		DTP vs NOP*		DNTP vs NOP*	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Sick sinus	1.89 (0.88–4.05)	0.102	2.37 (1.08–5.23)	0.032†	1.01 (0.43–2.40)	0.982	1.11 (0.68–1.82)	0.671	1.88 (1.07–3.29)	0.028†	1.94 (1.06–3.54)	0.032†
Atrioventricular block	4.11 (0.48–35.01)	0.196	2.37 (0.23–24.45)	0.469	2.62 (0.28–24.22)	0.397	1.02 (0.33–3.19)	0.972	4.24 (1.57–11.49)	0.005†	2.15 (0.69–6.75)	0.190
Combined	1.52 (0.84–27.50)	0.778	4.42 (0.21–93.53)	0.340	1.12 (0.04–32.15)	0.948	2.89 (0.92–9.04)	0.069	3.17 (0.79–12.80)	0.105	3.59 (0.50–25.85)	0.204

Sick sinus patterns include pauses caused by postatrial premature contraction block, postventricular premature contraction block, sinus pause, sinus arrest, and sinus exist block. Atrioventricular block pattern is intermediate pauses caused by Mobitz type I atrioventricular block. Combined patterns are intermediate pauses caused by both sick sinus and atrioventricular block patterns. CI indicates confidence interval; DNTP indicates daytime plus nighttime pause; DTP, daytime pause; HR, hazard ratio; NOP, no pause; NTP, nighttime pause.

*HRs were adjusted for patient age, sex, hypertension, diabetes mellitus, coronary artery disease, valvular heart disease, malignancy, and usage of medication.

†$P<0.05$.

pauses solely occurred at nighttime; and (3) in patients with intermediate pauses at daytime, those with sick sinus pattern and high occurrence frequency were at high risk for mortality.

Intermediate Versus Long Pauses on Mortality

Sinus pauses greater than 3 seconds in duration may cause syncope or presyncope, despite some patients only have giddiness or whirling.[1] Current American and European guidelines recommended that permanent cardiac pacing is indicated in patients with pauses ≥3.0 seconds for ventricular activity, either in sinoatrial node dysfunction or abnormality in atrioventricular conduction. However, the current 3-second criterion is an arbitrary clinical observation with a low specificity.[3] Hilgard et al found 47 asymptomatic patients with long (≥3 seconds) pause from 6470 consecutive 24-hour Holter recordings. They reported that no survival benefit was found in these patients receiving pacemaker therapy or not.[9] With this 3-second criteria, Saba et al compared the unpaced long (≥3 seconds) pause patients (n=70) with the no pause (<3 seconds) patients (n=81) and found no difference in survival rate after 2.2 years of follow-up.[10] Similarly, in patients with intermediate (≥2 seconds) pauses, Mazuz et al found no differences in clinical outcomes between paced and unpaced patients.[11] The lack of survival benefit in pacing the long/intermediate pause patients may arise from (1) short observation duration in these studies and (2) AF patients whose criteria for pacing is >5-second pause were not excluded.

In this study excluding patients with AF and followed up to 8 years, we found that intermediate pauses occurring at either daytime or nighttime increased the risk of adverse cardiovascular events, including all/cardiovascular cause of hospitalization, new-onset AF/HF, pacemaker implantation, and TIA. Intermediate pause at daytime was associated with increased mortality rate than that at nighttime. We also found that high pause occurrence frequency was associated with increased mortality rate, suggesting that these intermediate pauses affected patient outcome. To the best of our knowledge, this is the first study to analyze the long-term (>8 years) relationship between intermediate pauses and morbidities. Therefore, intermediate pause occurring at daytime might not be a benign course if patients are followed in a long-term duration. Future studies are warranted to elucidate the clinical significance of this association.

Intermediate Pause at Nighttime Versus Daytime on Cardiovascular Risk

Sinus pauses occurring in the daytime may cause syncope and were considered to be clinically significant. On the other hand, nighttime bradycardia and pause episodes are

Table 7. Frequency of Intermediate Pause on Mortality Rate

	NTP (N=248)			DTP (N=103)			DNTP (N=81)		
	3			3			23		
Median Frequency (times/day)	N	Death	Mortality (%)	N	Death	Mortality (%)	N	Death	Mortality (%)
High frequency	132	10	7.6	52	12	23.1	42	9	21.4
Low frequency	116	13	11.2	51	7	13.7	39	6	15.4
P value within group*	0.325			0.221			0.484		

High frequency is defined as the intermediate pause frequency≥the median number within 1 day. Low frequency is defined as the intermediate pause frequency<the median number within 1 day. DNTP indicates daytime plus nighttime pause; DTP, daytime pause; NTP, nighttime pause.
*The *P* value was obtained by Pearson's chi-square test.

frequently thought to be benign because they did not produce symptoms. In 50 medical students without cardiovascular diseases receiving 24-hour Holter monitoring, Brodsky found that 28% had sinus pause of >1.75 seconds during sleep, but no adverse events or mortality were reported.[12] Similarly, an observational study also showed that up to 4% to 10% of

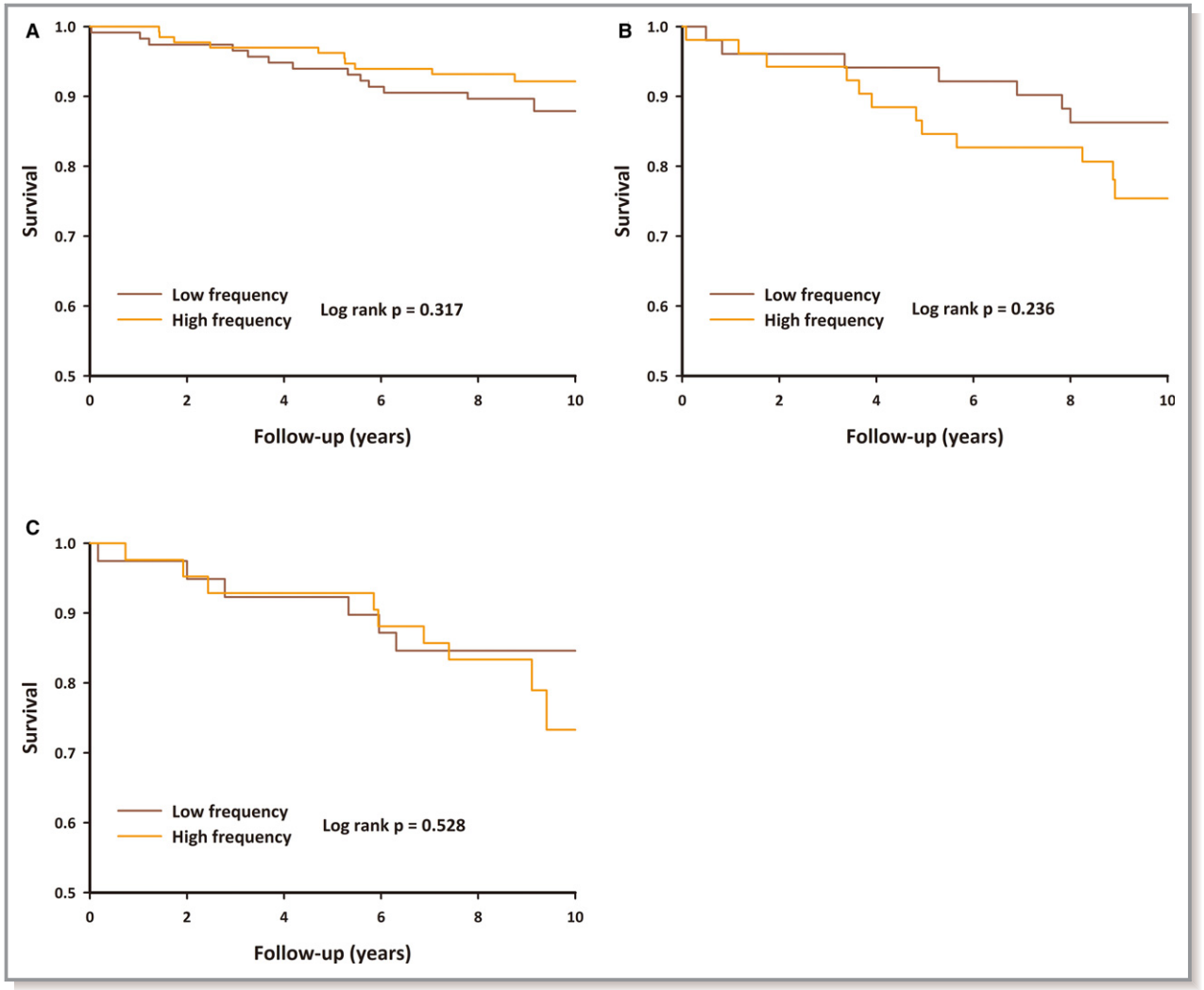

Figure 3. Intermediate pause frequency on mortality rates within the NTP (A, cut-off value is 3 times/day), DTP (B, cut-off value is 3 times/day), and DNTP (C, cut-off value is 23 times/day) groups. *P* values were calculated with the log-rank test in the Kaplan–Meier survival curves. NTP, nighttime pause; DTP, daytime pause; DNTP, daytime plus nighttime pause. The cuff-off value for high vs low frequency was the median values of pause frequency in each group.

Table 8. Frequency of Intermediate Pause on Mortality Rate Between Different Pause Groups

Frequency	DTP vs NTP*		DNTP vs NTP*		DNTP vs DTP*		NTP vs NOP*		DTP vs NOP*		DNTP vs NOP*	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
High frequency	3.42 (1.42–8.28)	0.006†	1.72 (1.08–2.75)	0.023†	0.97 (0.35–2.72)	0.959	1.28 (0.68–2.40)	0.449	2.64 (1.47–4.73)	0.001†	2.35 (1.21–4.59)	0.012†
Low frequency	1.42 (0.55–3.71)	0.469	1.30 (0.77–2.18)	0.323	0.97 (0.30–3.14)	0.959	0.78 (0.45–1.37)	0.386	1.78 (0.84–3.78)	0.134	1.70 (0.75–3.81)	0.202

High frequency is defined as the intermediate pause frequency≥the median number within 1 day. Low frequency is defined as the intermediate pause frequency<the median number within 1 day. CI indicates confidence interval; DNTP indicates daytime plus nighttime pause; DTP, daytime pause; HR, hazard ratio; NOP, no pause; NTP, nighttime pause.

*HRs were adjusted for patient age, sex, hypertension, diabetes mellitus, coronary artery disease, valvular heart disease, malignancy, and usage of medication.

†$P<0.05$.

healthy subjects had sinus pause of ≥2 seconds during sleep without adverse clinical events.[13] These findings suggested that nighttime pause was a benign physiological response because of the suppression of autonomic control during sleep. However, in this study, we found that intermediate pause at nighttime was associated with an increased risk of adverse cardiovascular events, including hospitalization, pacemaker implantation, new-onset AF/HF, and TIA, compared with those without pauses. One possibility for this discrepancy is that most of our enrolled patients are not healthy subjects, having chronic diseases of diabetes mellitus, hypertension, HF, and coronary heart disease. Our data represent a real-world practice results, and most of the patients in clinics did have multiple comorbidities. Further studies are needed to clarify the clinical significance of nighttime intermediate pause.

Intermediate Pauses and New-Onset AF

Sick sinus syndrome is the aging process involving the sinoatrial node and atrial myocardium, leading atrial fibrosis and the development of AF.[14,15] Bradycardia per se might stimulate atrial ectopic beats and enhance greater dispersion of atrial refractoriness, and both are vital factors for initiating AF.[16] An experimental study also found that interrupted electrical connection between the sinoatrial node and pulmonary veins might facilitate burst firing of the pulmonary veins and occurrence of AF.[17] Therefore, up to 50% of sick sinus syndrome patients with long pauses are accompanied by paroxysmal supraventricular tachycardia, and most of them were AF.[18,19] In this study, we observed that patients with only intermediate pauses, either at daytime or nighttime, are associated increased risk of new-onset AF, which is consistent with previous clinical and experimental studies. This finding suggests that patients with intermediate pauses might share similar pathophysiological processes with sick sinus syndrome patients. Early intervention, including medication and catheter ablation to prevent atrial remodeling, might decrease the risk of developing AF, even in patients with intermediate pauses. Further prospective studies are warranted to validate this hypothesis.

Intermediate pause occurring at daytime or nighttime increased the risk of adverse cardiovascular events, and these pauses occurring at daytime, either daytime only or daytime plus nighttime, were correlated to raising mortality rate in this study. Although PPM implantation is not indicated for patients with intermediate pause according to the current guidelines, these patients did have increased risk for future pacemaker implantation observed in this study.[1,5] Intermediate pause might therefore be a subclinical harbinger for future long pauses that warrant pacemaker implantation, especially in those who developed mild symptoms such as dizziness or

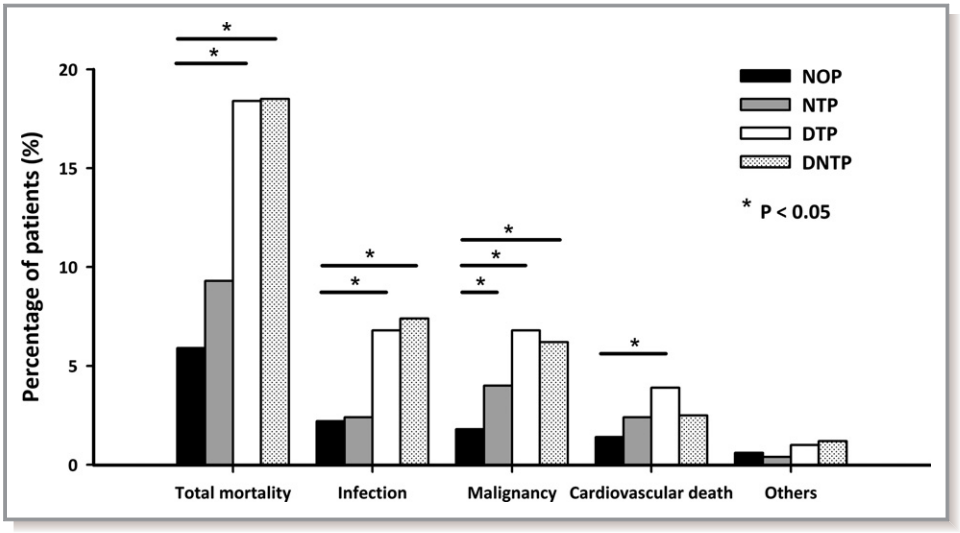

Figure 4. Mortality rate and causes of deaths in the 4 groups of patients. Causes of cardiovascular deaths included myocardial infarction, heart failure, and sudden cardiac death. Other causes of death included gastrointestinal bleeding, stroke, chronic obstructive pulmonary diseases, and uremia. DNTP indicates daytime plus nighttime pause; DTP, daytime pause; NOP, no pause; NTP, nighttime pause.

whirling. In daily clinical practice, physicians should pay more attention to this group of patients and intensively follow them up. An electrophysiology study might be considered to elucidate the uncovered sinus or atrioventricular nodal dysfunction in intermediate pause patients with presyncope or fainting.[20] Clinicians should also be aware of the symptoms of AF and HF, such as palpitations or exercise intolerance in patients with intermediate pauses because they have increased risk of new-onset AF and HF. Keeping an eye on these symptoms and timely administration/adjustment of anticoagulation and HF medication might prevent stroke and HF hospitalization in these patients. Finally, early and adequate treatment for underlying comorbidities might also be helpful to reduce future cardiovascular risk in intermediate pause patients.

Study Limitations

Several limitations exist in this study. First, our study was designed retrospectively with variable follow-up periods among patients. Further prospective studies are still necessary to validate our findings. Second, because of the lack of

Table 9. Causes of Death and Morality Rates in Patients With Intermediate Pauses

	NTP vs NOP	DTP vs NOP	DNTP vs NOP	DTP vs NTP	DNTP vs NTP	DNTP vs DTP
Causes of Death	Percentage (%), *P* Value	Percentage (%), *P* Value	Percentage (%), *P* Value	Percentage (%), *P* Value	Percentage (%), *P* Value	Percentage (%), *P* Value
Infection	2.4 vs 2.2 0.803	6.8 vs 2.2 0.002	7.4 vs 2.2 0.002	6.8 vs 2.4 0.048	7.4 vs 2.4 0.038	7.4 vs 6.8 0.872
Malignancy	4.0 vs 1.8 0.012	6.8 vs 1.8 <0.001	6.2 vs 1.8 0.004	6.8 vs 4.0 0.272	6.2 vs 4.0 0.423	6.2 vs 6.8 0.865
Cardiovascular death	2.4 vs 1.4 0.167	3.9 vs 1.4 0.032	2.5 vs 1.4 0.395	3.9 vs 2. 0.453	2.5 vs 2.4 0.980	2.5 vs 3.9 0.592
Others*	0.4 vs 0.6 0.751	1.0 vs 0.6 0.578	1.2 vs 0.6 0.420	1.0 vs 0.4 0.520	1.2 vs 0.4 0.403	1.2 vs 1.0 0.864
Mortality	9.3 vs 5.9 0.029	18.4 vs 5.9 <0.001	18.5 vs 5.9 <0.001	18.4 vs 9.3 0.016	18.5 vs 9.3 0.024	18.5 vs 18.4 0.990

Cardiovascular death, including myocardial infarction, heart failure, and sudden cardiac death. DNTP indicates daytime plus nighttime pause; DTP, daytime pause; NOP, no pause; NTP, nighttime pause.
*Others, including death of gastrointestinal bleeding, stroke, chronic obstructive pulmonary diseases, and uremia.

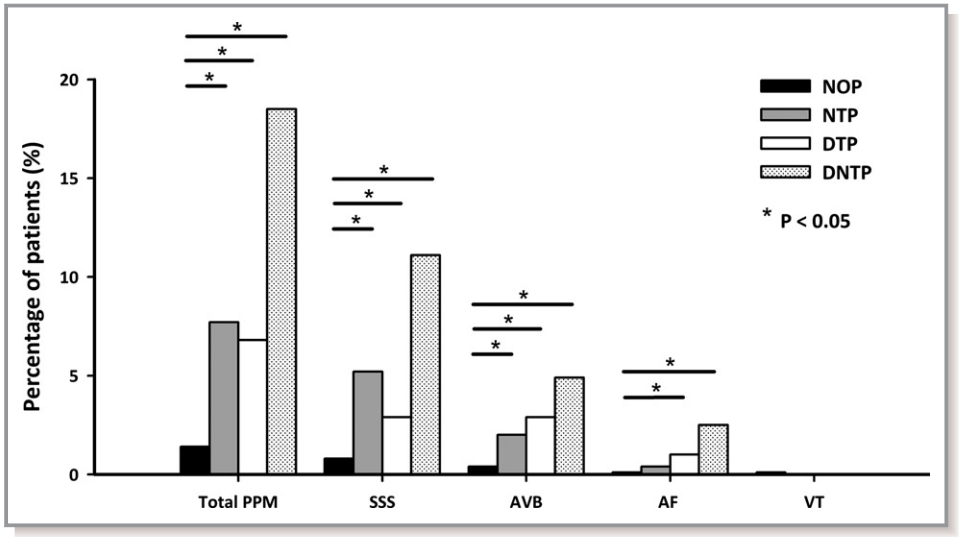

Figure 5. Causes for permanent pacemaker (PPM) implantation in the 4 groups of patients. Sick sinus syndrome (SSS) included long (>3 seconds in duration) sinus pause, tachybradycardia syndrome, and symptomatic sinus bradycardia. AF indicates atrial fibrillation plus atrioventricular nodal ablation and PPM implantation; AVB, high-degree atrioventricular block; DNTP, daytime plus nighttime pause; DTP, daytime pause; NOP, no pause; NTP, nighttime pause; VT, ventricular tachycardia plus implantable cardioverter-defibrillator implantation.

symptoms, patients with intermediate pauses did not routinely receive electrophysiological study. We therefore could not elucidate the causes of intermediate pauses, such as sinus node dysfunction or atrioventricular nodal dysfunction in these patients. Third, medications used might affect the heart rate and pauses. We did not know whether these patients were compliant with the prescribed medication. This factor might also confound our results. Fourth, a 24-hour Holter monitor is a relatively short monitoring period compared with new implantable/wearable loop recorders that can have up to 3 years of continuous rhythm monitoring. Further studies using loop recorders are still needed to verify our findings. Finally, elevated vagal tone during sleep might also contribute to the adverse cardiovascular events in patients with NTP. In this study, we did not record the exact sleep/awake time in the 24-hour monitoring period. We therefore defined the daytime (8:00 AM–8:00 PM) and nighttime (8:00 PM–8:00 AM) regardless patients' sleep/awake status. Previous studies showed that high vagal activity during sleep was associated with elevated heart rate variability, in particular the high-

Table 10. Causes of Pacemaker Implantation in Patients With Intermediate Pauses

Causes of PPM Implantation	NTP vs NOP Percentage (%), *P* Value	DTP vs NOP Percentage (%), *P* Value	DNTP vs NOP Percentage (%), *P* Value	DTP vs NTP Percentage (%), *P* Value	DNTP vs NTP Percentage (%), *P* Value	DNTP vs DTP Percentage (%), *P* Value
Total PPM	7.7 vs 1.4 <0.001	6.8 vs 1.4 <0.001	18.5 vs 1.4 <0.001	6.8 vs 7.7 0.778	18.5 vs 7.7 0.005	18.5 vs 6.8 0.015
SSS	5.2 vs 0.8 <0.001	2.9 vs 0.8 0.018	11.1 vs 0.8 <0.001	2.9 vs 5.2 0.341	11.1 vs 5.2 0.066	11.1 vs 2.9 0.025
AVB	2.0 vs 0.4 <0.001	2.9 vs 0.4 <0.001	4.9 vs 0.4 <0.001	2.9 vs 2.0 0.608	4.9 vs 2.0 0.162	4.9 vs 2.9 0.476
AF	0.4 vs 0.1 0.245	1.0 vs 0.1 0.023	2.5 vs 0.1 <0.001	1.0 vs 0.4 0.520	2.5 vs 0.4 0.089	2.5 vs 1.0 0.426
VT*	0.0 vs 0.1 0.613	0.0 vs 0.1 0.745	0.0 vs 0.1 0.773	0.0 vs 0.0 . . .	0.0 vs 0.0 . . .	0.0 vs 0.0 . . .

AF indicates atrial fibrillation plus atrioventricular nodal ablation; AVB, (high degree) atrioventricular block; DNTP, daytime plus nighttime pause; DTP, daytime pause; NOP, no pause; NTP, nighttime pause; PPM, permanent pacemaker; SSS, sick sinus syndrome, including long pause, tachybradycardia syndrome, and sinus bradycardia.
*VT: ventricular tachycardia plus implantable cardioverter-defibrillator (ICD) implantation.

frequency power of the spectral analysis.[21] Further studies are needed to elucidate how vagal tone reflected by heart rate variability parameters contributes to the cardiovascular risk in patients with NTP.

Conclusion

In patients with intermediate pauses, adverse cardiovascular risk is increased compared with those without intermediate pauses. Patients with intermediate pauses occurring at daytime are associated with a higher mortality rate than that occurring exclusively at nighttime during long-term follow-up.

Sources of Funding

This study was supported by NSC grants 100-2314-B-075-046-MY3, 101-2314-B-010-057-MY3, and 101-2314-B-075-056-MY3 and Taipei Veterans General Hospital grants V102C-054, V102E7-002, V103E7-001, V103C-095, and VGHUST102-G1-1-1.

Disclosures

None.

References

1. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, Cleland J, Deharo JC, Delgado V, Elliott PM, Gorenek B, Israel CW, Leclercq C, Linde C, Mont L, Padeletti L, Sutton R, Vardas PE, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Kirchhof P, Blomstrom-Lundqvist C, Badano LP, Aliyev F, Bansch D, Baumgartner H, Bsata W, Buser P, Charron P, Daubert JC, Dobreanu D, Faerestrand S, Hasdai D, Hoes AW, Le Heuzey JY, Mavrakis H, McDonagh T, Merino JL, Nawar MM, Nielsen JC, Pieske B, Poposka L, Ruschitzka F, Tendera M, Van Gelder IC, Wilson CM. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Eur Heart J*. 2013;34:2281–2329.
2. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA III, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Buller CE, Creager MA, Ettinger SM, Faxon DP, Halperin JL, Hiratzka LF, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura RA, Ornato JP, Page RL, Riegel B, Tarkington LG, Yancy CW. ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2008;51:e1–e62.
3. Ector H, Rolies L, De Geest H. Dynamic electrocardiography and ventricular pauses of 3 seconds and more: etiology and therapeutic implications. *Pacing Clin Electrophysiol*. 1983;6:548–551.
4. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2014;130:e199–e267.
5. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA III, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO, Tracy CM, Epstein AE, Darbar D, DiMarco JP, Dunbar SB, Estes NA III, Ferguson TB Jr, Hammill SC, Karasik PE, Link MS, Marine JE, Schoenfeld MH, Shanker AJ, Silka MJ, Stevenson LW, Stevenson WG, Varosy PD. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2013;61:e6–e75.
6. Breivik K, Ohm OJ, Segadal L. Sick sinus syndrome treated with permanent pacemaker in 109 patients. A follow-up study. *Acta Med Scand*. 1979;206:153–159.
7. Rasmussen K. Chronic sinus node disease: natural course and indications for pacing. *Eur Heart J*. 1981;2:455–459.
8. Lin CY, Chang SL, Lin YJ, Lo LW, Chung FP, Chen YY, Chao TF, Hu YF, Tuan TC, Liao JN, Huang YC, Chang Y, Chiou CW, Chen SA. Long-term outcome of multiform premature ventricular complexes in structurally normal heart. *Int J Cardiol*. 2015;180:80–85.
9. Hilgard J, Ezri MD, Denes P. Significance of ventricular pauses of three seconds or more detected on twenty-four-hour Holter recordings. *Am J Cardiol*. 1985;55:1005–1008.
10. Saba MM, Donahue TP, Panotopoulos PT, Ibrahim SS, Abi-Samra FM. Long-term mortality in patients with pauses in ventricular electrical activity. *Pacing Clin Electrophysiol*. 2005;28:1203–1207.
11. Mazuz M, Friedman HS. Significance of prolonged electrocardiographic pauses in sinoatrial disease: sick sinus syndrome. *Am J Cardiol*. 1983;52:485–489.
12. Brodsky M, Wu D, Denes P, Kanakis C, Rosen KM. Arrhythmias documented by 24 hour continuous electrocardiographic monitoring in 50 male medical students without apparent heart disease. *Am J Cardiol*. 1977;39:390–395.
13. Gula LJ, Krahn AD, Skanes AC, Yee R, Klein GJ. Clinical relevance of arrhythmias during sleep: guidance for clinicians. *Heart*. 2004;90:347–352.
14. Monfredi O, Boyett MR. Sick sinus syndrome and atrial fibrillation in older persons—a view from the sinoatrial nodal myocyte. *J Mol Cell Cardiol*. 2015;83:88–100.
15. Alings AM, Abbas RF, Bouman LN. Age-related changes in structure and relative collagen content of the human and feline sinoatrial node. A comparative study. *Eur Heart J*. 1995;16:1655–1667.
16. Amasyali B, Kilic A, Kilit C. Sinus node dysfunction and atrial fibrillation: which one dominates? *Int J Cardiol*. 2014;175:379–380.
17. Chen YC, Lu YY, Cheng CC, Lin YK, Chen SA, Chen YJ. Sinoatrial node electrical activity modulates pulmonary vein arrhythmogenesis. *Int J Cardiol*. 2014;173:447–452.
18. Hocini M, Sanders P, Deisenhofer I, Jais P, Hsu LF, Scavee C, Weerasoriya R, Raybaud F, Macle L, Shah DC, Garrigue S, Le Metayer P, Clementy J, Haissaguerre M. Reverse remodeling of sinus node function after catheter ablation of atrial fibrillation in patients with prolonged sinus pauses. *Circulation*. 2003;108:1172–1175.
19. Lamas GA, Lee KL, Sweeney MO, Silverman R, Leon A, Yee R, Marinchak RA, Flaker G, Schron E, Orav EJ, Hellkamp AS, Greer S, McAnulty J, Ellenbogen K, Ehlert F, Freedman RA, Estes NA III, Greenspon A, Goldman L. Ventricular pacing or dual-chamber pacing for sinus-node dysfunction. *N Engl J Med*. 2002;346:1854–1862.
20. ACC/AHA Task Force Report. Guidelines for Clinical Intracardiac Electrophysiological and Catheter Ablation Procedures. A report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee on Clinical Intracardiac Electrophysiologic and Catheter Ablation Procedures). Developed in collaboration with the North American Society of Pacing and Electrophysiology. *J Cardiovasc Electrophysiol*. 1995;6:652–679.
21. Verrier RL, Josephson ME. Cardiac arrhythmogenesis during sleep: mechanisms, diagnosis, and therapy a2. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. 6th ed. Philadelphia, PA: Elsevier Saunders; 2017:1237–1242.e1234.