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

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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. 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. However, the current 3-second criterion is an arbitrary clinical observation with a low specificity. Most patients with intermediate pauses (2–3 seconds in duration) are asymptomatic and not candidates for pacemaker implantation by current practical guidelines. However, some patients with intermediate pauses (ie, sinus pause of 2–3 seconds in...
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.

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 duration) did develop syncope that eventually leads to pacemaker implantation.\textsuperscript{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 autonomous 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.
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,
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, \(P<0.001\), respectively.

| 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 |
| **Beta-blocker** | 895 (18.4) | 38 (15.3) | 8 (7.8) | 15 (18.5) | 0.028 |
| **Diabetes mellitus** | 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.
Table 2. Cardiovascular Event Rates in Patients With Intermediate Pauses

|                | NOP (N=485) | NTP (N=248) | DNTP (N=103) | DTP (N=81) |
|----------------|-------------|-------------|--------------|------------|
| All-cause mortality, n (%) | 2756 (56.7) | 171 (36.0)  | 61 (59.3)    | 73 (90.1)  |
| Cardiovascular mortality, n (%) | 194 (19.8)  | 120 (42.0)  | 53 (51.5)    | 57 (70.4)  |
| PPM implantation, n (%) | 77 (16.2)   | 48 (18.6)   | 23 (22.1)    | 27 (33.3)  |
| TIA, n (%) | 39 (8.1)     | 20 (7.7)    | 12 (11.6)    | 10 (12.3)  |
| Ischemic stroke, n (%) | 43 (9.2)     | 27 (10.9)   | 11 (10.7)    | 9 (11.1)   |
| New-onset HF, n (%) | 43 (9.2)     | 27 (10.9)   | 11 (10.7)    | 9 (11.1)   |
| New-onset AF, n (%) | 329 (6.8)    | 14 (5.3)    | 11 (10.7)    | 19 (23.5)  |
| Cardiac arrest, n (%) | 97 (20.1)    | 9 (3.6)     | 4 (3.9)      | 8 (10.0)   |
| Hazard ratio (95% CI) | 1.00 (0.77--1.67) | 1.13 (0.83--1.52) | 1.22 (0.91--1.64) | 1.20 (0.94--1.53) |

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.

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 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=0.979) 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.
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.
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Table 3. Cardiovascular Event Rate in Patients With Intermediate Pauses

| Cardiovascular Event                  | DNTP vs NOP* | DNTP vs DTP* |
|---------------------------------------|--------------|--------------|
| All-cause hospitalization             | 1.47 (1.14–1.90) (HR, 1.72; *P*=0.006) | 1.20 (0.84–1.70) (HR, 1.34; *P*=0.007) |
| Cardiovascular-cause hospitalization  | 2.15 (1.53–3.02) (HR, 2.60; *P*=0.001) | 1.27 (0.77–2.10) (HR, 1.66; *P*=0.006) |
| PPM implantation                      | 10.92 (6.14–19.41) (HR, 2.64; *P*=0.001) | 2.64 (1.04–6.71) (HR, 1.23; *P*=0.001) |
| New-onset AF                          | 2.72 (1.66–4.45) (HR, 3.42; *P*=0.001) | 1.08 (0.54–2.14) (HR, 2.35; *P*=0.018) |
| New-onset HF                          | 1.70 (1.06–2.74) (HR, 2.57; *P*=0.001) | 1.34 (0.70–2.57) (HR, 1.12; *P*=0.001) |
| TIA                                   | 2.98 (1.93–6.60) (HR, 2.60; *P*=0.001) | 1.07 (0.43–2.64) (HR, 1.07; *P*=0.001) |
| Ischemic stroke                       | 1.12 (0.58–2.17) (HR, 1.04; *P*=0.001) | 0.743 (0.43–1.34) (HR, 1.04; *P*=0.001) |
| Mortality                             | 2.04 (1.21–3.44) (HR, 2.14; *P*=0.001) | 1.04 (0.50–2.17) (HR, 1.04; *P*=0.001) |

*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 NOP 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

| Kaplan–Meier Curve      | NTP vs NOP Log-Rank *P* Value | DTP vs NOP Log-Rank *P* Value | DNTP vs NOP Log-Rank *P* Value | DTP vs NTP Log-Rank *P* Value | DNTP vs NTP Log-Rank *P* Value | DNTP vs DTP 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                         | 0.010                         | <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                         | 0.922                         | 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.
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

Table 5. Patterns of Intermediate Pause on Mortality Rate

| Pause Patterns       | NTP (N=248) | DTP (N=103) | DNTP (N=81) |
|----------------------|-------------|-------------|-------------|
|                      | 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.

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.
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 who received pacemaker therapy may not have the same outcomes as those who were not followed in the same manner.

In this study excluding patients with AF and followed up to 8 years, we found that high pause occurrence frequency was associated with increased mortality rate at nighttime. Therefore, intermediate pause occurring at daytime or nighttime increased the risk of adverse cardiovascular events, including all-cause mortality, hospitalization, new-onset AF, pacemaker implantation, and IAH. Intermediate pause at nighttime was associated with increased mortality rate, suggesting that these intermediate pauses may affect patient outcome. The current study is the first study to analyze the long-term (≥8 years) relationship between intermediate pauses and mortality. Table 6 shows the patterns of intermediate pause on mortality rate between different pause groups.

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

| Pause Pattern         | DTP vs NTP* | P Value | DNTP vs NTP* | P Value | DNTP vs DTP* | P Value | NTP vs NOP* | P Value | DTP vs NOP* | P Value | DNTP vs NOP* | 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; DTP indicates daytime pause; DNTP, daytime plus nighttime 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.
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. Similarly, an observational study also showed that up to 4% to 10% of

| Table 7. Frequency of Intermediate Pause on Mortality Rate |
|----------------------------------------------------------|
| Median Frequency (times/day)                              |
|                                          | NTP (N=248) | DTP (N=103) | DNTP (N=81) |
|                                          | 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.

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 cut-off value for high vs low frequency was the median values of pause frequency in each group.
healthy subjects had sinus pause of ≥2 seconds during sleep without adverse clinical events. 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.

Intermediate Pauses and New-Onset AF

Sick sinus syndrome is the aging process involving the sinus node and atrial myocardium, leading atrial fibrosis and the development of AF. Bradycardia per se might stimulate atrial ectopic beats and enhance greater dispersion of atrial refractoriness, and both are vital factors for initiating AF. An experimental study also found that interrupted electrical connection between the sinus node and pulmonary veins might facilitate burst firing of the pulmonary veins and occurrence of AF. Therefore, up to 50% of sick sinus syndrome patients with long pauses are accompanied by paroxysmal atrial fibrillation, and most of them were AF. In this study, we observed that patients with intermediate pauses might have similar pathophysiological processes with sick sinus syndrome. Early intervention, including medication and catheter ablation, to prevent atrial remodeling might decrease the risk of developing AF.

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     |
| 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; DTP, daytime pause; DNTP, daytime plus nighttime 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.
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. 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**

| Causes of Death          | NTP vs NOP | DTP vs NOP | DNTP vs NOP | DTP vs NTP | DNTP vs NTP | DNTP vs DTP |
|--------------------------|------------|------------|-------------|------------|-------------|-------------|
|                          | Percentage (%) | Percentage (%) | Percentage (%) | Percentage (%) | Percentage (%) | Percentage (%) |
|                          | P Value     | P Value     | P Value     | P Value     | P Value     | P Value     |
| Infection                | 2.4 vs 2.2  | 6.8 vs 2.2  | 7.4 vs 2.2  | 6.8 vs 2.4  | 7.4 vs 2.4  | 7.4 vs 6.8  |
|                          | 0.803       | 0.002       | 0.002       | 0.048       | 0.038       | 0.872       |
| Malignancy               | 4.0 vs 1.8  | 6.8 vs 1.8  | 6.2 vs 1.8  | 6.8 vs 4.0  | 6.2 vs 4.0  | 6.2 vs 6.8  |
|                          | 0.012       | <0.001      | 0.004       | 0.272       | 0.423       | 0.865       |
| Cardiovascular death     | 2.4 vs 1.4  | 3.9 vs 1.4  | 2.5 vs 1.4  | 3.9 vs 2.0  | 2.5 vs 2.4  | 2.5 vs 3.9  |
|                          | 0.167       | 0.032       | 0.395       | 0.453       | 0.980       | 0.592       |
| Others*                  | 0.4 vs 0.6  | 1.0 vs 0.6  | 1.2 vs 0.6  | 1.0 vs 0.4  | 1.2 vs 0.4  | 1.2 vs 1.0  |
|                          | 0.751       | 0.578       | 0.420       | 0.520       | 0.403       | 0.864       |
| Mortality                | 9.3 vs 5.9  | 18.4 vs 5.9 | 18.5 vs 5.9 | 18.4 vs 9.3 | 18.5 vs 9.3 | 18.5 vs 18.4|
|                          | 0.029       | <0.001      | <0.001      | 0.016       | 0.024       | 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.
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-

![Figure 5](image)

**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.

### 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 0.016                    | 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.

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Disclosures

None.

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