Variation in heart rate range by 24-h Holter monitoring predicts heart failure in patients with atrial fibrillation

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Abstract

Aims The analysis of heart rate (HR) changes, such as the HR variability or HR turbulence, has been reported as a marker of cardiovascular events during sinus rhythm; however, those relationships during atrial fibrillation (AF) remain controversial, and those parameters are not commonly used in AF patients. We sought to investigate the relationship between a simple index focused on the HR and heart failure (HF) events in patients with permanent AF.

Methods and results We enrolled 198 patients with permanent AF and evaluated the HR range, defined as the maximum HR minus the minimum HR on 24-h Holter electrocardiogram recordings. The patients were divided into two groups, i.e., the larger (n = 101) and smaller (n = 97) HR range (HRR) groups, determined by the median value. The HF events were defined as hospitalizations for HF or urgent hospital visits due to exacerbations of one’s HF status. The observation period of this study was set at 5 years from registration. The median age was 73 (68–77) years, and 29% were female. The median HRR was 84 (63–118) beats per minutes (bpm). During the observational period of 1825 days (median), HF events occurred in 37 (0.047 per patient-year) patients. In a log-rank test, the larger HRR group had more frequent HF events than the smaller HRR group (P = 0.0078). In the adjusted Cox proportional hazards model using the significantly different factors from the univariate analysis (Model 1) and factors and medications associated with HF (Model 2), the larger HRR group had a higher prevalence of HF events than the smaller HRR group for both models [Model 1, adjusted hazard ratio = 3.21, 95% confidence interval (CI) 1.593–6.708, P = 0.0009; Model 2, adjusted hazard ratio = 3.12, 95% CI 1.522–6.685, P = 0.002]. When analysed using the time-dependent Cox proportional hazards model, the HRR was associated with HF with a statistically significant difference in both the univariate and multivariate analyses [hazard ratio = 1.01, 95% CI 1.006–1.020, P < 0.0001; Model 1, adjusted hazard ratio = 1.02, 95% CI 1.011–1.027, P < 0.0001; Model 2, adjusted hazard ratio = 1.01, 95% CI 1.008–1.021, P = 0.0003]. There was no significant difference in the chronotropic medications between the two groups.

Conclusions In patients with permanent AF, a larger HRR was associated with HF events.

Keywords Heart failure; Atrial fibrillation; Heart rate range; 24-h Holter electrocardiogram

Introduction

Atrial fibrillation (AF) is a common arrhythmia in clinical practice, and the prevalence of AF increases with age.1 2 AF is also associated with cardiovascular events such as cerebral infarctions, myocardial infarctions,3–7 heart failure (HF),8 and death.9 The heart rate (HR) variability and turbulence using 24-h Holter electrocardiograms (ECGs) are useful for predicting cardiovascular events in sinus rhythm.10 11 However, because the relationship between those evaluations...
and cardiovascular events in AF rhythm remains controversial, those parameters are not commonly used in AF patients. In this study, we investigated the relationship between HF events and a simple index focused on the HR using the 24-h Holter ECG in AF patients.

**Methods**

**Study population**

This study was a single-centre, nonrandomized, observational study. We retrieved the patient data between 2012 and 2014 from the Cardiovascular Secondary Prevention Center of Kitasato University. In this centre, patients with a history of HF, valvular heart disease, ischaemic heart disease, cardiomyopathy, or arrhythmias were registered and underwent an annual check-up that included a 12-lead ECG, 24-h Holter ECG, laboratory tests, chest X-ray, and echocardiogram. The study included patients that were able to visit the hospital by themselves to undergo the examinations and did not include those who were bedridden or had difficulty walking. The study was conducted with the approval of the ethics committee of Kitasato University Hospital.

**Definition of permanent atrial fibrillation and the calculation of the heart rate range**

Permanent AF was defined when all 12-lead ECGs and 24-h Holter ECGs (FUKUDA SCM 6000) showed AF rhythm. At least more than two 24-h Holter ECGs were recorded, and those examination intervals had surpassed at least 1 year. The patients in whom sinus rhythm was detected by regular ECG check-ups at general practice facilities during the same period were excluded. The data for the HR analysis from the first 24-h Holter ECG recording were used at the time of incorporation. A variation in the HR range was defined as the maximum HR minus the minimum HR on the 24-h Holter ECG recordings. Based on the median HR range in all patients, the patients were divided into larger HR range (HRR) and smaller HRR groups (Figure 1).

**Clinical outcome**

The primary outcome of interest was the first occurrence of HF. HF events were defined as hospitalizations for HF or urgent hospital visits requiring intravenous or oral diuretic therapy due to an exacerbation of the HF status. The observation period in this study was set at 5 years from registration.

**Statistical analysis**

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) and JMP 13 (SAS Institute, Cary, NC, USA) software. Continuous variables were compared by the Mann–Whitney U test or Welch’s t-test, as applicable. Data are presented as medians with interquartile ranges or as averages ± standard deviations. Dichotomous variables are presented as percentages and were compared using the χ² or Fisher’s exact test. The changes in the hazard ratio for the HF events across the HRR values were investigated by a fitting spline curve. The trend in the HR range and mean HR among the groups were tested using the Jonckheere–Terpstra test for continuous variables. The survival distribution in each group was calculated using the Kaplan–Meier method. A log-rank test was used to compare the prevalence of HF between the two groups during the observation period. A Cox proportional hazards model was used to compare the outcomes between the two groups, followed by a multivariate analysis to adjust for the significantly different factors in the univariate analysis (Model 1) and adjust for the factors and medications associated with HF (Model 2). Furthermore, we also performed univariate and multivariate Cox regression analyses because the HRR was a time-varying variable for the sensitivity analysis. The factors that significantly differed among the continuous variables were divided by the median and were calculated as dichotomous variables. All tests were two-tailed, and a P value of <0.05 was considered statistically significant.

**Results**

**Patient characteristics**

A total of 2366 patients were registered during the study period. The following patients were excluded: (1) those without AF (n = 1939), (2) those diagnosed with paroxysmal AF (n = 196), (3) those that did not undergo 24-h Holter ECG monitoring (n = 24), and (4) those that underwent an implantation of a cardiac implantable electronic device (n = 9). After that, 198 patients were finally enrolled in this study and were divided into the larger (n = 101) and smaller HRR (n = 97) groups (Figure 1).

Table 1 shows the clinical background and characteristics of all the patients. The median age was 73 (68–77) years, and 29% were female. The mean heart rate was 74 (68–81) bpm, and the HR range was 85 (63–118) bpm. Ten patients had non-ischaemic heart disease, 8 hypertrophic cardiomyopathy, and 2 dilated cardiomyopathy. The median LVEF was 63.0%, and the median BNP level was 128 pg/mL. More than 80% of the patients received oral anticoagulant (OAC)
therapy, with either a direct OAC or warfarin (12% and 78%, respectively).

**Comparison of the patient characteristics between the smaller HRR and larger HRR groups**

*Table 1* lists the patient characteristics and clinical manifestations in the larger and smaller HRR groups. The larger HRR group was younger and had a higher mean HR, higher haemoglobin, lower CHA2DS2-VASc score, and smaller left ventricular diastolic diameter than the smaller HRR group. The larger HRR group had a lower prevalence of strokes than the smaller HRR group. The two groups did not have any significant differences in the use of chronotropic medications such as beta-blockers, digoxin, and non-dihydropyridine calcium channel blockers.

*Figure 2A* shows the trend in the HR range during the observation period. At the start of the year, the mean HR range was $116 \pm 23$ bpm in the larger HRR group and $62 \pm 14$ bpm in...
the smaller HRR group. The mean HR range in the larger HRR group gradually decreased every year [100, 91, 87, and 86 bpm, respectively (P < 0.0001)]. Similarly, the mean HR range in the smaller HRR group also gradually decreased every year [74, 76, 68, and 68 bpm, respectively (P = 0.04 for trend)]. Notably, the mean HR range in the larger HRR group was consistently above the median and that in the smaller HRR group was below the median for all years. As shown in Figure 2B, the mean HR in both groups ranged from 65 to 80 bpm during the observation period, and there were no significant differences in the mean HR trend. No significant change was observed in the change in the dose of the rate-controlling drugs (β blockers, digoxin, and non-dihydropyridine calcium channel blockers) during the observational period (Supporting information, Figure S1).

### Clinical outcome

During the 1825 (1080–2370) day observational period, 26 HF events (0.068 per patient-year) occurred in the larger HRR group and 11 (0.027 per patient-year) in the smaller HRR group. Figure 3 shows the relationship between the HRR range and hazard ratio for the HF events using a fitting spline curve and exhibits an approximately linear relationship. Figure 4 shows the Kaplan–Meier curve of the prevalence

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Table 1 Univariate analysis of smaller HRR group and larger HRR group

| Clinical characteristics of patients | Total (n = 198) | Larger HRR (n = 101) | Smaller HRR (n = 97) | P value |
|--------------------------------------|---------------|---------------------|---------------------|---------|
| Age (years)                          | 73 (68–77)    | 71 (66–76)          | 75 (69–80)          | 0.0012* |
| Female, n (%)                        | 57 (29)       | 26 (26)             | 31 (32)             | 0.33    |
| Systolic BP (mmHg)                   | 127 (116–138) | 125 (118–134)       | 128 (114–140)       | 0.62    |
| Diastolic BP (mmHg)                  | 76 (68–85)    | 79 (69–87)          | 75 (67–81)          | 0.16    |
| History of hospitalization of HF, n (%) | 26 (13)    | 12 (12)             | 14 (15)             | 0.56    |
| Ischaemic heart disease, n (%)       | 42 (21)       | 17 (17)             | 25 (26)             | 0.12    |
| Non-ischaemic cardiomyopathy, n (%)  | 10 (5)        | 4 (4)               | 6 (6)               | 0.47    |
| Hypertension, n (%)                  | 128 (65)      | 61 (60)             | 67 (69)             | 0.20    |
| Dyslipidaemia, n (%)                 | 115 (58)      | 61 (60)             | 54 (56)             | 0.50    |
| DM, n (%)                            | 39 (20)       | 19 (19)             | 20 (21)             | 0.75    |
| Chronic kidney disease, n (%)        | 115 (58)      | 57 (56)             | 58 (60)             | 0.63    |
| Stroke/TIA, n (%)                    | 4 (2)         | 0 (0)               | 4 (4)               | 0.04*   |
| CHA2DS2-VASc score (points)          | 3 (2–4)       | 2 (2–3)             | 3 (2–4)             | 0.002*  |

Heart rate parameters (24-h Holter ECG)

| Mean HR (bpm)                        | 74 (66–81)    | 78 (71–84)          | 68 (62–76)          | <0.0001* |
| HR range (bpm)                       | 85 (63–118)   | 116 (98–137)        | 62 (51–73)          | <0.0001* |

Laboratory data

| Haemoglobin (g/dL)                   | 14.1 (12.9–15.1) | 14.4 (13.3–15.4) | 14.0 (12.1–14.6) | 0.003* |
| Total Bil (mg/dL)                    | 0.8 (0.6–1.0)    | 0.9 (0.7–1.0)     | 0.8 (0.6–1.0)     | 0.14   |
| AST                                  | 26 (22–32)       | 26 (22–33)        | 26 (22–33)        | 0.87   |
| ALT                                  | 23 (17–29)       | 23 (18–28)        | 23 (16–32)        | 0.79   |
| eGFR                                 | 57.9 (48.5–69.9) | 58.0 (49.2–69.9)  | 57.7 (48.2–69.9)  | 0.79   |
| LDL-C                                | 102 (84–123)     | 103 (88–125)      | 98 (79–118)       | 0.13   |
| HbA1c                                | 5.9 (5.6–6.2)    | 5.9 (5.5–6.2)     | 5.9 (5.6–6.3)     | 0.68   |
| BNP (pg/mL)                          | 128 (79–233)     | 125 (78–218)      | 135 (79–256)      | 0.30   |

Echocardiogram

| LAD (mm)                             | 49.0 (44.0–56.0) | 48.0 (43.5–55.0) | 51.0 (45.0–56.0) | 0.09   |
| LVDD (mm)                            | 49.5 (46.0–53.0) | 48 (44–52)       | 50 (46–53)       | 0.01*  |
| LVDs (mm)                            | 33.0 (29.0–37.0) | 33 (29–36)       | 34 (29–37)       | 0.16   |
| LVEF (%)                             | 63.0 (60.0–66.0) | 62.0 (60.0–66.0) | 63.0 (60.0–65.0) | 0.64   |
| MR (grade)                           | 2 (1–2)          | 2 (1–3)          | 2 (1–2)          | 0.18   |
| TR (grade)                           | 2 (1–3)          | 2 (1–2)          | 2 (2–3)          | 0.12   |

Medication

| β-blocker, n (%)                     | 104 (53)        | 51 (51)          | 53 (55)          | 0.56   |
| ACEI/ARB, n (%)                      | 136 (69)        | 67 (66)          | 69 (71)          | 0.47   |
| MRA, n (%)                           | 33 (17)         | 12 (12)          | 21 (22)          | 0.07   |
| Digoxin, n (%)                       | 84 (42)         | 41 (41)          | 43 (44)          | 0.59   |
| Statin, n (%)                        | 81 (41)         | 43 (43)          | 38 (39)          | 0.63   |
| Drugs for treating DM, (%)           | 30 (15)         | 14 (14)          | 16 (17)          | 0.58   |
| Non-dihydropyridine CCB, n (%)       | 19 (10)         | 9 (9)            | 10 (10)          | 0.72   |
| OAC, n (%)                           | 173 (87)        | 92 (91)          | 81 (84)          | 0.11   |

ACEI, angiotensin-converting enzyme inhibitor; ADP, angiotensin II receptor blocker; BP, blood pressure; CCB, calcium channel blocker; DM, diabetes mellitus; HF, heart failure; HR, heart rate; LAD, left atrium diameter; LVDD, left ventricular diastolic diameter; LVDs, left ventricular systolic diameter; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MRA, mineral corticoid receptor antagonist; OAC, oral anticoagulants; TR, tricuspid valve regurgitation.

Data given as n (%) or median (IQR), non-ischaemic heart disease (hypertrophic cardiomyopathy and dilated cardiomyopathy).

Statistically significant difference.
of HF in both groups. The larger HRR group had significantly more HF events than the smaller HRR group ($P = 0.0078$ for the log-rank test). In the Cox proportional hazard model, the number of HF events was 2.5 times higher in the larger HRR group than smaller HRR group, and in terms of the components of the HF, the larger HRR group had more events than the smaller HRR group (Table 2). As shown in Tables 3 and 4, the adjusted hazard model showed that the prevalence of HF events was higher in the larger HRR group than in the smaller HRR group [Model 1, adjusted hazard ratio = 3.21, 95% confidence interval (CI) 1.593–6.708, $P = 0.0009$; Model 2; adjusted hazard ratio = 3.12, 95% CI 1.522–6.685, $P = 0.002$] (Tables S1 and S2). Furthermore, as a sensitivity analysis, the analysis was performed using a time-dependent Cox proportional hazards model. In the univariate analysis, there was a statistically significant difference between the increase in the HRR and HF events (hazard ratio = 1.01, 95%CI 1.006–1.020, $P = 0.0002$). In the multivariate analysis, the HRR was associated with HF events as an independent factor when analysed using the factors mentioned earlier (Model 1, adjusted hazard ratio = 1.02, 95% CI 1.011–1.027, $P < 0.0001$; Model 2, adjusted hazard ratio = 1.01, 95% CI 1.008–1.021, $P = 0.0003$) (Tables S3 and S4).
Discussion

In the present study, we focused on the variation in the HR range in patients with permanent AF. Within 5 years of observation, the prevalence of HF events was 2.5 times higher in the larger HRR group than in the smaller HRR group. Furthermore, after adjusting for the significant factors in the univariate analysis and using factors and medications associated with HF, the prevalence of HF events was 3.21 and 3.12 times higher in the larger HRR group than in the smaller HRR group.

**Figure 3** Relationship between the HRR and HF events. Changes in the hazard ratio for HF events across the HRR values by fitting a spline curve showed an approximately linear relationship, at least not a J or U curve. It had been shown that as the HRR increases, HF events increase. HF, heart failure; HRR, heart rate range.

**Figure 4** Kaplan–Meier curve of the heart failure events. The larger HRR group had a higher prevalence of HF events than the smaller HRR group. HF, heart failure; HRR, heart rate range.

**Relationship between heart rate range and heart failure in atrial fibrillation patients**

During sinus rhythm, patients with larger HR variability had a better prognosis than those with smaller HR variability. However, it still remains controversial whether this relationship can apply to AF patients. Several reports have demonstrated that a higher prevalence of cardiovascular events is observed in AF patients with a small HR variability than in those with a large HR variability. On the other hand, Maisel and Stevenson reported that an irregular ventricular response during AF leads to cardiovascular events, including HF. In the present study, we focused on the HRR, defined as the HR range, rather than the beat-to-beat variability, and revealed that patients with a larger HR range had a higher prevalence of HF events. A possible mechanism for those results was that the patients in the larger HRR group might have a more irregular ventricular response than those in the smaller HRR group, resulting in a disturbance in the haemodynamics.

**Relationship between the heart rate and heart failure**

Several studies have investigated the relationship between the HR and HF. McAlister et al. reported that every 5-bpm HR reduction by beta-blocker treatment in patients with sinus rhythm led to an 18% reduction in the risk of death. In contrast, there is little evidence about this relationship in AF patients. Kotecha et al. and the Swedish registry demonstrated that a therapeutic reduction in the HR did not reduce the incidence of death or HF hospitalizations in AF patients with a reduced ejection fraction. Furthermore,
Cullington et al. reported that a low HR paradoxically increased the cardiovascular events in AF patients.

On the other hand, focusing on the increased HR, the cardiac output increases as the HR increases in general; however, a shorter diastolic filling time due to increasingly the HR reduces the stroke volume resulting in a reduction in the cardiac output. Kerr et al. reported that in patients with AF, the degree of the beat-to-beat variation in the stroke volume is augmented, and the stroke volume decreases when the ventricular rate increases over 120 bpm. Taking this evidence into account, it would be possible that the larger HRR group had those two adverse factors, that is, much higher and much lower HRSs, than the smaller HRR group, resulting in a higher prevalence of HF events in the present study. Moreover, as shown in Figure 2A, the larger HRR group trended towards a decrease. The reason is unclear; however, there is a possible hypothesis. It has been reported that in the early stage of AF, the autonomic nervous system tends to cause tachycardia, but afterwards, the HR decreases over time. The larger HRR group in the present study might have included more patients with permanent AF in the relatively early stage.

**Clinical implications**

This study suggested that we can assess the risk stratification of HF by focusing on the 24-h Holter ECG. The HRR is a useful index that can be obtained by a simple calculation. Patients with a large HR range have a higher risk of HF, so careful observation is needed. Regarding the medications, the two groups had no significant differences in the prescription rates of beta-blockers and digoxin as rate control medications. Based on the results, beta-blockers or digoxin might not improve the HR range and HF prevention. Further studies are necessary to clarify the optimal approach in those patients.

**Limitations**

Our investigation had several limitations. First, this study was an observational and a single-centre study with a limited number of patients; therefore, this research may have been influenced by biases and confounding factors. Second, because the definition of permanent AF was based on only 24-h Holter ECGs, patients with high-frequency paroxysmal AF might have been included. Third, because this study was a retrospective, observational study, it might have been influenced by biases and confounding factors. Second, because the definition of permanent AF was based on only annual 24-h Holter ECGs, patients with high-frequency paroxysmal AF might have been included. Third, because this study was a retrospective, observational study, it might have been possible that the patient activities were partially restricted during the 24-h Holter ECG or the maximum and minimum HR depended on the individual’s physical and mental activity. That might have affected the HR range. Fourth, because the 24-h Holter ECG can only be recorded on a certain day, the HR was unknown except for during the examination. Fifth, because the de

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**Table 2 Primary outcomes and components**

| Event Type | Smaller HRR group events (events rate per patients-year) | Larger HRR group events (events rate per patients-year) | Hazard ratio (95% CI) | P value |
|------------|----------------------------------------------------------|--------------------------------------------------------|----------------------|---------|
| HF events (composite) | 11 (0.027) | 26 (0.068) | 2.5 (1.270–5.283) | 0.0075* |
| HF hospitalization | 8 (0.020) | 16 (0.046) | 2.3 (1.008–5.655) | 0.04* |
| Urgent HF hospital visit | 3 (0.008) | 10 (0.028) | 3.6 (1.089–15.882) | 0.03* |

CI, confidence interval; HF, heart failure; HRR, heart rate range.

*Statistically significant difference.

**Table 3 Adjust hazards Model 1 (age, haemoglobin, stroke, mean HR, and LVDd)**

| Component | Hazard ratio | 95% CI       | P value |
|-----------|--------------|--------------|---------|
| Larger HRR group | 3.21 | 1.593–6.708 | 0.0009* |
| Age       | 1.06 | 1.007–1.117 | 0.03*  |
| Haemoglobin | 0.95 | 0.771–1.163 | 0.60   |
| Stroke    | 3.65 | 0.462–28.870| 0.22   |
| Mean HR   | 0.99 | 0.960–1.023 | 0.57   |
| LVDd      | 1.05 | 0.999–1.108 | 0.05   |

CI, confidence interval; HR, heart rate; HRR, heart rate range; LVDd, left ventricular diastolic diameter.

*Statistically significant difference.

**Table 4 Adjust hazards Model 2 (history of HF, hypertension, DM, β-blocker, ACEI/ARB)**

| Component | Hazard ratio | 95% CI       | P value |
|-----------|--------------|--------------|---------|
| Larger HRR group | 3.12 | 1.522–6.685 | 0.002* |
| History of HF | 1.79 | 0.714–4.465 | 0.22   |
| Hypertension | 1.80 | 0.758–4.284 | 0.18   |
| DM         | 1.59 | 0.760–3.334 | 0.22   |
| β-blocker  | 1.49 | 0.736–3.010 | 0.27   |
| ACEI/ARB   | 0.99 | 0.442–2.200 | 0.97   |

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CI, confidence interval; DM, diabetes mellitus; HF, heart failure; HRR, heart rate range.

*Statistically significant difference.
Conclusions

A larger HRR on the 24-h Holter ECG was associated with HF events. Further studies will be necessary to evaluate the HR using continuous monitoring such as with loop recorders or other long-term monitors to validate the hypothesis.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Trend in the dosage change of rate-controlling drugs. Changes in the dosage of β-blockers (S1-A), digoxin (S1-B), and non-dihydropyridine CCBs (S1-C). During the observational period, no change in dose was observed in either the larger HRR or smaller HRR groups. CCB = calcium channel blocker, HRR = heart rate range.

Table S1. Multicollinearity to model 1.
Table S2. Multicollinearity to model 2.
Table S3. Adjust hazards model 1 (Age, Haemoglobin, Stroke, HRR, LVDD).
Table S4. Adjust hazards model 2 (History of HF, hypertension, DM, β blocker, ACEI/ARB).

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Conflict of interest

None declared.

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