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ORIGINAL ARTICLE

Habitual coffee intake reduces all-cause mortality by decreasing heart rate

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Abstract
It is well known that subjects with metabolic syndrome show an elevated resting heart rate. We previously reported that elevated heart rate was significantly related to all-cause mortality, and that coffee consumption was inversely associated with metabolic syndrome. We hypothesized that higher coffee consumption may decrease all-cause mortality by reducing resting heart rate. We performed a longitudinal epidemiological study in Tanushimaru (a cohort of the Seven Countries Study). A total of 1920 residents aged over 40 years received health checkups in 1999. We measured components of metabolic syndrome, and eating and drinking patterns were evaluated by a food frequency questionnaire. We followed up the participants annually for 15 years. During the follow-up period, 343 of the participants died. Of these, 102 subjects died of cancer, 48 of cerebro-cardiovascular diseases, and 44 of infectious diseases. Multivariate analyses revealed that higher coffee consumption was inversely associated with resting heart rate. Kaplan–Meier curves found lower mortality rates in the higher coffee consumption groups. In the lower coffee consumption groups, elevated hazard ratios of all-cause death were observed in the increased heart rate quintiles, whereas heart rate was not associated with all-cause death in the higher coffee consumption groups. These significant associations remained after further adjustment for confounders. This prospective study suggests that higher coffee consumption may have a protective effect against all-cause death due to reducing resting heart rate.

Keywords Coffee intake · Mortality · Heart rate · Prospective study · Epidemiology

Introduction

Coffee is among the most widely consumed beverages, both in Japan and worldwide [1, 2]. A recent comprehensive meta-analysis demonstrated significant inverse associations between coffee consumption and deaths from all causes, as well as CVD-related mortality [3–5]. A large prospective U.S. Cohort study showed significant inverse associations of coffee consumption with deaths from all causes [6] and specifically with deaths from heart disease, respiratory disease, stroke, injuries, accidents, diabetes, and infections [1].

On the other hand, a Japanese prospective study found that habitual coffee intake was associated with lower risk of total mortality and inversely associated with mortalities from heart disease, cerebrovascular disease, and respiratory disease [2]. Moreover, several studies have demonstrated that coffee consumption decreased the risk of type 2 diabetes [7, 8]. Also, we have previously reported that coffee consumption was inversely associated with metabolic syndrome [9].

Elevated heart rate has been known to be an important predictor of death, especially from CV diseases [10–12], and has been proposed as a global index of the autonomic nervous system influence on the heart [13]. A growing body of evidence suggests that elevated heart rate is a risk factor for future hypertension and development of atherosclerotic lesions. Elevated heart rate may be associated with high blood pressure, obesity, increased plasma insulin level, and dyslipidemias [14]. We have also shown that an increased heart rate may predispose to obesity and diabetes mellitus in a 20-year longitudinal study in a general population [15].

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Elevated heart rate may be a key component of metabolic syndrome [16–18], and higher coffee consumption may protect against metabolic syndrome [9]. This in turn may reduce cardiovascular and all-cause death. However, no longitudinal studies have been available to confirm these associations. Therefore, the purpose of this study was to evaluate the relationships among coffee consumption, heart rate and all-cause death in a prospective epidemiological study.

Materials and methods

Study population

In 1999, we performed health checkups on the residents in a typical farming community, Tanushimaru (a cohort of the Seven Country Studies), located in Kyushu, the southwestern island of Japan. As previously reported, the demographic backgrounds of the subjects in this area were similar to those of the general Japanese population, and the dietary pattern in this district examined in 1999 was similar to that of the National Nutrition Survey in Japan [19].

There were a total of 3463 subjects in the town. A total of 1920 subjects over 40 years of age (48.2% men and 62.0% women), received the checkup. Of these, information on dietary habits was obtained from 1902 subjects (785 men and 1117 women) by means of a food frequency questionnaire. We followed up the participants annually for 15 years. Causes of death were determined based on a review of obituaries, medical records, death certificates, hospital charts, and interviews with primary care physicians, families of the deceased and other witnesses. Eventually, the 1902 subjects (785 men and 1117 women) were completely followed up for 15 years, and we analyzed their data.

Data collection

Smoking and drinking habits were ascertained by a questionnaire. Alcohol intake and smoking were classified as current habitual use or not. Height and weight were measured, and body mass index (BMI) was calculated from measurements of height and body weight. Waist circumference was measured at the level of umbilicus in the standing position. Blood pressure (BP) was measured twice with participants in the supine position. Blood samples obtained from the antecubital vein in the morning after a 12-h fast was used for determinations of lipids profiles [triglycerides, high-density lipoprotein cholesterol (HDL)], fasting plasma glucose (FPG), HbA_{1c} (NGSP), and insulin. Fasting blood samples were centrifuged within 1 h after collection. The homeostasis model assessment (HOMA) index [FPG (mg/dl) × insulin (μU/ml)/405] was calculated from FPG and insulin level as a marker of insulin resistance [20]. Resting heart rate was measured using a 12-lead electrocardiogram. Arrhythmias such as atrial fibrillation and pacemaker rhythm were excluded from this study.

We used a version of the ARIC study's food frequency questionnaire adapted for use in Japan [21]. It consisted of 105 items, and habitual nutrient intakes were estimated from reports of the frequency and average portion size of foods consumed during the past year [22]. Based on this questionnaire, we calculated quantities of coffee consumed using the Standard Tables of Food Composition in Japan. The frequency of consumption and frequency weights were classified into the following 9 categories: (1) once per day (×1.0); (2) two or three times per day (×2.5); (3) four to six times per day (×5); (4) more than six times per day (×7); (5) once per week (×0.14); (6) two to four times per week (×0.43); (7) five or six times per week (×0.79); (8) one to three times per month (×0.066); and (9) never (×0).

The present study was approved by the Ukiha and Tanushimaru Branches of the Japan Medical Association, the Tanushimaru City Council [23] and by the Research Ethics Committee of the Kurume University School of Medicine (process no. 9908/1999). The study conformed to the principles of the Declaration of Helsinki. All the participants provided written informed consent.

Statistical analyses

Results are presented as mean ± standard deviation (SD). Due to skewed distributions, natural logarithmic transformations were performed for triglycerides, insulin, and HOMA index. These variables were represented in the original scale after analysis using the log (natural)-transformed values. Mean coffee consumption (ml/day) was classified into quartiles as follows: 0–10 ml/day, 11–85.5 ml/day, 86–150 ml/day, and 151–1050 ml/day. Analysis of variance was used to compare the means of variables, stratified by quartile of coffee consumption. The χ^2 test was used to test differences between groups in categorical variables (Table 1). Multivariable analysis for correlation of coffee consumption adjusted for age, sex and total energy intake were performed by multivariable linear regression analysis (Table 2). Hazard ratios of all-cause death stratified by 4 coffee groups and 5 heart rate quintiles were evaluated by the Cox's proportional hazards regression model (Table 3). Hazard ratios were evaluated using 4 models after adjustment for related confounders. Survival curves of death from all causes for different levels of coffee consumption (ml/day) were estimated by the Kaplan–Meier method and compared using the log-rank statistic (Fig. 1). Statistical significance was defined as $p < 0.05$. All statistical analyses were performed using the SAS system (Release 9.4, SAS Institute, Cary, NC, USA).

Table 1 Characteristics of participants at baseline stratified by coffee consumption (ml/day) quartiles

Parameters	G1 (0–10)	G2 (11–85.5)	G3 (86–150)	G4 (151–1050)	*p*
Coffee (ml/day)	2.5 ± 4.3	49.6 ± 21.0	146.0 ± 10.6	448.4 ± 173.3	**< 0.0001**
N	689	360	431	422	
Age (years)	66.2 ± 9.9	64.3 ± 10.6	61.1 ± 10.3	56.9 ± 11.1	**< 0.0001**
Male sex (%)	46.2	38.1	37.1	40.3	**0.0091**
Waist (cm)	78.1 ± 9.4	77.2 ± 9.7	76.3 ± 8.8	76.0 ± 9.3	**0.0005**
BMI (kg/m^2)	23.1 ± 3.3	23.2 ± 3.1	23.0 ± 3.0	23.2 ± 3.1	0.57
Heart rate (bpm)	64.3 ± 10.5	65.2 ± 10.6	63.3 ± 9.2	62.8 ± 8.8	**0.0022**
Systolic BP (mmHg)	137.8 ± 21.0	134.9 ± 20.2	131.1 ± 20.6	127.9 ± 19.6	**< 0.0001**
Diastolic BP (mmHg)	80.1 ± 11.5	79.2 ± 11.9	77.8 ± 11.8	77.4 ± 11.3	**0.0003**
HDL-cholesterol (mg/dl)	55.6 ± 14.7	54.8 ± 12.9	57.1 ± 14.0	55.7 ± 13.9	0.15
Triglycerides (mg/dl)[a]	103.5 (31–1194)	100.5 (28–953)	93.7 (30–1284)	92.8 (28–963)	0.18
FPG (mg/dl)	100.2 ± 22.3	98.7 ± 20.0	96.8 ± 18.6	93.8 ± 17.0	**< 0.0001**
HbA_{1c} (NGSP) (%)	5.26 ± 0.80	5.26 ± 0.86	5.13 ± 0.64	5.09 ± 0.68	**0.0003**
Insulin (μU/ml)[a]	4.62 (1–96)	4.81 (1–79)	4.66 (1–56)	4.52 (1–39)	0.056
HOMA[a]	1.13 (0.20–24.9)	1.16 (0.23–23.6)	1.11 (0.22–16.3)	1.05 (0.18–8.4)	**0.017**
Creatinine (mg/dl)	0.88 ± 0.23	0.83 ± 0.16	0.84 ± 0.18	0.84 ± 0.16	**< 0.0001**
Uric acid (mg/dl)	5.14 ± 1.51	4.93 ± 1.30	4.74 ± 1.35	4.93 ± 1.40	**< 0.0001**
Total energy (kcal/day)	1866.3 ± 525.0	1986.6 ± 559.9	1976.4 ± 563.9	2014.4 ± 563.8	**< 0.0001**
Smoking habits (%)	13.8	17.3	13.7	25.8	**< 0.0001**
Alcohol intake (%)	23.8	22.2	20.7	20.9	0.55
History of hypertension (%)	26.5	19.7	16.7	11.9	**< 0.0001**
History of dyslipidemia (%)	5.0	5.3	4.7	3.8	0.78
History of diabetes (%)	3.6	5.0	2.1	1.4	**0.014**

Data are means ± standard deviations or %, unless otherwise indicated

Significant *p* values are in bold

BMI body mass index, *BP* blood pressure, *HDL* high-density lipoprotein, *FPG* fasting plasma glucose, *HOMA* homeostasis model assessment

[a]Log-transformed values were used for the calculation and reconverted to anti-logarithm forms

Results

There were 343 deaths (male, $n = 201$; female, $n = 142$) among 1902 individuals during the follow-up period of 15 years. The causes of death were as follows: cancer, $n = 102$ (29.7%); cerebro-cardiovascular disease, $n = 48$ (14.0%); infection, $n = 45$ (13.1%); other causes, $n = 69$ (20.1%); and unknown, $n = 79$ (23.0%). The 102 cancer deaths included malignancies of the digestive system ($n = 34$), liver, bile duct and pancreas ($n = 29$), malignancies of the respiratory system ($n = 19$), hematological malignancies ($n = 10$), and other types of malignancy ($n = 10$).

Characteristics of participants at baseline stratified by coffee consumption (ml/day) quartiles are shown in Table 1. The coffee consumption was significantly and positively associated with total energy and smoking habit, and inversely associated with age, male sex, waist, heart rate, systolic and diastolic blood pressures, FPG, HbA_{1c}, HOMA, creatinine, uric acid, and history of hypertension. Multivariate linear regression analysis for coffee consumption adjusted for age, sex and total energy intake found that waist (inversely), heart rate (inversely), systolic BP (inversely), diastolic BP (inversely), triglycerides (inversely), FPG (inversely), HbA_{1c} (inversely), smoking habits, alcohol intake (inversely), and history of hypertension (inversely) were significantly associated with coffee consumption (Table 2).

Figure 1 shows the Kaplan–Meier curves for cumulative survival rate stratified by coffee consumption groups. The lowest coffee consumption quartile (coffee group 1) showed the highest all-cause mortality ($p < 0.001$ by log-rank test)

In the lower coffee consumption groups (G1 and G2), hazard ratios of all-cause death in the increased heart rate quintiles were significantly elevated (Table 3). Whereas, in the higher coffee consumption groups (G3 and G4), heart rate was not associated with all-cause mortality. These associations remained significant even after further adjustment for confounding factors.

Table 2 Multivariate linear regression analysis for coffee consumption (ml/day) adjusted for age, sex and total energy intake

Parameters	β	SE	p value
Waist (cm)	− 1.38	0.49	**0.005**
BMI (kg/m^2)	− 0.29	1.34	0.830
Heart rate (bpm)	− 0.87	0.43	**0.040**
Systolic BP (mmHg)	− 0.74	0.21	**0.001**
Diastolic BP (mmHg)	− 1.08	0.36	**0.003**
HDL-cholesterol (mg/dl)	− 0.01	0.30	0.970
Triglycerides (mg/dl)[a]	− 0.15	0.05	**0.005**
FPG (mg/dl)	− 0.71	0.22	**0.001**
HbA_{1c} (NGSP) (%)	− 12.9	5.55	**0.019**
Insulin (μU/ml)[a]	− 0.86	0.75	0.250
HOMA[a]	− 9.15	6.51	0.160
Creatinine (mg/dl)	− 0.38	25.9	0.990
Uric acid (mg/dl)	− 4.19	3.44	0.220
Smoking habits; yes = 1, no = 0	60.3	12.7	**0.001**
Alcohol intake; yes = 1, no = 0	− 35.3	11.9	**0.003**
History of hypertension; yes = 1, no = 0	− 27.3	10.8	**0.011**
History of dyslipidemia; yes = 1, no = 0	− 10.3	19.8	0.600
History of diabetes; yes = 1, no = 0	− 28.1	24.4	0.250

Significant p values are in bold

BMI body mass index, *BP* blood pressure, *HDL* high-density lipoprotein, *FPG* fasting plasma glucose, *HOMA* Homeostasis model assessment

[a]Log-transformed values were used for the calculation and reconverted to anti-logarithm forms

Discussion

In this relatively large and long-term prospective cohort study, significantly higher hazard ratios of all-cause death were observed in the elevated heart rate quintiles in the lower coffee consumption groups. In contrast, heart rate was not associated with all-cause death in the higher coffee consumption groups. From these results, we suggested that habitual coffee consumption was significantly associated with lower mortality, possibly due to a reduction in resting heart rate.

Elevated heart rate has been proposed as a global index of the autonomic nervous system influence on the heart [13]. Elevated heart rate may be a key component of metabolic syndrome along with blood pressure, triglycerides and blood glucose [24, 25]. Moreover, elevated heart rate may predispose to the development of metabolic syndrome and/or diabetes and/or insulin resistance [26–28]. Our previous reports [15, 29] demonstrated a cross-sectional or longitudinal relationship between elevated heart rate and a cluster of cardio-metabolic factors. In addition, we have now demonstrated by means of this prospective study that higher coffee consumption at baseline was associated with lower all-cause death.

Although there are few reports on the association between consumption of beverages and resting heart rate [30, 31], we confirmed that coffee consumption was significantly and inversely associated with resting heart rate. Moreover, coffee consumption was inversely associated with not only heart rate but also other components of metabolic syndrome (Table 2).

Our results may suggest a causal role of sympathetic activation due to habitual coffee intake in the development of components of metabolic syndrome [29, 32]. Thus, the strong and inverse association between coffee consumption and all-cause death may well be explained by reducing resting heart rate by caffeine or chlorogenic acids intake.

One possible mechanism may be caffeine. Among patients with chronic kidney disease (CKD), there is an inverse association between caffeine consumption and all-cause mortality [33]. Caffeine is a xanthine with various effects and mechanisms of action in vascular tissue. In endothelial cells, it increases intracellular calcium and stimulates the production of nitric oxide through the expression of the endothelial nitric oxide synthase enzyme. Nitric oxide is diffused to the vascular smooth muscle cell to produce vasodilation [34]. Caffeine in coffee has favorable effects on metabolic syndrome, and decreases insulin resistance in humans [9, 35, 36]. Experimental studies have shown that caffeine may raise plasma levels of several stress hormones, such as epinephrine, norepinephrine [37, 38], and cortisol, all of which can lead to an increase in blood pressure [38, 39]. However, these experiments have been limited to relatively short periods of observation, typically less than 1 week. Physiological circulating levels of caffeine may enhance net hepatic glucose uptake during a glucose load, and the added glucose consumed by the liver is in part converted to lactate [40] .

Another possible mechanism has been reported as follows; chlorogenic acids (CGAs) are phenolic acids with vicinal hydroxyl groups on aromatic residues that are derived from esterification of cinnamic acids, including caffeic, ferulic and *p*-coumaric acids with quinic acid. Coffee arguably is one of the most popular consumed beverages in the world and is also a very rich source of CGAs.[41] A number of conjugated structures, such as caffeoylquinic acids (CQA), dicaffeoylquinic acids (diCQA), feruloylquinic acids (FQA), and *p*-coumaroylquinic acids (*p*-CoQA), exist in several isomeric forms in coffee beans. The major CGAs in coffee include 3-caffeoylquinic acid (3-CQA); 4-caffeoylquinic acid (4-CQA); 5-caffeoylquinic acid (5-CQA); 3,4-dicaffeoylquinic acid (3,4-diCQA); 3,5-dicaffeoylquinic acid (3,5-diCQA); and 4,5-dicaffeoylquinic acid (4,5-diCQA). Clearly, in vitro and in vivo data indicate that 5-CQA has antioxidant activity and can alleviate oxidative stress in various disease models. CGAs may have positive effects on weight loss and glucose metabolism, including

Table 3 Hazard ratios and 95% CI of all-cause death stratified by 4 coffee groups and heart rate quintiles

Heart rate quintiles	Q1 (38–55)	Q2 (56–59)	Q3 (60–64)	Q4 (65–70)	Q5 (71–123)
Coffee groups (ml/day)					
G1 (0–10), *N*	123	103	150	148	162
Model 1	Ref	0.78 (0.34–1.81)	1.70 (0.96–3.03)	**2.17 (1.22–3.87)****	**2.35 (1.35–4.07)****
Model 2	Ref	0.72 (0.31–1.67)	1.58 (0.88–2.84)	**2.12 (1.17–3.82)***	**2.21 (1.26–3.88)****
Model 3	Ref	0.63 (0.26–1.54)	1.48 (0.81–2.68)	**1.87 (1.02–3.44)***	**1.99 (1.11–3.55)***
Model 4	Ref	0.64 (0.26–1.57)	1.48 (0.80–2.72)	**1.86 (1.01–3.44)***	**1.94 (1.08–3.48)***
G2 (11–85.5), *N*	63	52	77	71	97
Model 1	Ref	2.51 (0.96–6.54)	0.86 (0.26–2.87)	0.85 (0.24–3.07)	**2.73 (1.05–7.09)***
Model 2	Ref	2.21 (0.82–5.99)	0.89 (0.26–3.07)	0.84 (0.22–3.18)	**2.72 (1.00–7.42)***
Model 3	Ref	2.67 (0.93–7.68)	1.07 (0.29–3.90)	0.81 (0.20–3.23)	2.63 (0.89–7.79)
Model 4	Ref	2.44 (0.84–7.10)	1.00 (0.27–3.65)	0.78 (0.19–3.20)	2.47 (0.82–7.41)
G3 (86–150), *N*	81	78	88	96	88
Model 1	Ref	0.77 (0.29–2.09)	1.17 (0.52–2.63)	0.73 (0.29–1.77)	0.92 (0.41–2.10)
Model 2	Ref	0.51 (0.18–1.42)	0.96 (0.42–2.20)	0.60 (0.24–1.49)	0.95 (0.40–2.21)
Model 3	Ref	0.56 (0.20–1.57)	0.97 (0.42–2.25)	0.69 (0.27–1.80)	1.05 (0.43–2.56)
Model 4	Ref	0.58 (0.21–1.63)	1.05 (0.45–2.45)	0.77 (0.30–1.99)	0.99 (0.39–2.46)
G4 (151–1050), *N*	83	75	107	92	65
Model 1	Ref	1.54 (0.61–3.95)	1.47 (0.55–3.95)	1.30 (0.52–3.27)	1.65 (0.64–4.24)
Model 2	Ref	1.21 (0.46–3.20)	1.32 (0.48–3.67)	1.04 (0.40–2.75)	1.57 (0.59–4.17)
Model 3	Ref	1.25 (0.47–3.36)	1.41 (0.50–3.99)	0.92 (0.34–2.51)	1.17 (0.41–3.35)
Model 4	Ref	1.15 (0.43–3.08)	1.16 (0.39–3.39)	0.85 (0.31–2.34)	1.11 (0.38–3.21)

Model 1: adjusted for age, sex and total energy intake; Model 2: adjusted for age, sex, total energy intake, BMI, smoking habits, and alcohol intake; Model 3: adjusted for age, sex, total energy intake, BMI, systolic BP, HbA_{1c} (NGSP), smoking habits, and alcohol intake; Model 4: adjusted for age, sex, total energy intake, BMI, systolic BP, HbA_{1c} (NGSP), history of hypertension, history of dyslipidemia, history of diabetes, smoking habits, and alcohol intake

AST aspartate aminotransferase, *BP* blood pressure, *CI* confidence interval, *FPG* fasting plasma glucose

*$p<0.05$, **$p<0.01$

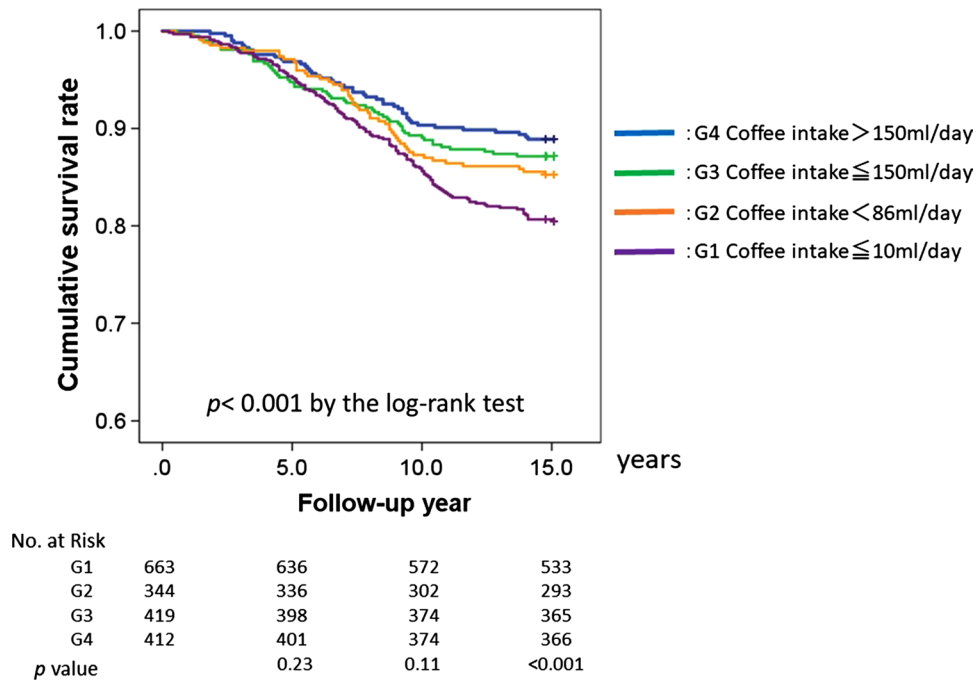

Fig. 1 Survival curves of death from all causes for each level of coffee consumption (ml/day) were estimated by the Kaplan–Meier method and compared using the log-rank statistic

enhancing the antioxidant effects of coffee, and decreasing glucose output in the liver [42, 43].

Study limitations

The first limitation of our study is that we have no other data to support validity, such as reproducibility, though our data obtained from the modified ARIC study's food frequency questionnaire [21] were similar to results of The National Nutrition Survey in Japan. Second, we used a single baseline measurement to predict the all-cause and cause-specific death. Third, coffees were prepared differently by each subject. The way that coffee is consumed in different countries could affect findings. Fourth, we could not examine the kinds of antihypertensive medication such as β-blocker which may effect on the heart rate. Finally, the total number of deaths from cancer or CV death was relatively small and this limited the statistical power for these outcomes, which is etiologically more relevant.

Conclusions

This prospective study suggests that higher coffee consumption may have a protective effect against all-cause death due to reducing resting heart rate.

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Compliance with ethical standards

Conflict of interest Y. Nohara-Shitama, H. Adachi, M. Enomoto, A. Fukami, S. Nakamura, S. Kono, N. Morikawa, A. Sakaue, H. Hamamura, K. Toyomasu, and Y. Fukumoto have no conflicts of interest.

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