Cardiovascular Innovations and Applications

Vol. 8 (2023) 26
ISSN 2009-8618
DOI 10.15212/CVIA.2023.0038

RESEARCH ARTICLE

Changes in Autonomic Nervous System Function in Patients >60 Years of Age with Coronary Heart Disease, and Normotension or Hypertension: An Observational Study

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Received: 11 February 2023; Revised: 29 April 2023; Accepted: 23 May 2023

Abstract

Aim: The aim of this observational study was to perform in-depth analysis of autonomic nervous system function in patients older than 60 years of age with coronary artery disease, and normotension or hypertension.
Method: A total of 104 patients older than 60 years with coronary heart disease (CHD) were divided into a normotension group and hypertension (HT) group, and 24-hour Holter monitoring was performed to assess autonomic function.
Result: Among the 104 patients with CHD analyzed, 52 had normotension, and 52 had hypertension. The 24-hour Holter results based on time-domain methods indicated that the values of the time-domain parameters of heart rate variability were significantly lower in the CHD+HT group than the CHD group. Furthermore, during both the daytime and nighttime, the time-domain parameters were significantly lower in the CHD+HT group than the CHD group. No difference was observed in autonomic function during the daytime and nighttime in each group. Values of frequency-domain parameters of heart rate variability were also significantly lower in the CHD+HT group than the CHD group. More patients in the CHD+HT group than the CHD group received percutaneous coronary intervention (57.69% vs. 50% $\chi^2=0.619$, P=0.55). In 12 months of follow-up, we found no significant differences in rehospitalization for unstable angina and target lesion revascularization between patients with CHD with normotension versus hypertension.
Conclusion: The heart autonomic nervous system dysfunction in patients older than 60 years with CHD with hypertension was more severe than that in patients with CHD with normotension, and therefore, should receive greater clinical attention.

Keywords: Heart rate variability; coronary heart disease; hypertension; time-domain methods; frequency-domain methods

Introduction

In 1898, John Newport Langley first proposed the term "autonomic nervous system" (ANS) and suggested the actions of the sympathetic and parasympathetic components [1]. ANS dysfunction tends to affect primarily the sympathetic nervous system [2]. ANS dysfunction is associated with many types of pathological changes, including cardiovascular disease, hypertension, hyperglycemia, high triglycerides, low high-density lipoprotein cholesterol, high body mass index, incident diabetes, and elevated cardiovascular mortality. Heart rate

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variability (HRV) is considered a specific noninvasive electrocardiographic measure of ANS function, both sympathetic and parasympathetic. HRV measures are commonly divided into time-domain measurements and frequency-domain measurements [2]. Time-domain estimates are obtained over 24 hours directly from a patient's heart rate or the duration between successive RR intervals. Frequency-domain measurements are calculated in 24 hours from spectral imaging of electrocardiology (ECG) recordings. The time-domain HRV parameters include the following: the standard deviation of all normal to normal NN intervals (SDNN), standard deviation of all mean 5-minute NN intervals (SDANN), mean of the standard deviation of all NN intervals for all 5-min segments in 24 hours (SDNN index), root mean square of successive differences between adjacent normal cycles (RMSSD), and percentage of NN50 in the total number of NN intervals (PNN50) [2]. Additionally, frequency-domain HRV parameters include the following indicators: low frequency (LF), high frequency (HF), and LF/HF [2]. In patients older than 60 years in our hospital, coronary heart disease (CHD) is usually accompanied by hypertension. Because clinical research in this field has been limited, better understanding of potentially significant associations between ANS circadian rhythms in patients with CHD with vs. without hypertension is needed. Therefore, our observational research was aimed at evaluating the relationship between HRV and CHD in patients older than 60 years with normotension or hypertension. Furthermore, we observed the ANS circadian rhythm changes in each group.

Methods

Patients and Ethics

We analyzed 104 consecutive patients (72.81±6.72 years of age) who had undergone 24-hour Holter monitoring after hospitalization at the First Affiliated Hospital of the University of Science and Technology of China between January 1, 2019, and January 1, 2021. The key enrollment criteria were as follows: (1) age >60 years; (2) signed informed consent provided; (3) guideline-appropriate diagnosis for CHD; (4) past history of myocardial infarction, or definitive CHD diagnosis through prior coronary angiography or coronary CT angiography before admission; (5) definitive CHD diagnosis through coronary angiography or coronary CT angiography during the hospital admission; and (6) guideline-appropriated diagnosis for hypertension. The exclusion criteria were as follows: (1) adult congenital heart disease; (2) arrhythmias, including atrial fibrillation, atrial flutter, pacing rhythm, or paroxysmal supraventricular tachycardia; (3) hyperthyroidism or hypothyroidism; (4) heart failure; (5) depression or anxiety; (6) liver or kidney dysfunction; (7) malignant tumors; (8) diabetes mellitus; or (9) incomplete patient information.

Measurement of Heart Rate Variability

HRV measures are commonly divided into time-domain and frequency-domain measurements. Time-domain estimates are obtained over 24 hours directly from the patient's heart rate or the duration between successive RR intervals. Frequency-domain measurements are obtained in 24 hours from spectral imaging of ECG recordings. The following time-domain HRV parameters were selected according to the suggestions of the Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology: SDNN, SDANN, SDNN index, RMSSD, and PNN50. Additionally, we examined one frequency-domain measure, and LF, HF, and LF/HF were statistically recorded and analyzed. Furthermore, we analyzed time-domain parameters during both the daytime and nighttime. The enrolled patients were required to avoid intense physical exercise, drinking alcohol, and smoking. They were recommended to cease movement at 10 p.m. and to sleep until 6 a.m. All examinations were performed in our hospital setting to limit the influences of other confounding factors, such as work stress and diet.

Clinical Patient Follow-Up

The follow-up period for enrolled patients was 12 months or until a fatal event occurred. Follow-up data were collected from patients from electronic medical records or through telephone interviews. We used a mailed questionnaire if a telephone interview could not be conducted. The primary endpoint was

cardiac death. The secondary endpoints included the recurrence of unstable angina and rehospitalization for target lesion revascularization. The methods followed the standards and procedures of the First Affiliated Hospital of the University of Science and Technology of China, and included data collection and follow-up under approval by the institutional review board. The local ethics committees approved our observational study, and enrolled patients provided signed informed consent forms.

Statistical Analysis

Continuous variables are expressed as mean and standard deviation. Data were analyzed with the Student's t-test, if applicable. We compared two groups using χ^2 test for discrete variables. We used the Shapiro-Wilk test to detect the normality of the data. All statistical tests are two-sided with a significance level of <0.05. All statistical analyses were performed in SPSS software, version 23.0 (SPSS, Inc., Chicago, IL).

Results

Between January 1, 2019, and January 1, 2021, 104 enrolled patients >60 years of age with CHD in our hospital were divided into a normotension group (group 1) and hypertension group (group 2). Of the 104 participants in our observational study, 65 were men. Among the enrolled patients, the male:female ratio was 1.67:1. The mean age was 72.81 years (SD 6.72). According to the obtained data (Table 1), statistical analysis indicated no differences in age, diastolic blood pressure, total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol in these two groups. All patients received 24-hour ambulatory electrocardiography to assess any arrhythmias; HRV; and minimum, mean, and maximum heart rate.

The 24-hour Holter results based on time-domain methods indicated that the SDNN (117.96±27.56 vs. 74.75±16.92, P<0.05), SDANN (98.94±28.40 vs. 64.79±14.78, P<0.05), SDNN index (54.19±17.76 vs. 32.94±11.53, P<0.05), RMSSD (38.48±28.90 vs. 24.02±13.08, P<0.05), and PNN50 (8.66±11.09 vs. 4.15±5.64, P<0.05) were significantly lower in patients with CHD with hypertension than in those with CHD with normotension (Tables 2–5). Furthermore, during the daytime, Holter monitoring indicated that the SDNN (88.12±25.94 vs. 57.25±16.73, P<0.05), SDANN (65.19±22.79 vs. 45.21±15.23, P<0.05), SDNN index (52.21±23.09 vs. 31.02±10.88, P<0.05), RMSSD (38.17±35.05 vs. 23.13±12.44, P<0.05), PNN50 (8.91±14.57 vs. 4.02±5.78, P<0.05), and triangular interpolation of the NN interval histogram (TINN; 327.92±112.91 vs. 211.89±70.89, P<0.05) were significantly lower in patients with CHD with hypertension than in those with CHD with normotension. During the nighttime, Holter monitoring also demonstrated that the SDNN (91.98±26.27 vs. 59.96±18.84, P<0.05), SDANN (60.81±17.77 vs. 44.35±17.19, P<0.05), SDNN index (59.83±21.73

Table 1 Baseline Characteristics of the Included Patients Enrolled in this Study (n=104).

	Group 1	Group 2	T-test/χ^2 test	P value
Male (n, %)	39 (75%)	26 (50%)	6.93	0.015
Age (year)	72.31±6.59	73.33±6.88	0.772	0.442
SBP (mmHg)	129.37±14.97	137.46±21.47	2.231	0.028
DBP (mmHg)	78.17±10.25	80.54±12.24	1.068	0.288
TC (mmol/L)	4.26±1.09	4.23±1.09	0.116	0.908
TG (mmol/L)	1.53±1.59	1.57±0.84	0.159	0.874
HDL-C	1.09±0.24	1.05±0.26	0.952	0.343
LDL-C	2.32±0.81	2.32±0.87	0.007	0.994

Group 1: patients older than 60 years with coronary heart disease and normotension. Group 2: patients older than 60 years with coronary heart disease and hypertension. Systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) are indicated.

Table 2 Time-Domain HRV Parameters during 24 Hours in Patients with Coronary Heart Disease with Normotension or Hypertension.

	N	SDNN	SDANN	SDNN index	rMSSD	pNN50
Group 1	52	117.96±27.56	98.94±28.4	54.19±17.76	38.48±28.90	8.66±11.09
Group 2	52	74.75±16.92	64.79±14.78	32.94±11.53	24.02±13.08	4.15±5.64
t value		9.636	7.689	7.238	3.287	2.619
P value		<0.01	<0.01	<0.01	<0.01	0.011

Group 1: patients older than 60 years with coronary heart disease and normotension. Group 2: patients older than 60 years with coronary heart disease and hypertension. The standard deviation of all normal to normal NN intervals (SDNN), standard deviation of all mean 5-minute NN intervals (SDANN), mean of the standard deviation of all NN intervals for all 5-min segments over 24 hours (SDNN index), root mean square of successive differences between adjacent normal cycles (RMSSD), and percentage of NN50 in the total number of NN intervals (PNN50) are indicated.

Table 3 Frequency-Domain Parameters during 24 Hours in Patients with Coronary Heart Disease with Normotension or Hypertension.

	N	LF/HF	LF	HF
Group 1	52	1.34±0.77	453.33±565.76	462.26±902.38
Group 2	52	0.96±0.62	141.00±143.32	179.88±196.99
t value		2.72	3.786	2.164
P value		0.008	<0.01	0.035

Group 1: patients older than 60 years with coronary heart disease and normotension. Group 2: patients older than 60 years with coronary heart disease and hypertension. LF: low frequency, HF: high frequency, LF/HF: ratio of low frequency and high frequency.

Table 4 Time-Domain Parameters during the Daytime in Patients with Coronary Heart Disease with Normotension or Hypertension.

	N	SDNN	SDANN	SDNN index	rMSSD	pNN50	TINN
Group 1	52	88.12±25.94	65.19±22.79	52.21±23.09	38.17±35.05	8.91±14.57	327.92±112.91
Group 2	52	57.25±16.73	45.21±15.23	31.02±10.88	23.13±12.44	4.02±5.78	211.89±70.89
t value		7.21	5.26	5.99	2.916	2.25	6.28
P value		<0.01	<0.01	<0.01	<0.05	<0.05	<0.01

Group 1: patients older than 60 years with coronary heart disease and normotension. Group 2: patients older than 60 years with coronary heart disease and hypertension. TINN: triangular interpolation of the NN interval histogram.

Table 5 Time-Domain Parameters during the Nighttime in Patients with Coronary Heart Disease with Normotension or Hypertension.

	N	SDNN	SDANN	SDNN index	rMSSD	pNN50	TINN
Group 1	52	91.98±26.27	60.81±17.77	59.83±21.73	39.19±26.56	9.65±10.24	290.73±99.96
Group 2	52	59.96±18.84	44.35±17.19	35.25±13.65	23.98±13.99	4.46±7.12	207.19±63.91
t value		7.142	4.802	6.907	3.654	2.995	5.077
P value		<0.01	<0.01	<0.01	<0.01	<0.01	<0.01

Group 1: patients older than 60 years with coronary heart disease and normotension. Group 2: patients older than 60 years with coronary heart disease and hypertension. The standard deviation of all normal to normal NN intervals (SDNN), standard deviation of all mean 5-minute NN intervals (SDANN), mean of the standard deviation of all NN intervals for all 5-min segments over 24 hours (SDNN index), root mean square of successive differences between adjacent normal cycles (RMSSD), and percentage of NN50 in the total number of NN intervals (PNN50) are indicated. TINN: triangular interpolation of the NN interval histogram.

vs. 35.25±13.65, P<0.05), RMSSD (39.19±26.56 vs. 23.98±13.99, P<0.05), PNN50 (9.65±10.24 vs. 4.46±7.12, P<0.05), and TINN (290.73±99.96 vs. 207.19±63.91, P<0.05) were significantly lower in patients with CHD with hypertension than in those with CHD with normotension. No difference in ANS function was observed during the daytime and nighttime within each group (P>0.05). The 24-hour Holter recordings with frequency-domain methods indicated that the LF (453.33±565.76 vs. 141.00±143.32, P<0.05), HF (462.26±902.38 vs. 179.88±196.99, P<0.05), and LF/HF (1.34±0.77 vs. 0.96±0.62, P<0.05) were significantly lower in patients with CHD with hypertension than patients with CHD with normotension.

The patients presented precardiac discomfort, such as chest tightness and pain. Among the 102 patients analyzed, 56 underwent percutaneous coronary intervention. Five patients with CHD with hypertension underwent coronary angiography, whereas 30 underwent both coronary angiography and percutaneous coronary intervention during the hospitalization. In the CHD group, 16 patients underwent coronary angiography, whereas 26 patients underwent coronary angiography and percutaneous coronary intervention during the hospitalization. More patients in the CHD with hypertension group than in the CHD group received PCI (57.69% vs. 50% χ^2=0.619, P=0.55), although this result was not statistically significant. Among the 104 patients analyzed, all patients completed 12 months of follow-up. During the follow-up, no patients had cardiac death, and 21 patients (20.19%, 21/104) were rehospitalized for unstable angina. Furthermore, no significant differences in rehospitalization rates for unstable angina were found between patients with CHD with normotension and patients with CHD with hypertension (10/52 vs. 11/52, χ^2=0.06, P=0.81). Among the 21 patients, 33.3% (7/21) followed target lesion revascularization. Meanwhile, no significant difference in target lesion revascularization was observed between patients with CHD with normotension and patients with CHD with hypertension (3/52 vs. 4/52, χ^2=0.153, P=0.69).

Discussion

Our observational clinical study included 104 patients with CHD who received 24-Holter monitoring. Among the 104 patients enrolled, 52 had CHD with normotension, and 52 had CHD with hypertension. Values of time-domain parameters (e.g., SDNN, SDANN, SDNN index, rMSSD, and pNN50) for HRV were significantly lower in patients with CHD with hypertension than in patients with CHD with normotension. Furthermore, during both the daytime and nighttime, the time-domain parameters (e.g., SDNN, SDANN, SDNN index, rMSSD, and pNN50) were significantly lower in patients with CHD with hypertension than in those with CHD. No difference in ANS function during the daytime and nighttime was observed in each group. Values of frequency-domain parameters (e.g., LF, HF, and LF/HF) for HRV were also significantly lower in patients with CHD with hypertension than in those with CHD. More patients with CHD with hypertension than patients with CHD received percutaneous coronary intervention (57.69% vs. 50% χ^2=0.619, P=0.55), although this result was not statistically different between groups. Moreover, during the 12 months of follow-up, no significant differences in rehospitalization for unstable angina and target lesion revascularization were observed between patients with CHD with normotension and patients with CHD with hypertension. HRV is considered a noninvasive measure of the variability in the intervals between subsequent heartbeats, and an indicator of the balance between sympathetic and parasympathetic modulation of the heart [3–6]. The sympathetic influence on heart rate is mediated by the release of neurotransmitters, such as norepinephrine and epinephrine. Activation of β-adrenergic receptors results in cyclic AMP-mediated phosphorylation of membrane proteins, and increased calcium ion flux and pacemaker current (If) [7–9]. Consequently, increased slow diastolic depolarization is observed. The parasympathetic influence on the heart rate is mediated through the release of acetylcholine by the parasympathetic nerve. Subsequently, muscarinic acetylcholine receptors increase cell membrane K^+ conductance [10]. Acetylcholine also inhibits the hyperpolarization-activated If [9, 11]. ANS dysfunction is associated with various pathological conditions, including cardiovascular disease, high blood pressure, and high mortality [12–17]. HRV is quantified by parameters calculated from ECG data to evaluate how successfully an individual's ANS exerts force on the heart, as indicated by variations in the time intervals

between each heartbeat [18]. HRV data collection is noninvasive, relatively easy, and inexpensive; therefore, it is a commonly used and valuable tool for evaluating ANS modulation.

First, HRV measures are commonly classified into time-domain and frequency-domain measurements. In the time-domain parameters, SDNN is generally regarded as a measure of "global HRV." These measures indicate all cyclic components that participate in temporal variation in heartbeats [19]. Critically, SDNN is a measure of the total variance. In our study, the 24-hour Holter recordings and the daytime/nighttime Holter recordings of SDNN were clearly lower in patients with CHD with hypertension rather than normotension. We concluded that the total variance was lower in patients older than 60 years with CHD with hypertension than in patients in the normotension group. Lower HRV is closely associated with an elevated risk of cardiovascular events and mortality [3, 6, 14]. Fang has performed a meta-analysis of 28 cohort studies involving 2094 participants to analyze the relationship between HRV and cardiovascular events or the risk of all-cause death in patients with cardiovascular disease during a follow-up of at least 1 year [20]. Low HRV has been closely associated with cardiovascular events and elevated risk of all-cause death. Previous findings have revealed that patients with postmyocardial infarction syndrome with low rather than high SDNN are nearly four times more likely to die in the subsequent 3 years [21]. According to our SDNN results (74.75 ± 16.92), patients with CHD with hypertension should receive close follow-up. Second, SDANN, the standard deviation of all mean 5-minute NN intervals [22], reflects changes in sympathetic tension and is negatively correlated with sympathetic activity. Thus, a decrease in SDANN indicates an increase in sympathetic activity. In our study, both the 24-hour Holter recordings and daytime/nighttime Holter recordings indicated significantly lower SDANN in patients with CHD with hypertension than in patients in the normotension group. Therefore, we concluded that patients older than 60 years with CHD with hypertension rather than normotension have elevated sympathetic activity. According to Fantoni, SDANN is a well-established marker for evaluating cardiac resynchronization treatment in patients with heart failure. Our SDANN findings also indicated that greater attention should be paid to patients with CHD with hypertension. Third, RMSSD is calculated by taking the square root of the mean of the squared differences between consecutive NN intervals. PNN50 represents the proportion of NN50 divided by the total number of normal QRS complexes (i.e., NN50/NN). Both RMSSD and PNN50 reflect changes in parasympathetic tone. Their values are positively correlated with parasympathetic activity; consequently, a decrease in RMSSD and pNN50 indicates diminished parasympathetic activity. In our study, both the 24-hour Holter recordings and the daytime/nighttime Holter recordings of RMSSD and PNN50 were lower in patients with CHD with hypertension than in patients in the normotension group; therefore, we concluded that parasympathetic tone was lower in the former group. Fourth, the TINN, approximating the NN interval distribution, is the baseline width of the distribution. TINN is considered a measure of HRV. In our study, both the daytime and the nighttime Holter recordings of TINN were significantly lower in patients with CHD with hypertension than in patients in the normotension group. Our results also demonstrated that HRV was lower in patients >60 years of age with CHD with hypertension than in patients in the normotension group. Fifth, the power variables widely applied to analyze HRV are LF and HF. Historically, LF oscillations have been used to assess sympathetic nervous system activation. Recently, the interpretation of LF oscillations has been demonstrated to be complicated, given that both parasympathetic and sympathetic activation affect this oscillatory region. Herein, the LF was significantly lower in patients with CHD with hypertension than in patients with CHD with normotension, thus, also indicating sympathetic and parasympathetic dysfunction. High frequency components indicate parasympathetic nervous system activation. The 24-hour Holter recordings of frequency-domain methods showed that HF was significantly lower in patients with CHD with hypertension than in patients with CHD with normotension. The high frequency results again demonstrated diminished parasympathetic tone. Furthermore, ANS plays a crucial role in the development of hypertension. The HRV was significantly lower in patients with CHD with hypertension rather than normotension. Lower levels of HRV indicate dysfunction in ANS control.

More patients in the CHD with hypertension group than the CHD group received PCI (57.69% vs. 50%, P=0.55), although the result was not statistically significant. However, no significant differences in outcomes were observed between groups in follow-up. These results suggest that early intervention treatment might improve the prognoses of patients with severely decreased HRV. The clinical utility of HRV in assessing therapy adequacy in secondary prevention, particularly in patients with CHD with hypertension, may improve patient prognosis.

Notably, according to our time-domain and frequency-domain results, heart autonomic dysfunction in patients >60 years of age with CHD was more severe among those with rather than without hypertension. According to the relationship between HRV and ANS function, we concluded that increased sympathetic nervous system activity and decreased parasympathetic nervous system activity occurred in patients with CHD and hypertension. Furthermore, according to the relationship between HRV and adverse events during follow-up, we concluded that both the time-domain parameters and frequency domain parameters of HRV may serve as markers of ANS dysfunction among patients with CHD with hypertension. Consequently, greater clinical attention should be paid to abnormal heart rate variability. Finally, our results suggested that more interventions are required to improve prognosis in patients with abnormal HRV.

Limitation

Several limitations might be inherent to our study. Because age is a risk factor for CHD, we included only patients older than 60 years. Moreover, we did not include patients with hypertension without coronary artery disease. In future research, we will include larger numbers of patients and will compare a CHD group, CHD+hypertension group, and hypertension group, to address these limitations.

Acknowledgements

None.

Author Contribution

Jing-Xiu Li and Jing Wang substantially contributed to data collection and manuscript preparation. Bei-Bei Ding and Min Gao performed the analysis with discussion. All authors have agreed to the order in which their names are listed in the article.

Conflict of Interest

Funders did not play any role in this study design, data collection, analysis, the decision to publish, or preparation of the manuscript.

Data Availability Statement

Data sharing does not apply to this article.

Ethics Statement

The ethics committee of The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, approved the study, which conforms to recognized standards, including the Declaration of Helsinki.

REFERENCES

1. Maehle AH. "Receptive substances": John Newport Langley (1852-1925) and his path to a receptor theory of drug action. Med Hist 2004;48(2):153–74.
2. Karim S, Chahal A, Khanji MY, Petersen SE, Somers VK. Autonomic cardiovascular control in health and disease. Compr Physiol 2023;13(2):4493–511.
3. Huikuri HV, Stein PK. Heart rate variability in risk stratification of cardiac patients. Prog Cardiovasc Dis 2013;56(2):153–9.
4. Hon EH, Lee ST. Electronic evaluation of the fetal heart rate. VIII. Patterns preceding fetal death, further observations. Am J Obstet Gynecol 1963;87:814–26.
5. Kawano H, Okada R, Yano K. Histological study on the distribution of autonomic nerves in the human heart. Heart Vessels 2003;18(1):32–9.

6. Schiweck C, Piette D, Berckmans D, Claes S, Vrieze E. Heart rate and high frequency heart rate variability during stress as biomarker for clinical depression. A systematic review. Psychol Med 2019;49(2):200–11.
7. Trautwein W, Kameyama M. Intracellular control of calcium and potassium currents in cardiac cells. Jpn Heart J 1986;27 Suppl 1:31–50.
8. Brown HF, DiFrancesco D, Noble SJ. How does adrenaline accelerate the heart? Nature 1979;280(5719):235–36.
9. DiFrancesco D, Ferroni A, Mazzanti M, Tromba C. Properties of the hyperpolarizing-activated current (if) in cells isolated from the rabbit sino-atrial node. J Physiol 1986;377:61–88.
10. Sakmann B, Noma A, Trautwein W. Acetylcholine activation of single muscarinic K+ channels in isolated pacemaker cells of the mammalian heart. Nature 1983;303(5914):250–3.
11. DiFrancesco D, Tromba C. Muscarinic control of the hyperpolarization-activated current (if) in rabbit sino-atrial node myocytes. J Physiol 1988;405:493–510.
12. Askin L, Cetin M, Turkmen S. Ambulatory blood pressure results and heart rate variability in patients with premature ventricular contractions. Clin Exp Hypertens 2018;40(3):251–6.
13. Patel VN, Pierce BR, Bodapati RK, Brown DL, Ives DG, Stein PK. Association of Holter-derived heart rate variability parameters with the development of congestive heart failure in the cardiovascular health study. JACC Heart Fail 2017;5(6):423–31.
14. Wu L, Jiang Z, Li C, Shu M. Prediction of heart rate variability on cardiac sudden death in heart failure patients: a systematic review. Int J Cardiol 2014;174(3):857–60.
15. Moors S, Staaks KJJ, Westerhuis MEMH, Dekker LRC, Verdurmen KMJ, Oei SG. Heart rate variability in hypertensive pregnancy disorders: a systematic review. Pregnancy Hypertens 2020;20:56–68.
16. Maciorowska M, Krzesiński P, Wierzbowski R, Gielerak G. Heart rate variability in patients with hypertension: the effect of metabolic syndrome and antihypertensive treatment. Cardiovasc Ther 2020;2020:8563135.
17. Vesela J, Osmancik P, Herman D, Prochazkova R. Changes in heart rate variability in patients with atrial fibrillation after pulmonary vein isolation and ganglionated plexus ablation. Physiol Res 2019;68(1):49–57.
18. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation 1996;93(5):1043–65.
19. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Eur Heart J 1996;17(3):354–81.
20. Fang SC, Wu YL, Tsai PS. Heart rate variability and risk of all-cause death and cardiovascular events in patients with cardiovascular disease: a meta-analysis of cohort studies. Biol Res Nurs 2020;22(1):45–56.
21. Goldenberg I, Goldkorn R, Shlomo N, Einhorn M, Levitan J, Kuperstein R, et al. Heart rate variability for risk assessment of myocardial ischemia in patients without known coronary artery disease: the HRV-DETECT (heart rate variability for the detection of myocardial ischemia) study. J Am Heart Assoc 2019;8(24):e014540.
22. Bai X, Li J, Zhou L, Li X. Influence of the menstrual cycle on nonlinear properties of heart rate variability in young women. Am J Physiol Heart Circ Physiol 2009;297(2):H765–74.