Int J Clin Exp Med 2020;13(11):8998-9004
www.ijcem.com /ISSN:1940-5901/IJCEM0116123

Original Article

Effects of amiodarone combined with recombinant human brain natriuretic peptide on blood pressure and serum myocardial enzymes in patients with arrhythmia

Zhoushan Gu, Xiaochen Lu, Qi Lu

Department of Cardiology, Affiliated Hospital of Nantong University, Nantong 226001, Jiangsu Provincial, China

Received June 12, 2020; Accepted August 10, 2020; Epub November 15, 2020; Published November 30, 2020

Abstract: Objective: This study aimed to investigate the effects of amiodarone combined with recombinant human brain natriuretic peptide (rhBNP) on blood pressure and serum myocardial enzymes in patients with arrhythmia. Methods: Altogether, 106 patients with arrhythmia who were admitted to our hospital were randomized into the control group (CON group) and the combined group (COM group). The CON group was treated by amiodarone alone, while the COM group was treated by amiodarone combined with rhBNP. The efficacy of treatment in the two groups was compared: the change in blood pressure and cardiac rhythm before and after treatment were recorded, the changes in the arrhythmia indexes and serum myocardial enzyme indexes after treatment were detected, and the effects of amiodarone combined with rhBNP on arrhythmia were evaluated. Results: The effective rate of the COM group was dramatically higher than that of the CON group. Before treatment, there was no remarkable difference in blood pressure and heart rate between both groups. After treatment, the blood pressure and heart rate of the COM group were dramatically lower than that of the CON group. With regard to postoperative adverse reactions, the incidence of adverse reactions in the COM group was lower than that in the CON group, with marked differences. After treatment, the AST, LDH and CK levels in the COM group were lower than those in the CON group ($P<0.05$). Conclusion: Amiodarone combined with rhBNP is effective in treating patients with arrhythmia, and it can effectively improve cardiac function and relieve myocardial injury.

Keywords: Amiodarone, recombinant human brain natriuretic peptide (rhBNP), combined therapy, arrhythmia, blood pressure, myocardial enzymogram

Introduction

Arrhythmia is currently a very common cardiovascular disease, and it usually shows changes in a normal electrical pulse signal [1]. It is relatively complex and it has high risks [2]. Cardiac rhythm disorder, palpitation, dizziness and fatigue are the main clinical symptoms, which are mainly caused by acquired or congenital heart disease. It can lead to cardiac blood supply disorders, myocardial ischemia, heart failure and even death of patients in serious cases [3]. There are many factors causing this disease, such as smoking [4], hypertension [5], diabetes [6], high cholesterol [7], obesity [8], and family history [9]. Some studies [10] have shown that arrhythmia can occur independently or secondary to other diseases such as hypertension and coronary heart disease; all of which have a high morbidity and are increasing annually in recent years. It is of vital importance to effectively stabilize the patients' heart rate, improve their treatment efficacy and quality of prognosis. At present, the mechanism of action of arrhythmia is mainly due to ion channels and genetics, but there has been no breakthrough of a cure. Drug therapy is still a complex problem. The use of class I drugs reached its peak in 1960s, but gradually decreased due to side effects and low treatment efficacy; and a such the status of class III drugs has been improved. Although class II drugs are broad-spectrum, they have certain limitations due to the side effects of iodine; and the prevention of sudden cardiac death and sympathetic storm has been noticed. Class IV drugs were almost forgotten about except for treatment of paroxysmal supraventricular tachycardia. Clinical applica-

tion of appropriate drugs for arrhythmia treatment can improve cardiac function, reduce malignant arrhythmia and sudden cardiac death, as well as advance the treatment rate and the prognosis overall.

At the moment, drugs are mostly used for conservative treatment of arrhythmia. There are many kinds of drugs for arrhythmia, but considering the comprehensive efficacy and safety, most drugs have poor comprehensive efficacy. Metoprolol succinate sustained-release tablets are commonly used clinically, which belong to class II antiarrhythmic drugs and can slow down the internal flow rate of calcium ions in the body, block epinephrine receptors, improve sympathetic nerve excitation, reduce oxygen consumption of myocardial cells in the body, and reduce heart rate and blood pressure [11, 12]. Although conventional anti-heart failure treatment can relieve the clinical symptoms of patients, long-term use of anti-arrhythmia drugs alone cannot control heart rate and blood pressure at normal levels, and poor prognosis results make it difficult to achieve the desired effect. It is necessary to incorporate other treatment schemes to strengthen the treatment efficacy [13]. Amiodarone belongs to class III antiarrhythmic drugs and it has a marked efficacy on cardiac function. By inhibiting potassium ion outflow, it can ameliorate the effective refractory period of the ventricles, atrium and atrioventricular node, effectively reduce signal reentry excitation, improve myocardial ischemia, dilate coronary artery blood vessels; and the negative muscle strength generated by the drugs is relatively mild, thus stabilizing the heart rate and improvinging cardiac function [14, 15]. Freeze-dried recombinant human brain natriuretic peptide (rhBNP) can increase coronary artery perfusion, prevent myocardial infarction lesions from expanding and improve ventricular function [16].

In this study, patients with arrhythmia were selected, and amiodarone and rhBNP were combined to explore the efficacy of combination therapy, as well as their effects on blood pressure and blood myocardial enzymes.

Materials and methods

Subjects of research

Altogether, 106 patients with arrhythmia who were admitted to our hospital from February 2017 to August 2019 were selected as the participants. They were randomized into the CON group and the COM group. There were 49 patients in the CON group, including 26 males and 23 females, with an average age of (60.3±7.9) years, and they were all treated by amiodarone alone. There were 57 cases in the COM group, including 31 males and 26 females, with an average age of 61.0±7.5 years, and they were all treated by amiodarone combined with rhBNP. There was no obvious difference between the general data of both groups (P>0.05). Inclusion criteria: Tachyarrhythmia was diagnosed by electrocardiogram; the main clinical symptoms were palpitation and chest tightness, and there was no severe liver, kidney, lung and cerebrovascular diseases. There was no contraindications for drug use in this study. Exclusion criteria were as follows: severe atrioventricular block, myocardial infarction, sick sinus syndrome, atrial mural thrombosis and other cardiac diseases; patients complicated with chronic obstructive pulmonary disease (COPD), asthma and other respiratory diseases; patients accompanied by diabetes and other serious metabolic system diseases; patients with malignancies, acute and chronic inflammation, immune system diseases or cachexia; and pregnant or lactating women recently taking anti-inflammatory drugs. This study was approved by the Hospital Ethics Committee, and all patients signed an informed consent form.

Methods

CON group: Amiodarone was given for treatment. Usage methods: 150 mg amiodarone was added into 20 mL glucose injection with a concentration of 5% for intravenous injection for a duration of >10 min; next, an intravenous pump was used for continuous injection treatment. The dosage for the first 6-hour injection was controlled at 1 mg/min, the speed was controlled at 0.5 mg/min, and the dosage for the first day was controlled at 2.2 g.

COM group: Freeze-dried rhBNP was given in addition to treatment in the CON group. The dosage was 1.5 μg/kg and it was injected intravenously; after 2-5 minutes the injection was completed, it was pumped with a dosage of 7.5 mg/(kg·min); the dosage was gradually reduced after 72 h, and the drug was stopped within 24 h.

Table 1. Comparison of blood pressure and heart rate of patients between the two groups

	SBP (mmHg)		DBP (mmHg)		HR (times/min)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Combined group (n=57)	150.25±14.82	125.64±12.75	98.26±10.62	82.18±8.56	122.36±15.20	88.69±10.68
Control group (n=49)	150.12±14.65	139.62±13.75	98.18±10.43	88.72±9.05	121.24±15.14	94.62±11.15
χ^2/t	0.0453	5.4278	0.0389	3.8194	0.3789	2.7928
P	0.9639	<0.0001	0.9689	0.0002	0.7055	0.0062

Outcome measures

Efficacy: Before and after treatment, LVEF, LVEDV and LVESV of patients in the two groups were measured by ultrasonic cardiogram. Grading was scored as: ineffective: LVEF increased <30% after treatment; effective: LVEF increased by 30%-50% after treatment; markedly effective: LVEF increased by more than 50% after treatment. Effective and marked effective cases were counted into the total effective rate.

Heart rate and blood pressure were monitored before treatment by electrocardiogram for 1 h. Records were made every 5 min, and the average value was regarded as the specific index.

Arrhythmia indexes of both groups after 30 days of treatment were recorded, including the total number of ventricular premature beats, the time required for arrhythmia to return to normal, and the number of short-term ventricular tachycardia attacks.

The adverse reactions of both groups during treatment were observed.

The levels of myocardial enzymes before and after treatment in both groups were measured. Altogether 5 mL of fasting blood was sampled in the morning. The levels of lactate dehydrogenase (LDH), aspartate aminotransferase (AST) and creatine kinase (CK) were measured by Lai's colorimetry using a fully automatic biochemical analyzer (AU5800, Beckman, USA).

Statistical methods

All the data were analyzed via SPSS 21.0. The measurement data were expressed as mean±standard deviation of at least three independent experiments. The comparison between groups was assessed via t test. The counting data were expressed as (n) %, analyzed by chi-square test, and plotted by GraphPad Prism 6. The difference was statistically significant with P<0.05.

Results

Comparison of blood pressure and heart rate of patients between both groups

Comparing the changes in blood pressure and heart rate between the two groups before and after treatment, we found that there was no remarkable difference in systolic blood pressure, diastolic blood pressure and heart rate before treatment (P>0.05). After treatment, all indexes decreased, but the decrease in the COM group was remarkably larger than that in the CON group (P<0.05) (**Table 1**).

Comparison of myocardial enzymogram of patients in both groups

The changes of myocardial enzymogram before and after treatment were compared between the two groups. There was no marked difference in AST, LDH and CK before treatment. After treatment, the indexes of the COM group were dramatically lower than those of the CON group (P<0.05) (**Table 2**).

Comparison of arrhythmia indexes between both groups of patients after treatment

After 30 days of treatment, the COM group was superior to the CON group (P<0.05) in terms of arrhythmia indexes such as the number of short-array atrioventricular tachycardia attacks, the total number of atrioventricular premature contractions and the time when patients' cardiac rhythm stabilized at the normal level (**Figure 1**).

Comparison of cardiac function and clinical efficacy of patients between both groups

There was no remarkable difference in LVEF, LVEDV and LVESV between the two groups

Table 2. Comparison of myocardial enzymogram of patients in the two groups

	AST (IU/L)		LDH (IU/L)		CK (mmol/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Combined group (n=57)	60.10±19.56	31.62±10.32	239.56±31.02	165.53±15.23	158.68±26.31	96.36±12.36
Control group (n=49)	61.02±19.82	41.36±13.25	241.51±32.52	203.65±19.68	159.94±26.82	116.52±15.26
χ^2/t	0.2399	4.2502	0.3156	11.2291	0.2436	7.5127
P	0.8108	<0.0001	0.7530	<0.0001	0.8080	<0.0001

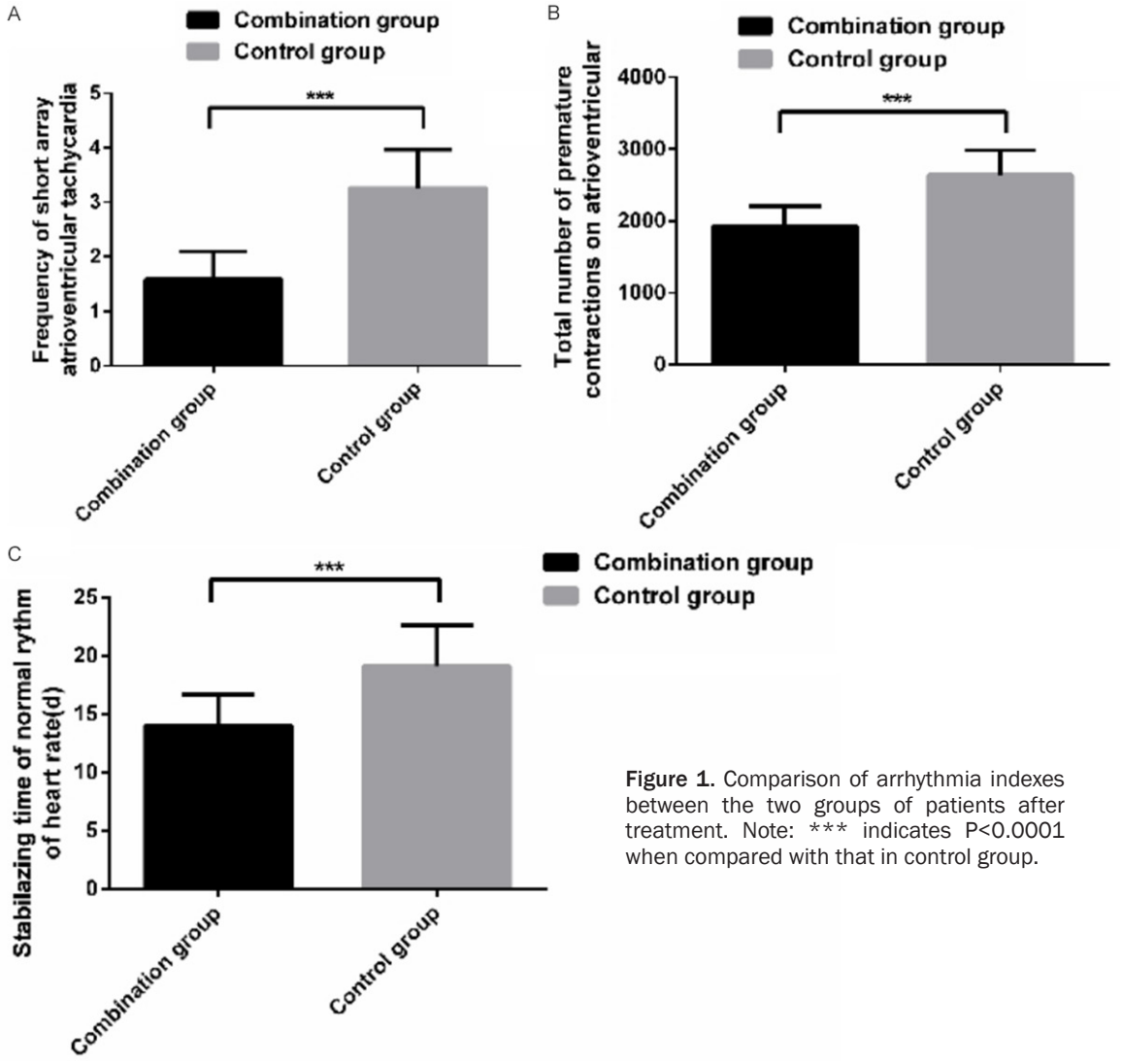

Figure 1. Comparison of arrhythmia indexes between the two groups of patients after treatment. Note: *** indicates P<0.0001 when compared with that in control group.

before treatment (P>0.05). After treatment, LVEF in the COM group was higher than that in the CON group, while LVEDV and LVESV were lower than that in the CON group, with obvious differences (P<0.05) (**Table 3**).

For the clinical efficacy of patients in both groups, the total effective rate of the treatment in the COM group was higher than that of the CON group, with marked differences (P<0.05) (**Table 4**).

Comparison of adverse reactions between both groups during treatment

Comparing the adverse reactions such as hypotension, bradycardia, dizziness and fatigue occurred in the two groups during treatment,

Table 3. Comparison of cardiac function of patients between the two groups

	LVEF (%)		LVEDV (mL)		LVESV (mL)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Combined group (n=57)	40.52±6.48	55.61±6.95	159.64±11.98	136.25±7.36	107.71±12.86	68.52±10.28
Control group (n=49)	40.12±6.25	49.35±6.53	158.75±11.75	144.22±8.15	106.84±12.93	79.25±11.25
χ^2/t	0.3221	4.7539	0.3847	5.2893	0.3463	5.1290
P	0.7480	<0.0001	0.7012	<0.0001	0.7297	<0.0001

Table 4. Comparison of clinical efficacy of patients between the two groups

	Ineffective	Effective	Markedly effective	Total effective rate
Combined group (n=57)	5 (8.77)	33 (57.89)	19 (33.34)	52 (91.23)
Control group (n=49)	12 (24.49)	26 (53.06)	11 (22.45)	37 (75.51)
χ^2/t				4.834
P				0.028

Table 5. Comparison of adverse reactions between the two groups during treatment

	Hypotension	Bradycardia	Dizziness and fatigue	Total incidence rate
Combined group (n=57)	1 (1.75)	0 (0)	1 (1.75)	2 (3.51)
Control group (n=49)	2 (4.08)	2 (4.08)	3 (6.12)	7 (14.3)
χ^2/t				4.456
P				0.034

we found that the incidence of adverse reactions in the COM group was remarkably lower than that in the CON group (P<0.05) (**Table 5**).

Discussion

Arrhythmia is caused by excitation occurring outside the sinus node or abnormal excitation of the sinus node, block, slow or abnormal ion channel conduction during the conduction of excitation, etc. Clinically, according to its physiological and pathological mechanism, it can be divided into two categories: abnormal origin of electrical impulse and abnormal conduction pathway; the former includes ventricular arrhythmia and ectopic arrhythmia, while the latter is a common clinical type, including abnormal impulse conduction and reentry excitation. After onset, it will pose a serious threat to quality of life of patients [17, 18]. There are many drugs for arrhythmia, including sodium channel inhibitors, β receptor blockers, calcium channel antagonists, potassium channel inhibitors, etc., which can effectively improve the symptoms of patients and promote the recovery of myocardial function [19].

This study compared the efficacy of amiodarone alone (CON group) and amiodarone combined with rhBNP (COM group) in patients with arrhythmia. The results showed that the effective rate of the COM group was dramatically higher than that of the CON group. After treatment, the left ventricular end-diastolic volume and left ventricular end-systolic volume in the COM group were lower than those of the CON group. Studies have shown that rhBNP therapy can dramatically reduce the levels of tumor necrosis factor and monocyte chemotactic factor and improve the treatment prognosis [20]; peptides can effectively improve myocardial oxygen supply and blood supply, thus promoting cardiac function recovery [21]; it can also increase coronary perfusion, prevent myocardial infarction from expanding, improve ventricular function and inhibit cardiac remodeling [22]. Similar to these results, this study also found that with the combination therapy of amiodarone and rhBNP, the cardiac function of patients was improved, better than that of amiodarone alone. The possible mechanism is that amiodarone plays a vital role in potassium channel regulation in the treatment, which can prolong the effective refractory period and action potential of myocardial tissue, so as to eliminate reentrant excitation; also, it can prolong the conduction time of atrionector to a cer-

tain extent, and effectively maintain the recovery time. Meanwhile, rhBNP can open ATP sensitive potassium channels through cGMP-dependent protein kinase pathway, increase potassium ion flux into the mitochondria, reduce transmembrane potential differences and calcium ion influx, and jointly improve cardiac function [23]. Before treatment, there was no obvious difference in blood pressure and heart rate between both groups. After treatment, the blood pressure and heart rate in the COM group were dramatically lower than those in the CON group. At the same time, this study found that amiodarone had the properties of class I, II and IV antiarrhythmic drugs, and could slightly and non-competitively inhibit adrenoceptors, expand coronary arteries and peripheral arteries, increase myocardial circulation and reduce peripheral vascular resistance, thus improving myocardial blood oxygen supply and cardiac function [24]. However, rhBNP has an antagonistic effect on renin-angiotensin-aldosterone system (RAAS), which can promote glomerular filtration, increase sodium excretion, reduce renin and aldosterone secretion, protect sodium, diuresis, and raise hypertension, further reduce systemic circulation resistance and volume, reduce ventricular anteroposterior load, and maintain hemodynamic balance of blood vessels and kidneys [25]. Our results showed that amiodarone combined with rhBNP could stabilize blood pressure and heart rate. The mechanism might be that amiodarone increased myocardial circulation and reduced peripheral vascular resistance, thus improving myocardial oxygen supply. Meanwhile, rhBNP reduced systemic circulation resistance and circulation capacity, and decreased ventricular preload and afterload. The synergetic effect of the two methods was better for improving blood pressure and heart rate. As to postoperative adverse reactions, the incidence of adverse reactions in the COM group was lower than that in the CON group, with marked differences. Amiodarone can affect the atrial node, extend the conduction time of the sinus node to a certain extent, and effectively maintains the recovery time of the sinus node. Meanwhile, it has an effect on the effective refractory period and action potentials. For instance, a patients' heart rate accelerates due to amiodarone [26]. rhBNP can be combined with guanylate cyclase coupled receptors to increase the content of intracellular cyclic guanosine monophosphate (cGMP) and relax smooth muscle. cGMP acts as a second messenger to rapidly reduce systemic arterial pressure, pulmonary capillary wedge pressure and right atrial pressure, thereby reducing anterior and posterior cardiac load and relieving clinical symptoms such as shortness of breath and palpitation of patients [27]. Therefore, amiodarone combined with rhBNP has a low adverse reaction rate in treating arrhythmia. In the detection of serum myocardial enzyme indexes, we found that after treatment, the AST, LDH and CK levels in the COM group were lower than those in the CON group ($P<0.05$). Thus, amiodarone combined with rhBNP can effectively reduce the level of myocardial enzyme spectrum and relieve myocardial injury in patients with arrhythmia. There are still some limitations in this study. On the one hand, there are only a few clinical studies on the combined use of the two drugs. On the other hand, we lack experience in the application of drug dosage, and the sample size is small. Hence, it is necessary to increase the sample size through multiple channels to further confirm the conclusions.

To sum up, rhBNP combined with amiodarone is effective in treating arrhythmia. It is more effective in stabilizing blood pressure of patients and improving serum myocardial enzyme indexes. What's more, it has good recovery effect on cardiac function, and is worthy of being popularized clinically.

Disclosure of conflict of interest

None.

Address correspondence to: Qi Lu, Department of Cardiology, Affiliated Hospital of Nantong University, No. 20 Xisi Road, Nantong 226001, Jiangsu Provincial, China. Tel: +86-513-81161301; E-mail: liqr1023@163.com

References

[1] Fu DG. Cardiac arrhythmias: diagnosis, symptoms, and treatments. Cell Biochem Biophys 2015; 73: 291-296.

[2] Meng XD, Gao WQ and Sun Z. Amiodarone and acupuncture for cardiac arrhythmia: study protocol for a systematic review. Medicine (Baltimore) 2019; 98: e14544.

[3] Kline J and Costantini O. Arrhythmias in congenital heart disease. Med Clin North Am 2019; 103: 945-956.

[4] Rezkalla S and Kloner RA. Cardiovascular effects of marijuana. Trends Cardiovasc Med 2019; 29: 403-407.
[5] Afzal MR, Savona S, Mohamed O, Mohamed-Osman A and Kalbfleisch SJ. Hypertension and Arrhythmias. Heart Fail Clin 2019; 15: 543-550.
[6] Fitzpatrick C, Chatterjee S, Seidu S, Bodicoat DH, Ng GA, Davies MJ and Khunti K. Association of hypoglycaemia and risk of cardiac arrhythmia in patients with diabetes mellitus: a systematic review and meta-analysis. Diabetes Obes Metab 2018; 20: 2169-2178.
[7] Goonasekara CL, Balse E, Hatem S, Steele DF and Fedida D. Cholesterol and cardiac arrhythmias. Expert Rev Cardiovasc Ther 2010; 8: 965-979.
[8] Csige I, Ujvarosy D, Szabo Z, Lorincz I, Paragh G, Harangi M and Somodi S. The impact of obesity on the cardiovascular system. J Diabetes Res 2018; 2018: 3407306.
[9] Kapur S, Kumar S, John RM, Stevenson WG, Tedrow UB, Koplan BA, Epstein LM, MacRae CA and Michaud GF. Family history of atrial fibrillation as a predictor of atrial substrate and arrhythmia recurrence in patients undergoing atrial fibrillation catheter ablation. Europace 2018; 20: 921-928.
[10] Traupe T, Keller M, Fojtu E, Bhattacharya I, Lang M, Ha HR, Jochum W, Mundy AL and Barton M. Antioxidant activity and sex differences of acute vascular effects of amiodarone in advanced atherosclerosis. J Cardiovasc Pharmacol 2007; 50: 578-584.
[11] Ajam T, Ajam S, Devaraj S, Mohammed K, Sawada S and Kamalesh M. Effect of carvedilol vs metoprolol succinate on mortality in heart failure with reduced ejection fraction. Am Heart J 2018; 199: 1-6.
[12] Rivinius R, Helmschrott M, Ruhparwar A, Rahm AK, Darche FF, Thomas D, Bruckner T, Ehlermann P, Katus HA and Doesch AO. Control of cardiac chronotropic function in patients after heart transplantation: effects of ivabradine and metoprolol succinate on resting heart rate in the denervated heart. Clin Res Cardiol 2018; 107: 138-147.
[13] Brunetti L, Lee SM, Nahass RG, Suh D, Miao B, Bucek J, Kim D, Kim OK and Suh DC. The risk of cardiac events in patients who received concomitant levofloxacin and amiodarone. Int J Infect Dis 2019; 78: 50-56.
[14] Haverkamp W, Israel C and Parwani A. Clinical aspects of treatment with amiodarone. Herzschrittmacherther Elektrophysiol 2017; 28: 307-316.
[15] Stein C, Migliavaca CB, Colpani V, da Rosa PR, Sganzerla D, Giordani NE, Miguel S, Cruz LN, Polanczyk CA, Ribeiro ALP and Falavigna M. Amiodarone for arrhythmia in patients with Chagas disease: a systematic review and individual patient data meta-analysis. PLoS Negl Trop Dis 2018; 12: e0006742.
[16] Liu K, Li D, Hao G, McCaffary D, Neely O, Woodward L, Ioannides D, Lu CJ, Brescia M, Zaccolo M, Tandri H, Ajijola OA, Ardell JL, Shivkumar K and Paterson DJ. Phosphodiesterase 2A as a therapeutic target to restore cardiac neurotransmission during sympathetic hyperactivity. JCI Insight 2018; 3.
[17] Kalyanasundaram A, Li N, Hansen BJ, Zhao J and Fedorov VV. Canine and human sinoatrial node: differences and similarities in the structure, function, molecular profiles, and arrhythmia. J Vet Cardiol 2019; 22: 2-19.
[18] Ambesh P and Kapoor A. Biological pacemakers: concepts and techniques. Natl Med J India 2017; 30: 324-326.
[19] Pereira L, Bare DJ, Galice S, Shannon TR and Bers DM. beta-Adrenergic induced SR Ca(2+) leak is mediated by an Epac-NOS pathway. J Mol Cell Cardiol 2017; 108: 8-16.
[20] Isaksen K, Halvorsen B, Munk PS, Aukrust P and Larsen AI. Effects of interval training on inflammatory biomarkers in patients with ischemic heart failure. Scand Cardiovasc J 2019; 53: 213-219.
[21] Puthanveetil P, Wan A and Rodrigues B. Lipoprotein lipase and angiopoietin-like 4 - Cardiomyocyte secretory proteins that regulate metabolism during diabetic heart disease. Crit Rev Clin Lab Sci 2015; 52: 138-149.
[22] Cao X, Xia HY, Zhang T, Qi LC, Zhang BY, Cui R, Chen X, Zhao YR and Li XQ. Protective effect of lyophilized recombinant human brain natriuretic peptide on renal ischemia/reperfusion injury in mice. Genet Mol Res 2015; 14: 13300-13311.
[23] Wang L, Xie L, Wei X and Xie Z. Beneficial effects of early administration of recombinant human B-type natriuretic peptide in ST-elevation myocardial infarction patients receiving percutaneous coronary intervention treatment. Singapore Med J 2019; 60: 621-625.
[24] Kotoda M, Ino H, Kumakura Y, Iijima T, Ishiyama T and Matsukawa T. Analgesic effects of amiodarone in mouse models of pain. J Pain Res 2019; 12: 1825-1832.
[25] Okamoto R, Ali Y, Hashizume R, Suzuki N and Ito M. BNP as a major player in the heart-kidney connection. Int J Mol Sci 2019; 20: 3581.
[26] Luo C, Wang K and Zhang H. Effects of amiodarone on short QT syndrome variant 3 in human ventricles: a simulation study. Biomed Eng Online 2017; 16: 69.
[27] Nakagawa Y, Nishikimi T and Kuwahara K. Atrial and brain natriuretic peptides: hormones secreted from the heart. Peptides 2019; 111: 18-25.