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Severe heart failure with rapid arrhythmia: Treatment with amiodarone and esmolol and its effect on TGF-β1, APN and PIIINP

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Rapid arrhythmia (RA) is a major complication of severe heart failure (SHF). Treatment with anti-arrhythmic drug amiodarone though improves the myocardial blood supply and suppress arrhthmia, its clinical application is not satisfactory. Amiodarone combined with another class II antiarrhythmic drug esmolol shows rapid onset and good efficacy. Here, we studied the effects of amiodarone and esmolol in severe heart failure (SHF) with rapid arrhythmia (RA) and its effect on TGF-β1, APN and PIIINP. A total of 180 SHF patients with RA treated at Zhejiang Provincial Hospital of Traditional Chinese Medicine were selected and divided into experimental group (n = 90) and control group (n = 90) according to the random number table method. The control group was given routine therapy + amiodarone therapy, and the experimental group was given routine therapy + amiodarone + esmolol therapy. Cardiac function measures including cardiac index (CI), mean arterial pressure (MAP) and ejection fraction (LVEF), diastolic blood pressure (DBP), systolic blood pressure (SBP) and heart rate (HR), serum TGF-β1, APN and PIIINP levels were observed in both groups before and 48 h after treatment. After treatment, the CI, MAP and LVEF of the experimental group were greater than those of the control group (P <0.05); DBP, SBP and HR were greater (or higher) in the experimental group than in the control group (P <0.05); serum TGF-β1 and PIIINP levels in experimental groups were all lower than in control group and serum APN levels were higher (P <0.05) than in control group. The total effective rate of the experimental group was less than that of the control group (P <0.05). There was no difference in the incidence of adverse effects between the two groups (P >0.05). The results indicate that treatment of severe heart failure (SHF) with rapid arrhythmia (RA) by amiodarone and esmolol may safely enhance cardiac function, blood pressure and heart rate, improve efficacy, inhibit the progression of myocardial fibrosis, and improve serum TGF-β1, APN and PIIINP levels.

Keywords: Adiponectin, Anti-arrhythmic drug, Blood pressure, Cardiac index, Heart rate, Mean arterial pressure Procollagen, Transforming growth factor-β1

Severe heart failure (SHF) is a cardiac circulatory disorder syndrome resulting from a sustained reduction in cardiac function and is the terminal stage of various cardiovascular diseases[1]. Rapid arrhythmia (RA) is a major complication of SHF because patients mostly present with significant atrial fibrillation (AF) and ventricular tachycardia (VT), which can increase myocardial oxygen consumption, promote myocardial necrosis, drive the progression of SHF and even lead to patient death[2]. For SHF combined with RA, clinically it recommends administration of amiodarone for treatment, in order to suppress arrhythmias and improve myocardial blood supply[3]. Although amiodarone treatment for SHF with RA can achieve the above purpose, because of its slower onset, it is often unsatisfactory in clinical application[4].

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Esmolol, a class II antiarrhythmic drug, applied in HF combined with RA is reported to have advantage of rapid onset and good efficacy[5]. Transforming growth factor-β1 (TGF-β1), adiponectin (APN) and amino telopeptide of type III procollagen (PIIINP) are closely related to HF and RA, and the altered levels are of great value for evaluating the efficacy of SHF combined with RA, and there are no clinical studies. Hence, in the present study, we explored combination of amiodarone and esmolol for treatment of Severe heart failure (SHF) with rapid arrhythmia (RA) patients in order to investigate its clinical efficacy and effect on TGF-β1, APN and PIIINP.

Materials and Methods

Clinical data

Severe heart failure (SHF) patients (180) with RA treated at Zhejiang Provincial Hospital of Traditional Chinese Medicine, Zhejiang, China from July 2017 to

July 2022 were selected, 102 males and 78 females; age ranged from 60 to 82 years, with a mean (65.64±6.83) years; primary disease: hypertensive heart disease (n = 84), coronary heart disease (n = 70), cardiomyopathy (n = 19), other (n = 7); NYHA functional class: 126 were class III and 54 were class IV. Inclusion criteria: SHF diagnosis fulfilled the relevant criteria according to the "Chinese Guidelines for Diagnosis and Treatment of Heart Failure"[6], RA diagnosis fulfilled the relevant criteria according to the "Expert Consensus on Emergency Management of Arrhythmia"[7]; Informed consent. Exclusion criteria: those with RA due to other factors; those with congenital heart disease; those with contraindications to the study drugs; those with abnormal liver and kidney function; comorbid with other major medical illnesses; those with poor adherence; those with comorbid malignancies. The 180 patients were divided into experimental group (n = 90) and control group (n = 90) according to the random number table method, and there was no difference in baseline data between the two groups (P >0.05) (Table 1).

Therapeutic methods

Both groups received routine therapies such as oxygen inhalation, diuresis, cardiac strengthening and dilated blood vessels.

The control group was given routine therapy + amiodarone therapy. Intravenous infusion of the first dose of amiodarone (150 mg/3 mL) 150 mg dissolved in 20 mL of 5% dextrose, the intravenous infusion time was <10 min and, depending on the patient, after 10-15 min amiodarone 150 mg was used again. After confirmation of patient recovery, it was maintained intravenously with a dosing rate of 1mg/min within the first 6 h and 0.5 mg/min for the next 18 h. Amiodarone dose did not exceed 2000 mg in the first 24 h and was maintained at 0.5 mg/min in the second 24 h, i.e., total 720 mg/24 h.

The experimental group was given routine therapy + amiodarone + esmolol therapy. Routine therapy + amiodarone therapy as above. Esmolol 0.5 mg/kg intravenously, completed within 1 min. The infusion pump maintained the injection at a dose of 0.05 mg/kg/min for 24 h. In case of poor efficacy, the dose was escalated to a maximum of 0.2 mg/kg/min by 0.05 mg/kg/min.

Table 1 — Comparison of baseline data between the two groups

Baseline data	Experimental group (n = 90)	Control group (n = 90)	χ^2/t	P
Gender (M/F)	50/40	52/38	0.0900	0.7642
Age (years)	65.60±6.79	65.69±6.87	0.0884	0.9297
Primary disease*	41/36/10/3	43/34/9/4	0.3003	0.9600
NYHA functional class (Class III/IV)	62/28	64/26	0.1052	0.7456

[*hypertensive heart disease/coronary heart disease/ cardiomyopathy/ other]

Observation criteria

Cardiac function measures including cardiac index (CI), mean arterial pressure (MAP) and ejection fraction (LVEF), diastolic blood pressure (DBP), systolic blood pressure (SBP) and heart rate (HR), serum TGF-β1, APN and PIIINP levels were observed in both groups before and 48 h after treatment.

Efficacy evaluation criteria

(i) Showing effect: Patients with heart failure symptom control, arrhythmia symptom disappearance, reduced cardiac function ≥ grade 2; (ii) Effective: Patients have partial control of heart failure symptoms, arrhythmia symptoms are reduced, number of episodes is reduced by ≥70%, and cardiac function is reduced by ≥ grade1; (iii) Ineffective: The patients' symptoms of heart failure and arrhythmia were not relieved or aggravated; and (iv) Total effective = showing effect + effective.

Statistical methods

The data were analyzed with SPSS 19.0 statistical software, and the quantitative data were described in ($\bar{x}$±s), with paired t-tests for comparisons within group and independent samples t-tests for comparisons between two groups; qualitative data were expressed as percentage of cases and χ2 test was performed for comparison between groups. Examination level α is 0.05.

Results

Comparison of indexes of cardiac function between two groups

Before treatment, there were no differences in CI, MAP and LVEF between the two groups (P >0.05); CI, MAP, and LVEF were increased in both groups after treatment compared with those before treatment (P <0.05); after treatment, CI, MAP, and LVEF of the experimental group were greater than those of the control group (P <0.05) (Table 2).

Comparison of DBP, SBP and HR in the two groups

Before treatment, DBP, SBP and HR did not differ between the two groups (P >0.05); after treatment, DBP and SBP were increased in both groups compared with those before treatment, and HR was lower than it before treatment (P <0.05); after

treatment, DBP and SBP were higher and HR lower in the experimental group than those in the control group (P <0.05) (Table 3).

Comparison of serum TGF-β1, APN and PIIINP levels in both groups

Before treatment, there were no differences of serum TGF-β1, APN and PIIINP levels in both groups (P > 0.05); after treatment, serum TGF-β1 and PIIINP levels were all decreased and the levels of APN were increased compared with those before treatment (P <0.05); after treatment, serum TGF-β1 and PIIINP levels in experimental group were all lower and serum APN levels were higher (P <0.05) than those in control group. (Table 4).

Table 2 — Comparison of indexes of cardiac function between two groups ($\bar{x}$±s)

Index	Time	Expt. Group (n = 90)	Control group (n = 90)	*t*	*P*
CI [L/(min•m)]	BT	2.20±0.25	2.22±0.26	0.5260	0.5995
	AT	2.51±0.28	2.40±0.27	2.6828	0.0080
	t/P	7.8348/0.0000	4.5557/0.0000		
MAP (mmHg)	BT	75.42±7.83	75.47±7.86	0.0428	0.9659
	AT	85.53±8.81	80.72±8.38	3.7529	0.0002
	t/P	8.1373/0.0000	4.3350/0.0000		
LVEF (%)	BT	31.65±3.39	31.70±3.42	0.0985	0.9216
	AT	43.39±4.53	38.96±4.03	6.9315	0.0000
	t/*P*	19.6846/0.0000	13.0306/0.0000		

[BT, Before treatment; and AT, After treatment]

Table 3 — Comparison of markers of myocardial injury between the two groups ($\bar{x}$±s)

Index	Time	Expt. Group (n = 90)	Control group (n = 90)	*t*	*P*
Heart rate (beats/min)	BT	78.67±7.96	78.52±7.94	0.1266	0.8994
	AT	65.78±6.79	70.14±7.28	4.1549	0.0001
	t/P	11.6879/0.0000	7.3800/0.0000		
Diastolic BP (mmHg)	BT	70.32±7.25	70.34±7.28	0.0185	0.9853
	AT	77.69±7.90	73.83±7.59	3.3426	0.0010
	t/P	6.5207/0.0000	3.1482/0.0019		
Systolic BP (mmHg)	BT	108.80±12.38	109.73±12.41	0.5033	0.6154
	AT	120.95±13.68	115.96±13.25	2.4857	0.0139
	t/*P*	6.2474/0.0000	3.2556/0.0014		

[BT, Before treatment; AT, After treatment; and BP. Blood pressure]

Table 4 — Comparison of serum TGF-β1, APN and PIIINP levels in both groups ($\bar{x}$±s)

Index	Time	Expt. Group (n = 90)	Control group (n = 90)	*t*	*P*
TGF-β1 (pg/mL)	BT	346.96±37.06	344.88±36.98	0.3769	0.7067
	AT	278.38±29.16	304.97±32.19	5.8078	0.0000
	t/P	13.7967/0.0000	7.7226/0.0000		
APN (mg/L)	BT	10.65±1.38	10.70±1.40	0.2413	0.8096
	AT	17.06±1.92	13.07±1.55	15.3400	0.0000
	t/P	25.7183/0.0000	10.7647/0.0000		
PIIINP (pg/L)	BT	142.59±16.87	141.48±16.83	0.4419	0.6591
	AT	120.62±14.36	129.88±15.19	4.2026	0.0000
	t/*P*	9.4080/0.0000	5.2725/0.0000		

[BT, Before treatment; and AT, After treatment]

Comparison of clinical efficacy and adverse effects between two groups

The total effective rate of the experimental group was greater than that of the control group (P <0.05) (Table 5). However, there was no difference in the incidence of adverse effects between the two groups (P >0.05) (Table 6).

Discussion

Studies have found that SHF and RA are often mutually causal, and the two promote each other and progress together[8]. After the occurrence of SHF combined with RA, it is often easy to aggravate myocardial ischemia if timely and effective treatment cannot be given, resulting in abnormal hemodynamic changes that endanger the patient's life. Therefore, rapid correction of arrhythmias is clinically required to improve patient outcomes[9]. However, many antiarrhythmic drugs commonly used in clinic have negative inotropic and negative frequency effect, and their application to patients with SHF combined with RA is often prone to aggravate arrhythmia and promote disease progression[10]. Amiodarone is not only effective in controlling arrhythmias, but also has mild negative inotropic and frequency effect, and its application in the clinic has a high safety[11].

After treatment in this study, CI, MAP, LVEF and DBP and SBP in the experimental group were higher than those in the control group, HR was smaller than it in the control group, and the total effective rate in the experimental group was larger than it in the control group, which indicated that the combination of amiodarone and esmolol in the treatment of SHF with RA could effectively enhance the cardiac function of patients, raise blood pressure, reduce heart rate, and improve the efficacy. Amiodarone can reduce myocardial oxygen consumption, promote vasodilation, correct myocardial ischemia, and

Table 5 — Comparison of clinical efficacy between two groups [n (%)]

Index	Experimental group (n = 90)	Control group (n = 90)	χ^2/t	*P*
Showing effect	39（43.33）	28（31.11）		
Effective	46（51.11）	42（46.67）		
Ineffective	5（5.56）	20（22.22）		
Total effective	85（94.44）	70（77.78）	10.3935	0.0013

Table 6 — Comparison of adverse effects between two groups [n (%)]

Index	Experimental group (n = 90)	Control group (n = 90)	χ^2/t	*P*
Hypotension	7（7.78）	4（4.44）		
Bradycardia	4（4.44）	3（3.33）		
Total	11（12.22）	7（7.78）	0.9822	0.3217

improve cardiac function by inhibiting adrenergic and Ca^{2+} channels, slowing HR and reducing peripheral resistance[12]. Amiodarone can inhibit atrioventricular junction site and sinoatrial node automaticity, induce myocardial action potential and refractory period prolongation, inhibit reentrant activation, affect the nodal region, intra atrial and sinoatrial conduction, relieve atrial and ventricular fibrillation, and promote sinus arrhythmia[13]. In myocardial tissue, esmolol can inhibit sympathetic nerves through competitive binding with catecholamines, block norepinephrine and epinephrine, reduce blood pressure and ventricular fibrillation threshold, reduce heart rate, reduce myocardial oxygen consumption, and stabilize arrhythmias[14]. Esmolol can induce a prolonged sinus cycle and sinus node recovery time, and inhibit conduction in the cardiac conduction system and myocardium, resulting in a prolonged refractory period[15]. Studies have proved that the combination of amiodarone and esmolol has a synergistic and synergistic effect, and the combination of the two has a positive effect on improving the efficacy[16].

After treatment in this study, serum TGF-β1 and PIIINP levels in the experimental group were all lower than those in the control group, and the APN was higher than that of the control group, which indicated that the combination of amiodarone and esmolol in the treatment of SHF with RA could effectively improve the serum TGF-β1, APN and PIIINP levels, and inhibite the progression of cardiac fibrosis. Studies have proved that myocardial fibrosis is an important factor leading to SHF and RA[17]. TGF-β1 has obvious promoting effect on myocardial fibrosis. TGF-β1, when activated, promotes collagen and extracellular matrix synthesis in cardiomyocytes and inhibits their degradation, leading to myocardial fibrosis[18]. APN is an active polypeptide produced in adipocytes, which can inhibit collagen production by inhibiting angiotensin II activity and intervening in the expression of TGF-β1 mRNA, antagonizing myocardial fibrosis progression[19]. APN can inhibit macrophage infiltration and up-regulation of inflammatory factors, reduce matrix protease activity, and inhibit myocardial fibrosis[20]. PIIINP is an important component that constitutes the myocardial collagen network and is important for maintaining myocardial elasticity and stiffness[21]. Over-expression of PIIINP could promote the massive production of myocardial collagen fibers, accelerate the process of matrix remodeling and myocardial fibrosis, and eventually lead to and drive the progression of myocardial remodeling[22].

Conclusion

The above results have demonstrated that the combination of antiarrythmic drugs amiodarone and esmolol is effective for severe heart failure (SHF) with rapid arrhythmia (RA). It enhances cardiac function, blood pressure and heart rate, improve efficacy, inhibit the progression of myocardial fibrosis, and improve serum Transforming growth factor-β1 (TGF-β1), adiponectin (APN) and amino telopeptide of type III procollagen (PIIINP) levels, without significantly increasing adverse effects and with high safety.

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Conflict of interest

Authors declare no competing interests.

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