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Original Article

Amiodarone-metoprolol co-administration enhances heart rate variability and suppresses inflammatory cytokines in tachyarrhythmia patients

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Abstract: Objective: To elucidate the efficacy of amiodarone (AMD)-metoprolol (MET) co-administration in tachyarrhythmia patients, and to assess its impact on heart rate (HR) variability (HRV) and serum inflammatory cytokines (SICs). Methods: This study included 188 tachyarrhythmia patients who were treated at the Qinghai Provincial Fourth People's Hospital, including 88 patients treated with AMD (control group) and 100 patients treated with AMD+MET (research group). We compared the following clinical data between groups: curative effects, frequency and duration of arrhythmia episodes, vital signs, cardiac function (left ventricular [LV] ejection fraction [LVEF], LV systolic diameter [LVSD], LV end-diastolic diameter [LVEDD]), HRV, SICs, oxidative stress (superoxide dismutase [SOD], malondialdehyde [MDA]), and side effects. In addition, we explored factors influencing patients' curative effects. Results: A higher total effective rate was observed in the research group compared with the control group (91.00% vs. 79.55%, P=0.025). In addition, the research group experienced fewer arrhythmia episodes with shorter durations (P<0.001), and a lower incidence of total adverse events (9.00% vs. 23.86%, P=0.006). A more pronounced drop in post-treatment vital signs, LVSD, LVEDD, various SICs, and MDA (all P<0.001), as well as a rise in LVEF (P<0.001), HRV indices (P<0.001), and SOD (P=0.002), were determined in the research group. LVEF, SDNN, and LF at baseline, as well as therapeutic method, independently influenced patients' efficacy. Conclusion: AMD in combination with MET yields superior efficacy in tachyarrhythmia patients, significantly improving HRV and suppressing SICs.

Keywords: Amiodarone, metoprolol, tachyarrhythmia, therapeutic effect, heart rate variability, serum inflammatory cytokines

Introduction

Arrhythmia arises when the coordinated activities of ion channels and transporters - essential for maintaining normal heart rhythm - are disrupted, thereby preventing orderly propagation of electrical signals in the myocardium [1]. As the most prevalent arrhythmia type, tachyarrhythmia is etiologically related to cardiac impulse frequency abnormalities, disordered rhythms, and interrupted conduction velocity [2]. Meanwhile, decreased heart rate (HR) variability (HRV) and activated inflammatory reactions also play a critical role in tachyarrhythmia onset and progression [3, 4]. Those affected mainly show symptoms of accelerated HR like atrial tachycardia, atrial flutter, ventricular tachycardia, and ventricular fibrillation. When seriously ill, there may be blood circulation dysfunction that can induce cardiac insufficiency and even death [5]. Characterized by sudden onset, low spontaneous remission rates, and increasing frequency with disease progression, tachyarrhythmia is intimately linked to factors such as population aging, obesity, and chronic diseases [6]. For now, tachyarrhythmia is mainly managed by antiarrhythmic drugs, aiming at quickly and effectively controlling the condition and preventing acute complications [7]. Despite the certain effect, the current drug therapy also brings side effects, necessitating updates to current treatment plans to optimize clinical tachyarrhythmia management [8].

Amiodarone (AMD), as a class III antiarrhythmic drug, can be used to treat patients with atrial and ventricular arrhythmia [9]. It exerts antiarrhythmic effects by targeting the human ether-

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à-go-go-related gene (hERG)-encoded potassium channel, potassium voltage-gated channel subfamily H member 2 (KCNH2), thereby contributing to the regulation of action potential repolarization and improvement of myocardial electrophysiological properties [10]. It demonstrates superior 2-hour rhythm control compared to propafenone in septic shock patients with supraventricular arrhythmia (SVA) [11]. Metoprolol (MET) is also an extensively applied antiarrhythmic in clinics, which belongs to the β-adrenergic antagonist class, used in cardiovascular diseases. It exerts therapeutic effects by selectively inhibiting β-1 adrenergic receptors, thereby reducing myocardial contractility, HR, and blood pressure [12]. Its application to patients with atrial fibrillation helps ameliorate left atrial hemodynamics and improve their quality of life [13]. Current evidence suggests limited efficacy of monotherapy with either AMD or MET. Their combined use in patients with coronary heart disease and arrhythmia, on the contrary, shows a synergistic and enhanced therapeutic effect, enhancing heart function and HRV while boasting high clinical safety [14].

How AMD-MET co-administration works in patients with tachyarrhythmia and impacts curative effects, HRV, and serum inflammatory cytokines (SICs) remains insufficiently clarified. Therefore, this study makes a relevant analysis and reports the findings. In addition, this study is innovative in its comprehensive evaluation of the therapeutic effectiveness, safety, and other clinical impacts of AMD-MET co-administration for tachyarrhythmia from the perspectives of curative effect, arrhythmia attack frequency and duration, vital signs, cardiac function, HRV, SICs, oxidative stress (OS), and side effects of medication, which can provide better treatment options for such patients. Meanwhile, efficacy determinants are screened out based on the above indicators, helping identify the population that can achieve the greatest clinical benefits and providing useful references for clinical decisions.

Information and methods

Patient selection

Inclusion criteria: (1) treatment-naive patients with tachyarrhythmia diagnosed by electrocardiogram [15]; (2) grade II-III cardiac function assessed by the New York Heart Association (NYHA); (3) ventricular rate ≥120 beats/min; (4) accompanied by different degrees of palpitations, chest tightness, and other symptoms; (5) normal cognitive and communication skills; (6) complete clinical data. Exclusion criteria: (1) sick sinus syndrome, chronic/acute obstructive pulmonary disease, or asthma; (2) atrioventricular block of second degree above; (3) blood diseases, abnormal vital organs, or malignant tumors; thyroid dysfunction; (4) corrected QT interval (QTc) ≥500 ms; (5) sinus bradycardia (<50 beats/min); (6) hypotension (systolic blood pressure [SBP] <90 mmHg); (7) implantation with a pacemaker; (8) allergies to the drugs studied; (9) antiarrhythmic use within 15 days; or (10) pregnant or lactating women.

This study included 188 patients with tachyarrhythmia who were treated at Qinghai Provincial Fourth People's Hospital between November 2022 and November 2025. Patients were allocated to either the AMD group (control, n=88) or the AMD+MET group (research, n=100) based on the treatment they received. Instead of randomization, the treatment scheme was determined by the patients themselves or their guardians, who were fully aware of the advantages and limitations of each treatment. This study was approved by the Ethics Committee of Qinghai Provincial Fourth People's Hospital. Patient screening flowchart is shown in **Figure 1**.

In this study, the total effective rate served as the primary endpoint for sample size estimation. Setting the significance level α=0.05 (two-tailed) and power (1-β)=0.80, and employing the sample size calculation formula $n=(Z_{\alpha/2}+Z_{\beta})^2[p_1(1-p_1)+p_2(1-p_2)]/(p_1-p_2)^2$, a minimum sample size of 86 cases per group was required. This study finally enrolled 188 patients (88 controls and 100 cases in the research group), meeting the minimum sample size requirements for statistical inference.

Intervening methods

Both groups received routine care, including education on disease pathogenesis and pharmacological treatment principles. In addition, the nursing staff patiently answered patients' and their families' questions regarding the treatment. Furthermore, the ward environment was maintained by ensuring appropriate temperature, humidity, and lighting to ensure patients could obtain adequate rest.

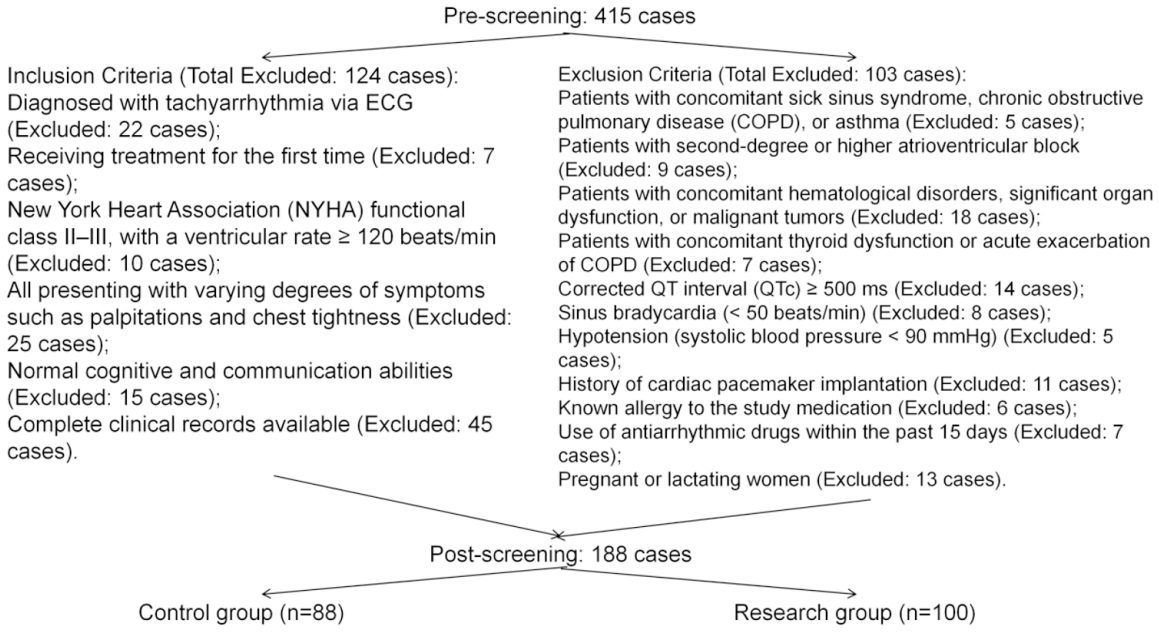

Figure 1. Flowchart of patient screening. ECG, electrocardiogram.

Table 1. Comparison of baseline information between the two groups

Variable	Control group (n=88)	Research group (n=100)	χ^2/t/Z	P
Sex			0.127	0.722
Male	47 (53.41)	56 (56.00)		
Female	41 (46.59)	44 (44.00)		
Average age (years)	61.50±4.59	62.27±6.21	0.956	0.340
BMI (kg/m^2)	23.60±2.21	22.99±2.40	1.804	0.073
Disease course (years)	4.00 (3.00, 5.75)	4.00 (3.00, 5.00)	-1.127	0.260
NYHA classification			0.030	0.862
Grade II	46 (52.27)	51 (51.00)		
Grade III	42 (47.73)	49 (49.00)		
Arrhythmia type			0.369	0.544
Ventricular arrhythmia	34 (38.64)	43 (43.00)		
Supraventricular arrhythmia	54 (61.36)	57 (57.00)		
Comorbid hypertension	44 (50.00)	47 (47.00)	0.169	0.681
Coronary heart disease	30 (34.09)	35 (35.00)	0.017	0.896
Comorbid diabetes	22 (25.00)	28 (28.00)	0.216	0.642
Smoking history	32 (36.36)	30 (30.00)	0.858	0.354
Alcoholism history	20 (22.73)	24 (24.00)	0.042	0.837

Note: BMI, body mass index; NYHA, New York Heart Association.

The control patients were given AMD. Treatment: AMD (300 mg) was diluted with 5% glucose injection (40 mL) for an intravenous drip over 15-30 min. Then continuous intravenous AMD administration via pump was performed, with the rate controlled at 1 mg/min for the first 6 hours and then 0.5 mg/min thereafter. On day 1, the AMD dosage was controlled within 2200 mg. HR alterations were vigilantly monitored throughout the treatment. After the HR reached the standard, the AMD infusion duration was controlled within 2-4 h, with appropriate adjustments made according to the patient's condition.

Table 2. Comparison of treatment efficacy between the two groups

Variable	Control group (n=88)	Research group (n=100)	χ^2	P
Marked response	35 (39.77)	48 (48.00)		
Response	35 (39.77)	43 (43.00)		
Non-response	18 (20.45)	9 (9.00)		
Overall response	70 (79.55)	91 (91.00)	4.994	0.025

MET, added after 30 min of AMD treatment, was used in the research group: 5 mg of MET was mixed with 20 mL of 50 g/L glucose solution for a >5-minute intravenous injection at 0.5-1.0 mg/min. In case of unsatisfactory therapeutic effects, the treatment was repeated following 5 minutes of MET injection, with the MET dosage not exceeding 15 mg.

Data extraction and outcome measures

Efficacy. Efficacy was evaluated as follows: Marked response was defined as an improvement of ≥2 New York Heart Association (NYHA) cardiac function classes compared with baseline, accompanied by complete resolution of symptoms (e.g., ventricular premature beat [VPB], arrhythmia) and significant alleviation of heart failure. Response was defined as an improvement of one NYHA class, with obvious symptom relief (VPBs and arrhythmia) and improvement in heart failure. Non-response was defined as failure to meet the above standards. The total effective rate was calculated as the proportion of patients classified as either marked response or response among the total number of patients. Curative efficacy was evaluated 3 months post-treatment.

Number and duration of arrhythmia episodes. We observed and recorded the number and duration of arrhythmia attacks in the two groups post-treatment.

Vital signs. Patients were monitored for their SBP and diastolic blood pressure (DBP) by a sphygmomanometer before and 3 months following the treatment, with HR alterations also tracked.

Cardiac function. Cardiac function indices of both cohorts, including left ventricular (LV) ejection fraction (LVEF), LV systolic diameter (LVSD), and LV end-diastolic diameter (LVEDD), were measured before the treatment and three months after it.

HRV. All patients underwent pre- and post-treatment (at 3 months) testing of the standard deviation of normal-to-normal (NN) intervals (SDNN), the percentage of successive NN intervals that differ by more than 50 milliseconds (PNN50), high frequency (HF), and low frequency (LF).

SICs. Tumor necrosis factor (TNF)-α, interleukin (IL)-6, and high sensitivity-C reactive protein (hs-CRP) in the serum, isolated from early-morning fasting venous blood draws (6 mL) from patients before and 3 months after treatment, were determined by enzyme-linked immunosorbent assay (ELISA).

Oxidative stress (OS). Quantification of serum superoxide dismutase (SOD) and malondialdehyde (MDA) was also performed at baseline and three months post-treatment.

Side effects of medication. The post-treatment adverse events (phlebitis, hypotension, and sinus bradycardia) in both cohorts were observed and recorded, and the number of occurrences and their composition ratios were counted.

Primary outcomes included efficacy and medication-related adverse effects, whereas secondary outcomes included the number and duration of arrhythmia episodes, vital signs, cardiac function, HRV, SICs, and OS.

Statistical analysis

Measurement data were first subjected to normality testing by the Shapiro-Wilk test. If normally distributed, the data were shown as the mean ± standard deviation (SD), with differences examined by independent sample t-tests (between groups) and paired t-tests (before and after the intervention within groups). Otherwise, the median (interquartile range) [M (Q1, Q3)] was used for statistical description, and the differences between groups and within groups (pre- vs. post-intervention) were evaluated by the Mann-Whitney U test and the Wilcoxon signed rank test, respectively. Counting data, represented by counts/percentages (n/%), underwent χ^2 testing for inter-group dif-

Table 3. Comparison of frequency and duration of arrhythmia episodes between the two groups

Variable	Control group (n=88)	Research group (n=100)	Z/t	P
Frequency of arrhythmia episodes (times/week)	5.00 (4.00, 6.00)	3.00 (2.00, 4.00)	-6.578	<0.001
Arrhythmia duration (min)	8.11±2.84	5.69±2.03	6.779	<0.001

Table 4. Comparison of vital signs between the two groups

Variable	Control group (n=88)	Research group (n=100)	t	P
SBP (mmHg, pre-treatment)	147.58±23.21	146.41±23.60	0.342	0.733
SBP (mmHg, post-treatment)	132.67±18.46	115.80±15.13	6.882	<0.001
DBP (mmHg, pre-treatment)	97.35±7.43	96.04±8.78	1.096	0.274
DBP (mmHg, post-treatment)	89.64±7.19	77.74±7.26	11.265	<0.001
HR (beats/min, pre-treatment)	138.00±15.75	140.17±18.81	0.851	0.396
HR (beats/min, post-treatment)	98.06±12.83	74.91±8.76	14.591	<0.001

Note: SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate.

Table 5. Comparison of cardiac function between the two groups

Variable	Control group (n=88)	Research group (n=100)	t	P
LVEF (%, pre-treatment)	37.65±2.65	37.23±3.00	1.011	0.313
LVEF (%, post-treatment)	43.52±3.82	48.89±3.92	9.485	<0.001
LVSD (mm, pre-treatment)	55.85±4.68	56.97±5.10	1.561	0.120
LVSD (mm, post-treatment)	53.27±4.17	45.20±4.39	12.875	<0.001
LVEDD (mm, pre-treatment)	75.07±5.50	75.75±5.37	0.794	0.428
LVEDD (mm, post-treatment)	64.07±6.33	60.41±5.15	4.368	<0.001

Note: LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic diameter; LVEDD, left ventricular end-diastolic diameter.

ferences. To clarify efficacy determinants, univariate and binary Logistic regression analyses were conducted successively, with variable inclusion criterion set at P<0.05. SPSS 20.0 was the data analysis and processing tool used in this study. Statistical significance was present when *P*-values fell below 0.05.

Results

General patient information

As shown in **Table 1**, the research and control groups were not markedly different in sex, average age, body mass index (BMI), disease course, NYHA classification, arrhythmia type, comorbidities (hypertension, coronary heart disease, diabetes), or smoking/alcoholism history, demonstrating clinical comparability (P> 0.05).

Efficacy comparison

As shown in **Table 2**, the research group demonstrated superior efficacy than the control group (P=0.025), with overall response rates of 91.00% and 79.55%, respectively.

Frequency and duration of arrhythmia episodes

Table 3 shows that the research group experienced significantly fewer and shorter arrhythmia episodes than the control group (P<0.001).

Vital sign analysis

Table 4 shows comparable baseline SBP, DBP, and HR between the groups (P>0.05). Post-treatment, both groups exhibited significant reduction in these vital signs, with more pronounced decreases in the research group (P<0.001).

Cardiac function evaluation

As shown in **Table 5**, baseline LVEF, LVSD, and LVEDD were comparable between the groups (P>0.05). Following the treatment, the two groups exhibited significant increases in LVEF

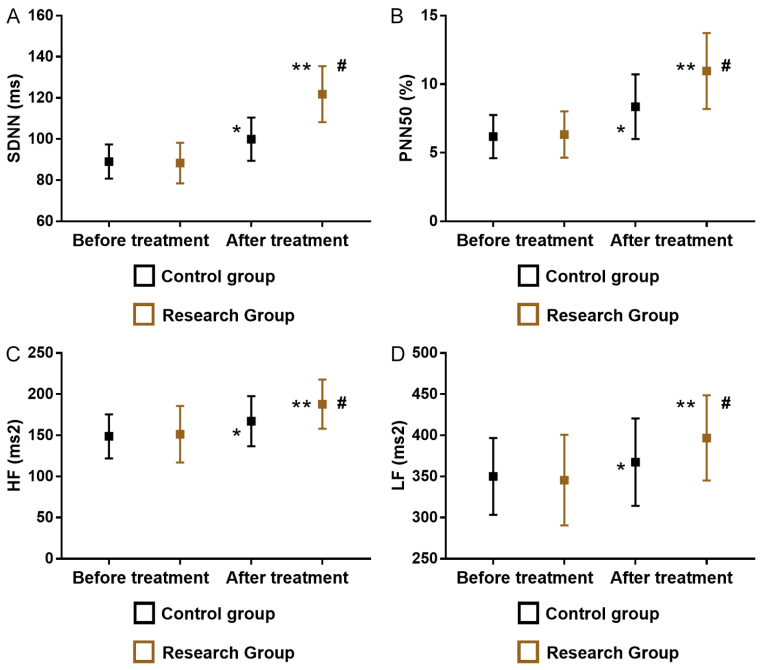

Figure 2. Comparison of heart rate parameters between the two groups before and after treatment. A. SDNN. B. PNN50. C. HF. D. LF. Note: *P<0.05, **P<0.01 *vs.* before treatment; #P<0.05 *vs.* Control. SDNN, standard deviation of normal-to-normal [NN] intervals; PNN50, the percentage of successive NN intervals that differ by more than 50 milliseconds; HF, high frequency; LF, low frequency.

and significant reductions in LVSD and LVEDD (P<0.01), with the research group showing greater LVEF and lower LVSD and LVEDD (P<0.001).

HRV across the groups

As shown in **Figure 2**, the baseline SDNN, PNN50, HF, and LF of the two groups were not statistically significant (P>0.05); all the indices presented an evident elevation post-treatment (P<0.05), especially in the research group (P<0.01).

SICs across groups

SICs changes, displayed in **Figure 3**, indicated similar TNF-α, IL-6, and hs-CRP contents across the cohorts at baseline (P>0.05). In both groups, each index lowered statistically post-treatment (P<0.05), with even lower TNF-α, IL-6, and hs-CRP in the research group (P<0.05).

OS assessment

Similarly, the groups did no differ much in pre-treatment SOD and MDA (P>0.05; **Table 6**). The corresponding intervention induced an increase in SOD and a decline in MDA (P<0.05), with the combination therapy used in the research group causing greater changes relative to controls (P<0.05).

Side effects of medication

The incidence of total drug side effects, such as phlebitis, hypotension, and sinus bradycardia, was lower in the research group than that in the control group (P=0.006; **Table 7**).

Evaluation of efficacy determinants

Further efficacy-based allocation was carried out, resulting in an ineffective group with 27 cases and an effective group with 161 cases. In the initial univariate screening, gender, average age, BMI, disease course, NYHA classification, arrhythmia type, comorbidities (hypertension, coronary heart disease, diabetes), smoking/alcoholism history, some baseline measurements (SBP, DBP, HR, LVEDD, PNN50, TNF-α, IL-6, hs-CRP, SOD, MDA) showed no marked connection with efficacy (P>0.05); however, LVEF, LVSD, SDNN, HF, and LF, all at baseline, as well as therapeutic method, correlated closely to the curative effect of patients (P<0.05). The above-mentioned statistically significant indicators were incorporated as independent variables, with the curative effect as the dependent variable, to assign values (**Tables 8**, **9**).

Multivariate analysis showed that baseline LVEF (OR=0.261, 95% CI: 0.098-0.693, P=0.007), baseline SDNN (OR=0.350, 95% CI: 0.130-0.940, P=0.037), baseline LF (OR=0.318, 95% CI: 0.118-0.856, P=0.023) , and therapeutic method (OR=0.314, 95% CI: 0.117-0.846, P=0.022) were independent protective factors for patients' efficacy. To be more specific, higher baseline LVEF (≥37%), SDNN (≥88.50 ms), and LF (≥348 ms^2) reduced the risk of ineffective treatment by ~73.9%, ~65.0%, and ~68.2%, respectively. AMD-MET

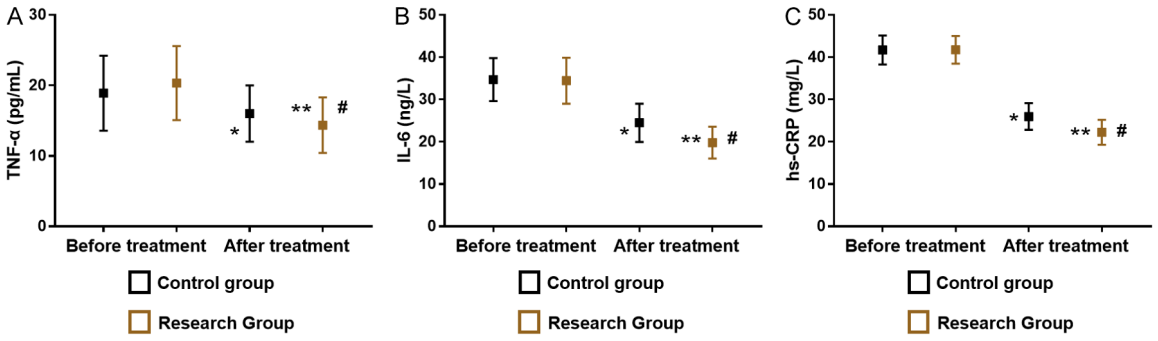

Figure 3. Comparison of serum inflammatory markers between the two groups before and after treatment. A. TNF-α. B. IL-6. C. hs-CRP. Note: *P<0.05, **P<0.01 *vs.* pre-treatment; #P<0.05 *vs.* Control. TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; hs-CRP, high sensitivity-C reactive protein.

Table 6. Comparison of oxidative stress markers between the two groups

Variable	Control group (n=88)	Research group (n=100)	t	P
SOD (U/mL, pre-treatment)	66.32±19.74	69.41±19.82	1.069	0.287
SOD (U/mL, post-treatment)	97.23±21.90	107.80±24.44	3.106	0.002
MDA (nmol/L, pre-treatment)	15.86±4.64	16.91±4.80	1.520	0.130
MDA (nmol/L, post-treatment)	12.39±3.30	10.76±3.01	3.541	<0.001

Note: SOD, superoxide dismutase; MDA, malondialdehyde.

Table 7. Comparison of medication-related adverse effects between the two groups

Variable	Control group (n=88)	Research group (n=100)	χ^2	P
Phlebitis	4 (4.55)	2 (2.00)		
Hypotension	8 (9.09)	4 (4.00)		
Sinus bradycardia	9 (10.23)	3 (3.00)		
Total	21 (23.86)	9 (9.00)	7.711	0.006

co-administration was associated with a ~68.6% reduced risk of ineffective treatment compared with monotherapy (**Table 10**).

Discussion

This study found that AMD-MET co-administration exerted a higher curative effect on patients with tachyarrhythmia. Although AMD is somewhat effective in arrhythmia treatment, high doses may carry a high risk of adverse reactions. Therefore, combination therapy with MET is often employed to optimize efficacy and minimize toxicity. AMD suppresses tachyarrhythmia by blocking sodium, potassium, and L-type calcium channels, thereby preventing delayed and early afterdepolarizations [16]. MET, by inhibiting adrenaline release and blocking the pathway through which the renin-angiotensin system regulates blood pressure, reduces oxygen consumption and ameliorates the myocardium [17]. It can also cross the blood-brain barrier to bind to β receptors within the central nervous system, effectively inhibiting sympathetic nerve tension and activating cardiac vagus nerve excitation, thus alleviating arrhythmia [18]. Their co-administration for tachyarrhythmia can act on different pathways, thereby synergistically enhancing the therapeutic effect. Additionally, the combination regimen led to fewer arrhythmia attack times and shorter durations, further validating the higher curative effect of the co-medication.

Combination therapy effectively reduced SBP, DBP, and HR, suggesting its capacity to ameliorate hemodynamic abnormalities. This is related to MET-enabled blocking of sympathetic drive in patients [19]. According to the evaluation of cardiac function indices, the co-administration was effective in increasing LVEF and decreasing LVSD and LVEDD in tachyarrhythmia patients to improve their cardiac function. MET enhances vasoconstriction among tach-

Table 8. Univariate analysis of factors associated with treatment efficacy

Variable	Ineffective group (n=27)	Effective group (n=161)	χ^2	P
Sex			0.110	0.741
Male (n=103)	14 (51.85)	89 (55.28)		
Female (n=85)	13 (48.15)	72 (44.72)		
Average age (years)			0.009	0.925
<61 (n=82)	12 (44.44)	70 (43.48)		
≥61 (n=106)	15 (55.56)	91 (56.52)		
BMI (kg/m^2)			0.043	0.835
<23.18 (n=94)	13 (48.15)	81 (50.31)		
≥23.18 (n=94)	14 (51.85)	80 (49.69)		
Disease course (years)			0.758	0.384
<4 (n=77)	9 (33.33)	68 (42.24)		
≥4 (n=111)	18 (66.67)	93 (57.76)		
NYHA classification			0.646	0.422
Grade II (n=97)	12 (44.44)	85 (52.80)		
Grade III (n=91)	15 (55.56)	76 (47.20)		
Arrhythmia type			0.674	0.412
Ventricular arrhythmia (n=77)	13 (48.15)	64 (39.75)		
Supraventricular arrhythmia (n=111)	14 (51.85)	97 (60.25)		
Comorbid hypertension			0.198	0.656
No (n=97)	15 (55.56)	82 (50.93)		
Yes (n=91)	12 (44.44)	79 (49.07)		
Comorbid coronary heart disease			0.085	0.771
No (n=123)	17 (62.96)	106 (65.84)		
Yes (n=65)	10 (37.04)	55 (34.16)		
Comorbid diabetes			1.761	0.185
No (n=138)	17 (62.96)	121 (75.16)		
Yes (n=50)	10 (37.04)	40 (24.84)		
Smoking history			1.875	0.171
No (n=126)	15 (55.56)	111 (68.94)		
Yes (n=62)	12 (44.44)	50 (31.06)		
Alcoholism history			1.734	0.188
No (n=144)	18 (66.67)	126 (78.26)		
Yes (n=44)	9 (33.33)	35 (21.74)		
Baseline SBP (mmHg)			0.072	0.789
<147 (n=93)	14 (51.85)	79 (49.07)		
≥147 (n=95)	13 (48.15)	82 (50.93)		
Baseline DBP (mmHg)			0.847	0.357
<97 (n=92)	11 (40.74)	81 (50.31)		
≥97 (n=96)	16 (59.26)	80 (49.69)		
Baseline HR (beats/min)			0.318	0.573
<138 (n=93)	12 (44.44)	81 (50.31)		
≥138 (n=95)	15 (55.56)	80 (49.69)		
Baseline LVEF (%)			12.213	<0.001
<37 (n=75)	19 (70.37)	56 (34.78)		
≥37 (n=113)	8 (29.63)	105 (65.22)		
Baseline LVSD (mm)			5.252	0.022
<56 (n=87)	7 (25.93)	80 (49.69)		
≥56 (n=101)	20 (74.07)	81 (50.31)		

Baseline LVEDD (mm)			2.119	0.146
<75.50 (n=94)	10 (37.04)	84 (52.17)		
≥75.50 (n=94)	17 (62.96)	77 (47.83)		
Baseline SDNN (ms)			5.233	0.022
<88.50 (n=94)	19 (70.37)	75 (46.58)		
≥88.50 (n=94)	8 (29.63)	86 (53.42)		
Baseline PNN50 (%)			0.043	0.835
<6.19 (n=94)	14 (51.85)	80 (49.69)		
≥6.19 (n=94)	13 (48.15)	81 (50.31)		
Baseline HF (ms^2)			5.511	0.019
<151 (n=93)	19 (70.37)	74 (45.96)		
≥151 (n=95)	8 (29.63)	87 (54.04)		
Baseline LF (ms^2)			7.973	0.005
<348 (n=92)	20 (74.07)	72 (44.72)		
≥348 (n=96)	7 (25.93)	89 (55.28)		
Baseline TNF-α (pg/mL)			0.022	0.882
<20 (n=93)	13 (48.15)	80 (49.69)		
≥20 (n=95)	14 (51.85)	81 (50.31)		
Baseline IL-6 (ng/L)			0.318	0.573
<34 (n=86)	11 (40.74)	75 (46.58)		
≥34 (n=102)	16 (59.26)	86 (53.42)		
Baseline hs-CRP (mg/L)			0.110	0.741
<42 (n=85)	13 (48.15)	72 (44.72)		
≥42 (n=103)	14 (51.85)	89 (55.28)		
Baseline SOD (U/mL)			0.389	0.533
<67.50 (n=94)	15 (55.56)	79 (49.07)		
≥67.50 (n=94)	12 (44.44)	82 (50.93)		
Baseline MDA (nmol/L)			0.106	0.745
<16.00 (n=82)	11 (40.74)	71 (44.10)		
≥16.00 (n=106)	16 (59.26)	90 (55.90)		
Therapeutic method			7.030	0.008
Amiodarone (n=88)	19 (70.37)	69 (42.86)		
Amiodarone+metoprolol (n=100)	8 (29.63)	92 (57.14)		

Note: BMI, body mass index; NYHA, New York Heart Association; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic diameter; LVEDD, left ventricular end-diastolic diameter; SDNN, standard deviation of normal-to-normal intervals; PNN50, the percentage of successive NN intervals that differ by more than 50 milliseconds; HF, high frequency; LF, low frequency; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; hs-CRP, high sensitivity-C reactive protein; SOD, superoxide dismutase; MDA, malondialdehyde.

yarrhythmia patients, which aids in promoting systemic circulation and enhancing cardiac function [20]. HRV evaluation results indicated a valid improvement in HRV by AMD+MET, evidenced by significantly elevated SDNN, PNN50, HF, and LF in tachyarrhythmia-affected individuals. MET helps inhibit calcium ion inflow, prolong atrioventricular conduction time and effective refractory period without causing sympathetic activity, and reduce myocardial oxygen consumption [21, 22], which can explain the improvement of HRV in the research group. Consistent with our findings, Fu et al. [14] reported enhanced curative effects, improved HR, cardiac function, and HRV, and a significantly lowered incidence of adverse events in patients with coronary heart disease complicated by arrhythmia receiving AMD+MET compared to those given AMD alone.

From the perspective of SICs, the AMD-MET combination exhibited efficacy in lowering TNF-α, IL-6, and hs-CRP levels in tachyarrhythmia patients, demonstrating its ability to effec-

Table 9. Assignment table

Indicator	Variable	Assignment
Baseline LVEF (%)	X1	<37=0, ≥37=1
Baseline LVSD (mm)	X2	<56=0, ≥56=1
Baseline SDNN (ms)	X3	<88.50=0, ≥88.50=1
Baseline HF (ms^2)	X4	<151=0, ≥151=1
Baseline LF (ms^2)	X5	<348=0, ≥348=1
Therapeutic regimen	X6	Amiodarone =0, Amiodarone+metoprolol =1
Efficacy	Y	Effective =0, ineffective =1

Note: LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic diameter; SDNN, standard deviation of normal-to-normal intervals; HF, high frequency; LF, low frequency.

Table 10. Multivariate analysis of independent factors associated with treatment efficacy

Indicators	B	SE	WALD	P	OR	95% CI
Baseline LVEF (%)	-1.343	0.498	7.266	0.007	0.261	0.098-0.693
Baseline LVSD (mm)	0.811	0.511	2.515	0.113	2.249	0.826-6.126
Baseline SDNN (ms)	-1.050	0.504	4.339	0.037	0.350	0.130-0.940
Baseline HF (ms^2)	-0.789	0.496	2.535	0.111	0.454	0.172-1.200
Baseline LF (ms^2)	-1.147	0.506	5.135	0.023	0.318	0.118-0.856
Therapeutic method	-1.158	0.506	5.243	0.022	0.314	0.117-0.846

Note: LVEF, left ventricular ejection fraction; LVSD, left ventricular systolic diameter; SDNN, standard deviation of normal-to-normal intervals; HF, high frequency; LF, low frequency; SE, Standard Error; OR, Odds Ratio; 95% CI, 95% Confidence Interval.

tively suppress the abnormally activated serum inflammatory response. MET-mediated anti-inflammation is related to its biased agonism of β-inhibin 2 and the regulation of nuclear factor (NF)-κB signaling, which helps inhibit the inflammatory reaction of cardiomyocytes [23]. Regarding OS, the AMD+MET combination led to marked increases in SOD and decreases in MDA, indicating significant alleviation of OS. MET has been shown to protect cardiomyocytes from aging by inhibiting arginine vasopressin-induced OS, activating Sirtuin1 signaling, and down-regulating acetylated tumor protein p53 (p53)/cyclin-dependent kinase inhibitor 1A (p21) expression [24]; this helps reveal the regulatory mechanism of MET on OS in tachyarrhythmia. Regarding clinical safety, we observed significantly fewer total side effects (phlebitis, hypotension, and sinus bradycardia) in patients receiving the combined medication, suggesting the clinical safety of this therapy. This may be related to the mild inhibition of AMD on CYP2D6, as well as the adjustment of the daily MET dose as a key covariate, which avoids the additional dose-dependent side effects (e.g., bradycardia, hypotension) caused by increased MET concentrations by AMD [25]. A previous study similarly supports the certain clinical safety of AMD+MET in a rat model of congestive heart failure-induced arrhythmia, noting no myocardial contractility decline or bradycardia aggravation [26]. Finally, it was found that higher LVEF (≥37%), SDNN (≥88.50 ms), and LF (≥348 ms^2), all at baseline, as well as the combination therapy, were independent protective factors for treatment ineffectiveness in patients with tachyarrhythmia. In another word, patients with the above characteristics have a reduced risk of ineffective treatment.

This study is not without limitations. First, single-center sample enrollment may lead to insufficient sample representativeness, warranting multi-center recruitment to enhance the representativeness and generalizability of the findings. Second, the basic mechanism of AMD-MET co-administration remains unclear, necessitating further in vitro and in vivo studies. Third, there is no comparative analysis of the economic effectiveness of the two schemes; a subsequent supplement of relevant data may help to promote the combination therapy.

To summarize, AMD-MET co-administration in tachyarrhythmia patients can achieve higher curative effects, faster disease control, greater improvements of vital signs, cardiac function, and HRV, more effective suppression of serum inflammation and OS, and high clinical safety, justifying its clinical popularization. In addition, the risk of ineffective treatment is reduced in patients with higher LVEF (≥37%), SDNN (≥88.50 ms), or LF (≥348 ms^2) at baseline, as well as those receiving the combination therapy.

Disclosure of conflict of interest

None.

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