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Original Article

Effect of combined Zhuang medicine treatment on tricuspid annular displacement and heart rate variability in rheumatoid arthritis patients

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Abstract: Objectives To assess the benefits of Zhuang medicine in treating rheumatoid arthritis (RA), with a focus on cardiac tricuspid annulus displacement and heart rate variability (HRV), thereby providing evidence supporting Zhuang medicine theories. Methods: This retrospective study analyzed echocardiographic data and HRV of 30 healthy subjects and 60 RA patients. RA patients were divided into two groups for a 6-month treatment: 30 received iguratimod (control group), and 30 underwent combined Zhuang medicine and needle-pricking therapy (test group). Echocardiographic assessments and HRV measures were recorded both before and after treatment. Results: Compared to the healthy group, RA patients showed increased late diastolic tricuspid annular velocity. However, early diastolic tricuspid annular velocity to late diastolic tricuspid annular velocity ratios, tricuspid annular plane systolic excursion (TAPSE), and the standard deviation of average normal RR intervals (SDANN) were significantly lower (all $P<0.05$). After treatment, the test group exhibited higher clinical efficacy (90% vs. 56.67% in the control group). Significant improvements were observed in TAPSE and HRV indices [SDANN, standard deviation of the RR intervals (SDNN), root mean square of successive RR interval differences (RMSSD), and the percentage of adjacent RR interval differences greater than 50 milliseconds (PNN50)] in the test group (all $P<0.05$). Additionally, a positive correlation was noted among these measurments. Conclusion: Zhuang medicine significantly enhances right ventricular function and autonomic balance in RA patients, thus affirming its therapeutic potential.

Keywords: Rheumatoid arthritis, tricuspid annular displacement, heart rate variability, Zhuang medicine

Introduction

Rheumatoid arthritis (RA) is a chronic systemic disease characterized by inflammatory cell infiltration into the synovium, leading to vascular proliferation, cartilage erosion, and eventual cartilage damage [1]. RA primarily affects small joints, but RA progressively involves multiple organs and tissues, including the cardiovascular system, lungs, kidneys, and connective tissue-rich bone [2]. Cardiovascular complications are particularly significant, contributing to 42% of RA-associated mortality and include conditions such as heart valve damage, myocarditis, cardiomyopathy, atherosclerosis, and heart failure [2]. The chronic nature of RA and the complexity of its treatment represent a significant challenge, often resulting in disability and a significant societal economic burden. Current treatment regimens primarily involve pharmacotherapy, including methotrexate (MTX), conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biological DMARDs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs). Although these medications improve disease activity, many patients experience inadequate response, leading to progressive disease - a recognized “treatment bottleneck” [3].

Globally, RA affects approximately 0.5% to 1.0% of the population, with over 5 million individuals affected in China alone [4, 5]. Within the framework of traditional medicine, Zhuang medicine offers a distinct approach to RA treatment, categorized as “Fungcaep” in Zhuang medical ter-

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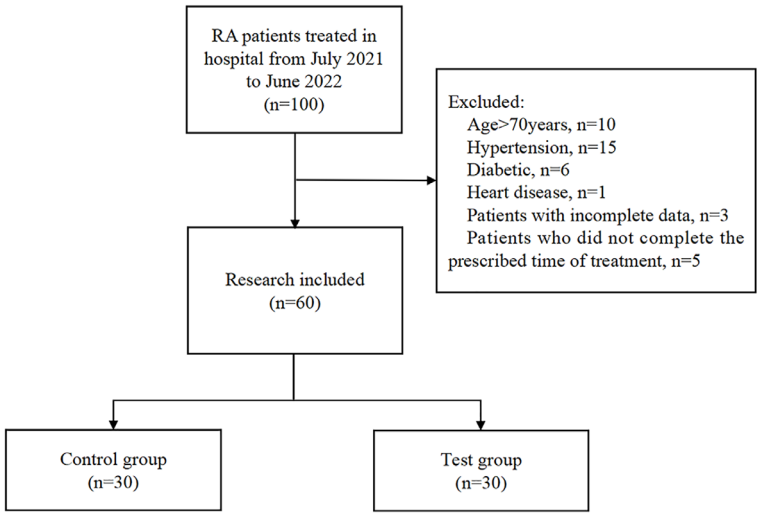

Figure 1. Flow chart of the study. RA, rheumatoid arthritis.

minology. This approach includes diverse treatments such as drug therapy, medicated thread moxibustion, needle pick therapy, and heat-sensitive point acupuncture [6-9]. While preliminary studies suggest Zhuang medicine may positively affect RA [6], these effects are not widely corroborated by strong evidence-based medical data, and their mechanisms remain largely unexplored by modern medical contexts.

This study aims to bridge traditional Zhuang medicine with contemporary medical science by evaluating the effects of combined Zhuang medicine treatments on cardiac tricuspid annulus displacement and heart rate variability (HRV) in RA patients. Our research seeks to provide a novel scientific basis for integrating Zhuang medicine into RA management, offering safer and more effective treatment alternatives.

Materials and methods

Patient selection

This study evaluated echocardiographic results from 60 RA patients and 30 healthy subjects. The RA patients were divided into a control group (n = 30) and a test group (n = 30). From October 2020 to October 2021, these groups received different treatments over a 6-month period at Guangxi International Zhuang Medicine Hospital. **Figure 1** illustrates the participant flow for the study.

Inclusion criteria: Patients must meet both Zhuang and western medicine diagnostic standards for RA [10]; aged between 18 and 70 years old; newly diagnosed patients; no participation in other clinical trials within six months prior to the current study; complete baseline data; and absence of complications such as hypertension, heart disease, diabetes, or other underlying health conditions.

Exclusion criteria: Patients with suppurative or traumatic arthritis; those with cardiovascular, cerebrovascular, liver, kidney, hematopoietic system diseases, malignant tumors, or mental health disorders; patients unable to tolerate or comply with treatment protocols; and patients unable to be effectively assessed for treatment efficacy.

Ethics

This study adhered to the ethical standards of the Guangxi International Zhuang Medicine Hospital and was approved by its Ethics Committee (GZZC2020136).

Diagnostic standards

Zhuang medicine diagnoses “Fungcaep” based on symptoms including joint pain, restricted joint movement, temperature sensitivity, muscle soreness, numbness, ulnar hand deviation, joint flexion, swan neck or boutonniere deformity, difficulty walking, a blue complexion, a dark red tongue with thin white fur, thick swollen sublingual veins, and a tight, purple pulse. In contrast, the diagnosis of RA according to western medicine adheres to the 2010 RA classification criteria, with a score of >6 points [10], confirming the diagnosis [10].

Intervention

Patients in the control group received standard western medical treatment with iguratimod (42200903, Hainan Simcere Pharmaceutical Co., Ltd.), administered at a dose of 5 mg twice daily for 6 months. The test group underwent a

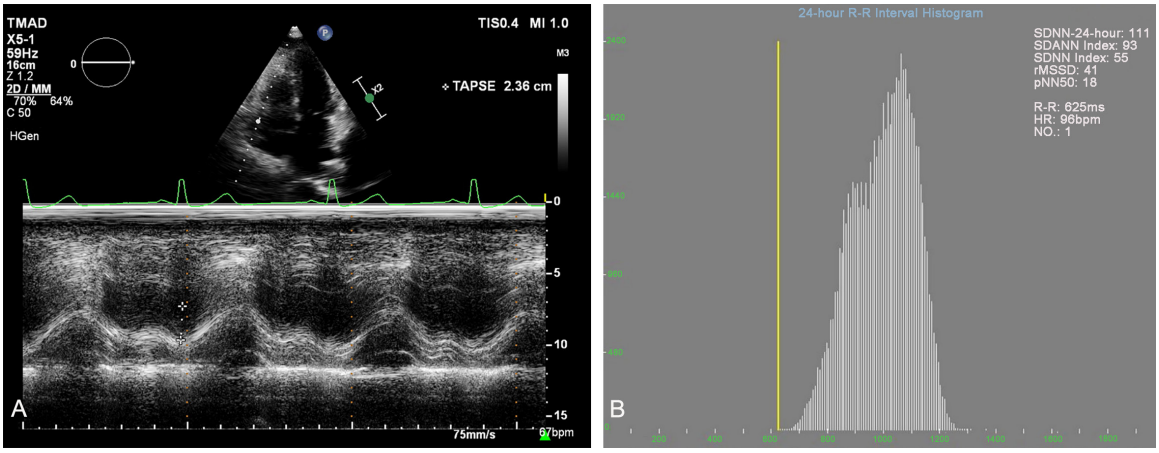

Figure 2. TAPSE and HRV related index images detected by echocardiography. A. Echocardiographic images of TAPSE; B. Echocardiographic images of HRV. TAPSE, tricuspid annular plane systolic excursion; HRV, heart rate variability.

combination of oral Zhuang medicine and Zhuang medicine needle-picking therapy.

(i) Zhuang medicine treatment: Patients were administered the Qingdu Shenjin Decoction orally, prepared by the Pharmacy Department of Guangxi International Zhuang Medicine Hospital. The decoction included Z. nitidum (15 g), Spatholobus suberectus Dunn (15 g), Caulis Lonicerae (20 g), Ilex rotunda Thunb. (20 g), Herba Sarcandrae (20 g), Sinomenii Caulis (15 g), and Herba Lycopodii (15 g). It was taken once daily in two divided doses, morning and evening after meals, for a duration of 6 months.

(ii) Zhuang medicine needle-picking therapy: This treatment was applied to swollen and painful joints. Three to five points were selected for treatment every 5 days, over a 6-month period. The procedure involved selecting a tender point around the joint or skin nodules, followed by routine disinfection. The operator held the skin tightly with the left thumb at the pick point, while the right thumb, index, and middle fingers grasped a three-edged needle to quickly insert and lift at the pick point. The action was repeated to loosen subcutaneous fibers approximately 1 cm in diameter around the pricking point. A small amount of blood was then expressed, or cupping was applied to induce bleeding. After about 10 minutes, irrigation was performed following routine disinfection.

Echocardiography and HRV examination

Echocardiography was conducted using a Philips EPIQ7C color Doppler ultrasound diagnostic instrument (Netherlands) equipped with an S5-1 probe operating at a frequency of 1-5 MHz. Patients were positioned in the left lateral decubitus position. In a high frame rate setting, the apical four-chamber view was used to obtain two-dimensional images. Right ventricular inflow measurements at the sternal level included the early diastolic blood flow velocity (E) and the late diastolic blood flow velocity (A), from which the E/A ratio was calculated. In PW-TDI mode, maintaining a frame rate above 100 fps, peak early diastolic (E') and late diastolic (A') tricuspid annular velocities were measured to calculate the E'/A' ratio. The M-mode ultrasound sampling line was positioned at the anterior tricuspid annulus to measure the tricuspid annular plane systolic excursion (TAPSE) (**Figure 2A**). Additionally, the right ventricular end-diastolic area (RVEDA) and end-systolic area (RVESA) were determined by endocardial tracking, and the right ventricular fractional area change (RVFAC) was calculated using the formula: RVFAC = (RVEDA - RVESA)/RVEDA. HRV was assessed using a portable tester from Huntleigh Healthcare, Cardiff, UK. Patients sat with a wire clip clamping the wrist and forearm, measuring the R-R interval every 5 minutes. The data were analyzed using software to determine the standard deviation of the R-R intervals (SDNN), the standard deviation of the means of all normal RR intervals (SDANN), the root mean square of successive differences (RMSSD), and the percentage of adjacent RR interval differences greater than 50 milliseconds (PNN50) (**Figure 2B**).

Table 1. Comparison of characteristics of patients

Variable	Control group (n = 30)	Test group (n = 30)	*P* value
Gender, M/F	11/19	7/23	0.260
Ages (years)	52.40±6.49	49.83±7.72	0.168
Courses (month)	44.40±23.86	51.73±24.49	0.245
BMI (kg/m^2)	21.34±2.83	20.70±3.49	0.434
Resting heart rate (time/min)	75.47±7.95	75.77±7.41	0.880
SBP (mmHg)	121.37±15.74	126.33±13.99	0.202
DBP (mmHg)	76.00±8.57	77.60±7.67	0.449

M/F, males/females; BMI, Body Mass Index; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure.

Data gathered

Demographic and baseline clinical data were collected, including gender, age, and duration of disease. Vital signs, such as heart rate and systolic and diastolic blood pressures, were also documented. Post-treatment data were collected initially and after 6 months, including total joint count (TJC), swollen joint count (SJC), disease activity score (DAS28), duration of morning stiffness, and levels of C-reactive protein (CRP), rheumatoid factor (RF), and erythrocyte sedimentation rate (ESR).

Evaluation of therapeutic efficiency

The therapeutic responses were classified as follows: marked effect if DAS28 reduction was greater than 1.2; effective if DAS28 reduction was between 0.6 and 1.2; and no effect if DAS28 reduction was 0.6 or less, or if DAS28 was still above 5.1. The overall response rate was calculated using the formula: Overall response rate = [(markedly effective + effective cases/total cases] × 100%.

Statistical methods

Data analysis and processing were performed using SPSS version 21.0. PASS software was used to determine the sample size needed for the study, based on a power analysis that considered the expected effect size (δ), standard deviation (σ), desired level of statistical significance (α), and power (1-β). The sample size formula is as follows: $n=[(Z_\alpha+Z_\beta)^2\times2\sigma^2\div\delta^2]$. The counted data and measured data for the control and test groups were expressed as the number of cases (n) and mean ± standard deviation respectively. Differences between groups were analyzed using the Chi-square test and independent sample t-test, respectively. Pearson's linear regression analysis was used to explore correlations between TAPSE and HRV parameters. Statistical significance was set at $P<0.05$.

Results

Comparison of patient characteristics

Table 1 presents the overall characteristics of the patients. There were no significant differences in gender, age, disease duration, body mass index, resting heart rate, systolic blood pressure, or diastolic blood pressure between the control and test groups (all P>0.05).

Comparison of indicators before and after treatment

To evaluate the therapeutic effects of Zhuang medicine combined with acupuncture on RA patients, various clinical indicators were assessed before and after treatment. Initially, no significant differences were observed in the TJC, SJC, morning stiffness time, CRP, ESR, or RF between the test and control groups (**Figure 3**). However, after treatment, significant reductions in TJC, SJC, morning stiffness duration, CRP, ESR, and RF levels were noted in the test group compared to the control group (all P<0.05), indicating that the combined treatment significantly improved these clinical indicators.

Clinical efficacy

The DAS28 is widely used to assess the therapeutic effect of treatments for RA. In this study, the DAS28 scores of the test group were 5.52±1.25 before treatment and 3.10±1.04 after treatment, showing a significant decrease. The distribution of clinical outcomes, as presented in **Table 2**, included 15 cases with a marked effect, 12 cases as effective, and 3

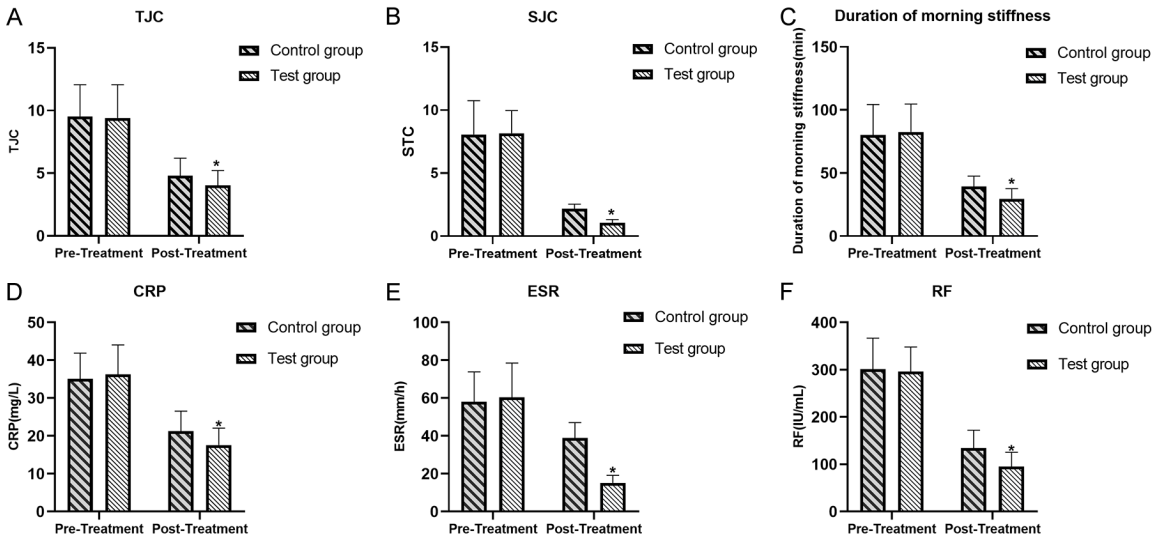

Figure 3. Comparison of indicators before and after treatment in the two groups. A. TJC; B. SJC; C. Duration of morning stiffness; D. CRP; E. ESR; F. RF. TJC, total joint count; SJC, swollen joint count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor. Compared with control group, **P*<0.05.

Table 2. Comparison of clinical efficacy

	n	Marked effect	Effective	No effect	Overall response rate
Control group	30	12 (40.00)	5 (16.67)	13 (43.33)	17 (56.67)
Test group	30	15 (50.00)	12 (40.00)	3 (10.00)	27 (90.00)
Chi-square value					8.523
P value					0.007

Table 3. Comparison of indexes between RA group and healthy group

Index	Healthy group (n = 30)	RA group (n = 60)	*T* value	*P* value
E (m/s)	0.72±0.10	0.75±0.26	0.615	0.540
A (m/s)	0.58±0.15	0.57±0.13	0.299	0.766
E/A	1.34±0.45	1.40±0.68	0.460	0.647
E' (m/s)	13.97±3.44	12.86±3.21	1.513	0.134
A' (m/s)	13.11±3.08	15.84±4.12	3.199	0.002
E'/A'	1.11±0.32	0.89±0.39	2.703	0.008
RVFAC (%)	48.26±10.93	49.18±9.88	0.406	0.647
TAPSE (mm)	23.40±1.07	21.62±1.69	5.272	<0.001
SDNN (ms)	125.20±13.72	123.97±14.59	0.385	0.701
SDANN (ms)	120.57±5.12	110.62±10.00	5.117	<0.001
RMSSD (ms)	35.50±10.78	34.00±9.01	0.697	0.488
PNN50 (ms)	8.54±2.35	7.90±2.21	1.276	0.205

E, early diastolic blood flow velocity; A, late diastolic blood flow velocity; E', Peak early diastolic tricuspid annular velocity; A', late diastolic tricuspid annular velocity; RVFAC, right ventricular fractional area change; TAPSE, tricuspid annular plane systolic excursion; SDNN, standard deviation of the R-R interval; SDANN, means of all normal RR intervals; RMSSD, root mean square of successive differences; PNN50, percent of differences of adjacent RR intervals >50 msec; RA, rheumatoid arthritis.

cases as ineffective in the test group, yielding an overall response rate of 90.00%. This was significantly higher than the 56.67% observed in the control group (P = 0.007).

Comparison of indexes between RA group and healthy group

We compared eight right ventricular function indicators and four HRV indicators between RA patients and healthy controls. The results, presented in **Table 3**, showed significant differences in three of the eight right ventricular function indicators: E', the E'/A' ratio, and tricuspid annular plane systolic excursion (TAPSE). RA group exhibited higher E' values and lower E'/A' ratios and TAPSE compared to healthy individuals (all P<0.05). TAPSE, which reflects the longitudinal systolic function of the right ventricle and is unaffected by ventricular geometry, is highly repeat-

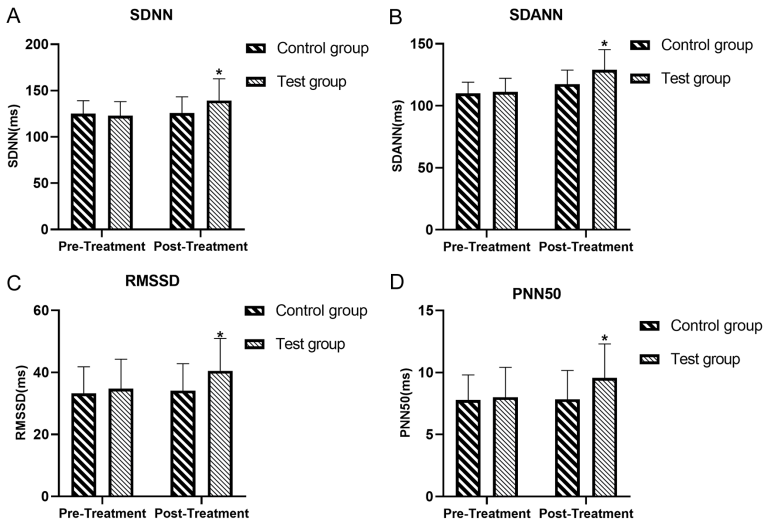

Figure 4. Changes of HRV indices before and after treatment in patients. A. SDNN; B. SDANN; C. RMSSD; D. PNN50. SDNN, standard deviation of the R-R interval; SDANN, means of all normal RR intervals; RMSSD, root mean square of successive differences; PNN50, percent of differences of adjacent RR intervals >50 msec. Compared to control group, *P<0.05.

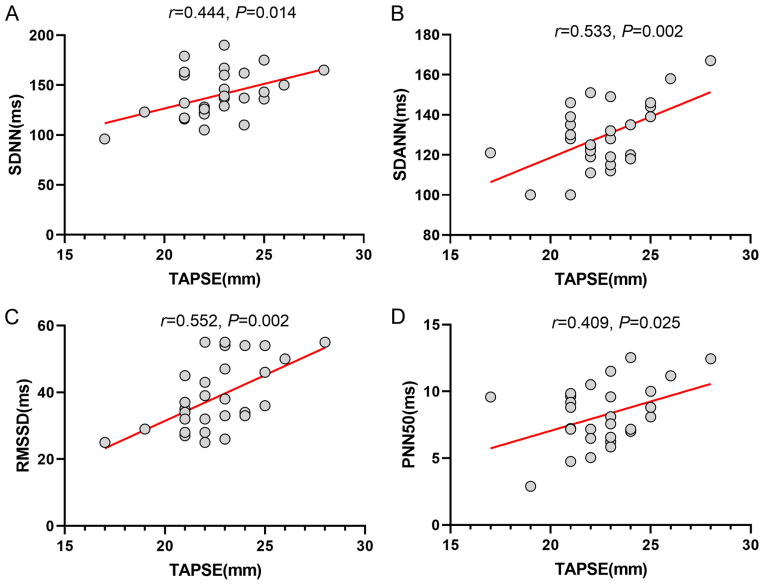

Figure 5. Scatter plot shows the correlation between TAPSE and HRV parameters. A. TAPSE and SDNN; B. TAPSE and SDANN; C. TAPSE and PMSSD; D. TAPSE and PNN50. TAPSE, tricuspid annular plane systolic excursion; SDNN, standard deviation of the R-R interval; SDANN, means of all normal RR intervals; RMSSD, root mean square of successive differences; PNN50, percent of differences of adjacent RR intervals >50 msec; HRV, heart rate variability.

able and operationally straightforward. Therefore, TAPSE was selected to assess the right ventricular function in RA patients before and after treatment. Additionally, significant differences were found in SDANN, with RA patients displaying lower values than healthy controls (P<0.05), indicating possible abnormalities in HRV among RA patients.

Changes of TAPSE and HRV indexes before and after treatment

Before treatment, the control group had a TAPSE of 21.60±1.60 mm, which slightly decreased to 21.30±1.69 mm after six months. Conversely, the test group's TAPSE increased from 21.63±1.97 mm before treatment to 22.57±2.11 mm after treatment. Additionally, HRV indices (SDNN, SDANN, RMSSD, and PNN50) in the test group showed significant improvements post-treatment (all P<0.05, **Figure 4**).

Correlation between TAPSE and HRV Parameters after treatment

After treatment, significant positive correlations were observed between TAPSE and HRV indices (SDNN, SDANN, RMSSD, and PNN50) in the test group, with correlation coefficients of 0.444, 0.535, 0.552, and 0.409, respectively (all P<0.05). These correlations are depicted in the scatter plot shown in **Figure 5**.

Discussion

Modern medicine identifies genetic factors, environmental influences, and dietary habits as principal contributors to the etiology of rheumatoid arthritis (RA), with the pathogenesis involving a complex interplay of cellular components, inflammatory mediators, and signaling pathways [11]. Despite the intricate origins and mechanisms, an effective cure for RA remains elusive. In contrast, Zhuang medicine is grounded in the theo-

ries of “three-way and two-way” and “three-qi synchronization”. These theories emphasize the importance of maintaining the patency of the three ways and two roads, which is considered vital for the synchronized function of the body’s three qi and the preservation of normal physiological operations [12]. The etiological framework in Zhuang medicine attributes all diseases to “toxin” and “deficiency”. Disease is believed to arise when innate bodily strength is inadequate, or when external malign influences such as wind, cold, and dampness invade, obstructing the three ways and two roads, disrupting the synchronization of heaven and earth, and consequently leading to “Fungcaep”. Zhuang medicine. Therefore, Zhuang advocates for treatment strategies that focus on detoxification to eliminate pathogenic factors, reinforcement of healthy qi, and tonification to correct deficiencies.

Zhuang medicine has demonstrated notable therapeutic effects in treating RA [13]. The Qingdu Shenjin Decoction, an empirical formula devised by Dr. Li Fengzhen for “Fungcaep”, includes ingredients such as Z. nitidum, Spatholobus suberectus Dunn, Caulis Lonicerae, Ilex rotunda Thunb., Herba Sarcandrae, Sinomenii Caulis, Herba Lycopodii, among others. This decoction is valued for its ability to dispel wind-cold, remove dampness, detoxify, promote blood circulation, and dredge collaterals. Modern pharmacologic research has revealed that these ingredients exhibit anti-inflammatory, analgesic, antioxidant, and antibacterial properties, and are effective in mitigating the inflammatory processes associated with RA. Z. nitidum, frequently used in Chinese medicine, is celebrated for promoting qi, alleviating pain, detoxifying, and reducing swelling, primarily employed for toothaches and injuries [14]. Its key active component, nitidine chloride, has been shown to counteract RA inflammation by targeting KCNH1 and continuously inhibiting AKT phosphorylation [15]. Extracts from Spatholobus suberectus Dunn regulate T cell division and diminish the production of pro-inflammatory cytokines (IL-17, TNF-α, IL-6), while enhancing anti-inflammatory cytokines (IL-4, IL-10) [16]. Chlorogenic acid, found in Caulis Lonicerae, helps inhibit synovial inflammatory hyperplasia in RA by modulating JAK/STAT and NF-κB pathways, thereby inducing apoptosis in synovial cells [17]. Additionally, pedunculoside, derived from Ilex rotunda Thunb., has been identified to impede the proliferation and migration of synovial cells, suggesting its use as a therapeutic agent for RA [18].

Zhuang medicine needle-pricking therapy is an external treatment using special needles to prick the superficial skin or extract subcutaneous fibers using various techniques. Our study indicates that combining Zhuang medicine with acupuncture needle therapy for RA yields a clinical efficiency rate of 90% and significantly enhances HRV indices, including SDNN, SDANN, RMSSD, and PNN50. Acupuncture at swollen joints has been shown to regulate the Th1/Th2 balance similarly to pharmaceutical interventions [19]. RA is a systemic autoimmune disease that often affects the cardiovascular system, leading to conditions such as heart valve damage, myocarditis, cardiomyopathy, atherosclerosis, and heart failure. Autoimmune abnormalities and systemic chronic inflammation in RA patients are key factors contributing to impaired cardiac function [20].

This study analyzed eight indicators of right ventricular function, with only three - E’, A’, and TAPSE - showing significant differences between RA patients and healthy subjects. TAPSE, which reflects right ventricular longitudinal systolic function, is unaffected by ventricular geometry, highly repeatable, and straightforward to operate. According to the 2010 American echocardiographic guidelines, TAPSE is a standard measure for evaluating right ventricular function, with values less than 16 mm indicating dysfunction [21]. Our patients’ pretreatment TAPSE values averaged around 21 mm, suggesting normal right ventricular function, which may be attributed to the slow progression of right heart function damage in these patients [22]. Notably, after six months of combined treatment with Zhuang medicine, there were significant improvements in TAPSE and several HRV indices in the test group. HRV serves as a marker of sympathetic and parasympathetic nervous system function. Acupuncture is recognized for its regulatory effects on the autonomic nervous system, influencing both sympathetic and parasympathetic activities, which may contribute to its therapeutic benefit by restoring balance in physiological functions disrupted by disease or injury [23]. Acupuncture may enhance HRV by decreasing

neuropeptide expression in the paraventricular nucleus of the thalamus or by reducing reactive oxygen species (ROS) release in peripheral tissues [24]. Furthermore, acupuncture has demonstrated positive outcomes in treating conditions such as depression, functional dyspepsia, and hypertension [25-27]. The needle-pricking and acupuncture therapies employed in our study likely share similar mechanisms, regulating autonomic nerve functions to reduce cardiac load, preserve heart function, and potentially decrease cardiovascular disease incidence.

Our findings indicate a positive correlation between TAPSE and HRV time domain indices (SDNN, SDANN, RMSSD, PNN50) in the observation group after treatment. This correlation underscores the interplay between right ventricular systolic function and the regulatory balance of the autonomic nervous system. Current research confirms the significant value of HRV in assessing changes in autonomic nervous function within the cardiovascular system [28]. HRV acts as a gauge of the cardiac autonomic nervous system (cANS), which includes both sympathetic and parasympathetic components. Disruptions in cANS are associated with poorer clinical outcomes, especially following myocardial infarction or in the context of heart failure [29]. Notably, the right-sided cardiac structures, particularly the right atrium, exhibit a higher degree of independent innervation compared to the left-sided structures, making HRV analysis particularly valuable for assessing autonomic nervous system activity in patients with conditions predominantly affecting the right heart chambers [30]. The results of our study not only underscore the likely therapeutic benefits of Zhuang medicine in enhancing right ventricular function and autonomic balance but also encourage further investigation into the synergistic effects of traditional and conventional treatments in managing RA and its cardiovascular complications.

This study has several limitations. First, it uses a retrospective design with a small sample size, limiting the robustness of the findings. The treatment duration was relatively short, and while the Zhuang medicine Qingdu Shenjin Decoction's main active ingredients are known for their anti-inflammatory effects, inflammatory markers were not included among the observational indicators. Additionally, the absence of a group receiving only Zhuang medicine precludes a clear assessment of its isolated impact on RA. This omission hinders a comprehensive evaluation of Zhuang medicine's efficacy relative to other treatments. To address these limitations, future research should consider: (1) Adopting a prospective, randomized design with a larger and more diverse sample to enhance the validity and generalizability of the results. (2) Extending the treatment duration to better assess long-term effects and understand the chronic nature of RA. (3) Including a group treated solely with Zhuang medicine to isolate and evaluate its specific effects. (4) Incorporating inflammatory markers into the study design to directly measure the treatment's impact on disease activity. (5) Investigating the biologic mechanisms underlying Zhuang medicine and needle-pricking therapy to provide a more evidence-based understanding of their therapeutic actions. By addressing these points, subsequent studies should offer more evidence for the use of Zhuang medicine and needle-pricking therapy in treating RA.

In conclusion, Zhuang medicine combined with needle-pricking therapy significantly enhances right ventricular function and autonomic balance in RA patients, thus affirming its therapeutic potential.

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Disclosure of conflict of interest

None.

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