Original Article

Effects of a Qur'an recitation intervention on *SERCA2a* and *PIEZO1* gene expression, psychological well-being, and cardiac contractility in patients with heart failure with reduced ejection fraction: A randomized controlled trial

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Abstract

Existing studies have shown that Quranic recitation could improve anxiety, depression, and quality of life; however, whether these psychological benefits translate into objective improvements in cardiac function or modulation of myocardial molecular pathways remains unknown. The aim of this study was to evaluate the effects of structured Quranic recitation on *SERCA2a* and *PIEZO1* gene expression, psychological outcomes, and cardiac contractility in patients with heart failure with reduced ejection fraction (HFrEF). In this randomized controlled trial, 30 patients with stable HFrEF were allocated in a 1:1:1 ratio to a one-juz recitation group, a half-juz recitation group, or a control group receiving standard medical therapy alone. Quranic recitation was performed daily for 30 days. Assessments were conducted at baseline, day 15, and day 30 and included *SERCA2a* and *PIEZO1* mRNA expression, Depression Anxiety Stress Scales–42 (DASS-42) scores, left ventricular ejection fraction (LVEF), left ventricular outflow tract velocity–time integral (LVOT-VTI), and LVOT peak velocity (LVOT Vmax). In the one-juz recitation group, depression, anxiety, and stress scores decreased significantly (all $p<0.05$), accompanied by improvements in LVOT-VTI ($p=0.019$), LVOT Vmax ($p=0.001$), and LVEF ($p=0.011$). The half-juz recitation group also showed significant reductions in depression ($p=0.039$) and anxiety ($p=0.012$), but not in stress scores ($p=0.277$), along with improvements in LVOT-VTI ($p=0.044$) and LVEF ($p=0.012$). No significant changes were observed in *SERCA2a* or *PIEZO1* gene expression in any group ($p>0.05$), although a trend toward increased SERCA2a expression was observed in the one-juz recitation group. These findings suggest that daily Quranic recitation for 30 days improved psychological well-being and cardiac contractility in patients with HFrEF. Although no significant changes were observed in *SERCA2a* or *PIEZO1* expression, a trend toward *SERCA2a* upregulation was observed, warranting further investigation in larger studies with longer follow-up.

Keywords: Heart failure, Quranic recitation, gene expression, psychological distress, heart contractility

Introduction

Heart failure (HF) affects an estimated 64.3 million individuals worldwide and remains a leading cause of morbidity, hospitalization, and premature mortality [1,2]. Despite substantial

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advances in pharmacological and device-based therapies, the clinical burden of HF remains significant, particularly among patients with heart failure with reduced ejection fraction (HFrEF), which accounts for approximately 60% of all HF cases [1-4]. Beyond its cardiovascular manifestations, HFrEF is frequently accompanied by psychological comorbidities. Depression affects approximately 20–40% of patients [5,6]. These conditions are associated with poorer treatment adherence, reduced functional capacity, diminished quality of life, increased healthcare utilization, and adverse clinical outcomes [3,7].

At the molecular level, impaired myocardial contractility in HFrEF is closely associated with disturbances in intracellular calcium homeostasis [8,9]. Chronic neurohormonal activation disrupts excitation–contraction coupling through suppression of the sarco/endoplasmic reticulum calcium-ATPase 2a (*SERCA2a*), a key regulator of calcium reuptake into the sarcoplasmic reticulum during diastole [9]. Reduced *SERCA2a* expression impairs calcium cycling, leading to cytosolic calcium accumulation, defective myocardial relaxation, diminished systolic contractility, and progressive ventricular dysfunction [10]. Previous studies have demonstrated reduced *SERCA2a* expression in failing myocardium, highlighting its central role in the pathophysiology of HFrEF [8-10].

Mechanical stress also contributes substantially to disease progression [11]. Chronic ventricular dilation and pressure overload activate mechanotransduction pathways within cardiomyocytes, including signaling mediated by *PIEZO1*, a mechanosensitive ion channel expressed on the cellular membrane [11,12]. Under physiological conditions, *PIEZO1* participates in the detection and adaptation to mechanical stimuli [13]. However, persistent mechanical overload may induce aberrant *PIEZO1* activation, resulting in excessive calcium influx and activation of downstream pathways associated with maladaptive ventricular remodeling, myocardial fibrosis, cardiomyocyte apoptosis, and arrhythmogenesis [11-13]. Together, dysregulation of *SERCA2a* and *PIEZO1* represents two interconnected molecular mechanisms underlying impaired cardiac function in HFrEF [10,12].

Although substantial progress has been made in characterizing the molecular and psychological dimensions of HFrEF, therapeutic strategies integrating both domains remain limited. Contemporary management relies predominantly on pharmacological interventions, including β-blockers, angiotensin receptor–neprilysin inhibitors, mineralocorticoid receptor antagonists, and sodium–glucose cotransporter-2 inhibitors [14-17]. While these therapies effectively target neurohormonal pathways and improve clinical outcomes, psychological distress frequently persists and continues to contribute to symptom burden, impaired self-care, and recurrent hospitalization [18]. This unmet need has prompted growing interest in complementary approaches capable of addressing both psychological well-being and physiological health.

Growing evidence suggests that spiritual well-being and psychological resilience are important determinants of health-related quality of life among patients with chronic cardiovascular disease [19-21]. Higher levels of spirituality have been associated with reduced psychological distress, improved coping capacity, and greater treatment adherence in patients with advanced HF [19-21]. Among Muslim populations, recitation of the Holy Quran represents a central spiritual practice and has been reported to promote relaxation, reduce stress, and improve emotional well-being [19-21]. Although Quranic recitation has been associated with improvements in psychological well-being [19-21], its potential effects on molecular determinants of myocardial function remains unexplored. In particular, to the best of our knowledge, no study has explored whether Quranic recitation affects *SERCA2a* expression or *PIEZO1*-mediated mechanosensitive signaling in patients with HFrEF. Therefore, the aim of this study was to evaluate the effects of structured Quranic recitation on *SERCA2a* and *PIEZO1* gene expression, psychological outcomes, and cardiac contractility in patients with HFrEF.

Methods

Study design and setting

A randomized controlled trial was conducted at the Cardiology Outpatient Clinic of Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia. Participants were recruited and followed for 30 days. Thirty adults with stable HFrEF were recruited and randomly assigned in a 1:1:1 ratio to a one-

juz recitation group, a half-juz recitation group, or a control group receiving standard medical therapy alone. *SERCA2a* and *PIEZO1* gene expression levels were measured using quantitative real-time polymerase chain reaction (RT-PCR), psychological status was assessed using the Depression Anxiety Stress Scales-42 (DASS-42), and cardiac contractility was evaluated by echocardiographic measurement of left ventricular ejection fraction (LVEF), left ventricular outflow tract velocity–time integral (LVOT-VTI), and LVOT peak velocity (LVOT Vmax) at baseline, day 15, and day 30. The study protocol was registered in the Thai Clinical Trials Registry (TCTR20260710025).

Sample size, sampling method, and eligibility criteria

Sample size was estimated using G*Power version 3.1 (Heinrich Heine University Düsseldorf, Germany). Assuming a moderate effect size (f=0.40), α=0.05, and 80% power, a minimum of 27 participants was required; therefore, 30 participants (10 each group) were enrolled. Participants were recruited using a consecutive sampling approach. Eligible participants were adults aged 30–65 years who met the following inclusion criteria: (1) a diagnosis of stable chronic HFrEF with LVEF of 15–40% confirmed by echocardiography; (2) stable clinical status and receipt of guideline-directed medical therapy for at least three months before enrollment, including angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β-blockers, mineralocorticoid receptor antagonists, diuretics, statins, antiplatelet agents, and nitrates, as clinically indicated; (3) sinus rhythm on electrocardiography; and (4) the ability to comply with all study procedures. Patients were excluded if any of the following criteria were present: (1) a history of stroke with residual neurological deficits; (2) acute or chronic inflammatory diseases; (3) severe valvular heart disease; (4) atrial or ventricular arrhythmias; or (5) treatment with medications known to substantially affect heart rate or myocardial contractility beyond standard HF therapy, including ivabradine, diltiazem, verapamil, or amiodarone. Participants were withdrawn from the study if any of the following occurred during follow-up: (1) acute decompensated HF requiring hospitalization; (2) coronary intervention during the study period; or (3) active smoking after enrollment.

Randomization, allocation concealment, and blinding

Participants were randomized in a 1:1:1 ratio to the one-juz recitation group, half-juz recitation group, or control group using a computer-generated randomization sequence. Allocation concealment was maintained using sequentially numbered, opaque, sealed envelopes opened after baseline assessment. Due to the nature of the intervention, participant and investigator blinding was not feasible; however, laboratory personnel performing RT-PCR analyses and cardiologists conducting echocardiographic assessments remained blinded to group allocation.

Quranic recitation intervention

All participants continued to receive guideline-directed medical therapy for HFrEF throughout the study period without modification unless clinically indicated by the cardiologist. Participants assigned to the one-juz recitation group were instructed to recite one juz of the Quran daily for 30 consecutive days, whereas participants in the half-juz recitation group were instructed to recite half a juz daily for the same duration. Participants were encouraged to perform the recitation after obligatory prayers, particularly during the morning and evening, although recitation at other times was permitted. All participants used their personal Quran and were instructed to continue the recitation sequence from the last verse completed during the preceding session. Adherence to the intervention was monitored using daily recitation logs documenting the starting and ending surahs and verses completed during each session. Compliance was further supervised by a trained religious instructor who served as a research assistant and maintained regular communication with participants throughout the study period. In addition, periodic home visits were conducted to verify adherence to the prescribed recitation protocol. Participants in the control group received standard medical therapy and routine clinical follow-up but did not participate in a structured Quranic recitation program.

Study assessments and follow-up

Participants were evaluated at baseline (day 0), day 15, and day 30. At each time point, peripheral venous blood samples were collected for *SERCA2a* and *PIEZO1* gene expression analysis, psychological status was assessed using the DASS-42 questionnaire, and transthoracic echocardiography was performed to measure LVEF, LVOT-VTI, and LVOT Vmax. Baseline assessments were conducted before intervention initiation. For participants in the one-juz and half-juz recitation groups, follow-up assessments on days 15 and 30 were performed immediately after the scheduled morning Quranic recitation session at the Raudhatul Jannah Mosque, Dr. Zainoel Abidin Hospital. Participants in the control group underwent identical assessments at corresponding time points without a preceding recitation session.

Study outcomes

The outcomes in this study were: (a) *SERCA2a* and *PIEZO1* gene expression, measured from peripheral blood samples using quantitative RT-PCR and reported as relative expression values using the 2^-ΔCt method; (b) psychological status assessed using the DASS-42 and reported as depression, anxiety, and stress scores; and (c) LVEF, measured by transthoracic echocardiography using the Teichholz method and reported as a percentage; and (d) LVOT-VTI and LVOT Vmax, measured by Doppler echocardiography and reported in centimeters and cm/s, respectively.

Gene expression analysis

Approximately 1 mL of peripheral venous blood was collected for quantification of *SERCA2a* and *PIEZO1* gene expression. Molecular analyses were performed at the Molecular Biology Laboratory, Prodia Clinical Laboratory, Jakarta, Indonesia, using a CFX96 Touch Real-Time PCR Detection System (Bio-Rad Laboratories, Hercules, CA, USA). Total RNA was isolated from whole blood using the High Pure RNA Isolation Kit (Roche Diagnostics, Mannheim, Germany), followed by reverse transcription into complementary DNA (cDNA) using the High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Foster City, CA, USA). Quantitative RT-PCR was subsequently performed using TaqMan Gene Expression Assays for *SERCA2a*, *PIEZO1*, and glyceraldehyde-3-phosphate dehydrogenase gene (*GAPDH*) as the endogenous reference gene. Amplification consisted of an initial incubation at 50°C for 2 minutes and 95°C for 10 minutes, followed by 40 cycles of denaturation at 95°C for 15 seconds and annealing-extension at 60°C for 60 seconds. Gene expression levels were quantified using the comparative cycle threshold method and expressed as ΔCt values, calculated as the difference between the cycle threshold (Ct) of the target gene and *GAPDH*. Lower ΔCt values indicated higher relative gene expression. Primer sequences for *SERCA2a* and *PIEZO1* were selected according to previously validated protocols [22,23].

Psychological assessment

Psychological status was assessed using the Indonesian version of DASS-42, a validated self-report instrument consisting of 42 items distributed across three domains: depression, anxiety, and stress [24]. Each item was scored on a four-point Likert scale, with higher scores indicating greater psychological distress. The instrument has been psychometrically validated in the Indonesian population and demonstrated excellent internal consistency, with Cronbach's alpha coefficients of 0.95 for the overall scale, 0.90 for the depression subscale, 0.84 for the anxiety subscale, and 0.89 for the stress subscale [24].

Transthoracic echocardiography assessment

Transthoracic echocardiography was performed using a Vivid Series ultrasound system (GE Healthcare, Chicago, IL, USA). Serial echocardiographic examinations were performed to minimize interobserver variability by the same cardiologist. Cardiac contractility was assessed using LVEF, LVOT-VTI, and LVOT Vmax. LVEF was measured from the parasternal long-axis view using M-mode echocardiography. Left ventricular internal diameters at end-diastole (LVIDd) and end-systole (LVIDs) were obtained, and LVEF was calculated using the Teichholz method and expressed as a percentage. LVOT-VTI was measured from the apical five-chamber view using continuous-wave Doppler across the aortic valve. The Doppler velocity envelope was

traced to calculate the velocity–time integral, which was expressed in centimeters and used as an index of stroke distance and left ventricular systolic performance.

Statistical analysis

Normality and homogeneity of variance were assessed using the Shapiro–Wilk and Levene's tests, respectively. Between-group comparisons were performed using one-way analysis of variance (ANOVA) with Bonferroni post hoc correction for normally distributed data with equal variances, Welch's ANOVA with Games–Howell post hoc testing for unequal variances, or the Kruskal–Wallis test with Mann–Whitney U post hoc comparisons for non-normally distributed data. Categorical variables were compared using the chi-squared test or Fisher's exact test, as appropriate. Longitudinal changes in *SERCA2a* expression, *PIEZO1* expression, DASS-42 scores, LVEF, LVOT-VTI, and LVOT Vmax across baseline, day 15, and day 30 were analyzed using repeated-measures ANOVA or the Friedman test, as appropriate. All tests were two-sided, and a $p<0.05$ was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics of participants

A total of 30 patients with HFrEF were enrolled and equally allocated to the one-juz recitation group, half-juz recitation group, and control group (n=10 per group) (**Table 1**). Body mass index, hemodynamic parameters, smoking status, hypertension, and diabetes mellitus frequencies were comparable across groups (all $p>0.05$). Dyslipidemia was more prevalent in the one-juz recitation group (80.0%) than in the half-juz recitation (20.0%) and control groups (50.0%) ($p=0.027$). Baseline DASS-42 depression, anxiety, and stress scores did not differ significantly among groups (all $p>0.05$).

Table 1. Baseline characteristics of patients with heart failure with reduced ejection fraction (HFrEF) (n=30)

Variable	Study group			*p*-value
	One-juz recitation (n=10)	Half-juz recitation (n=10)	Control (n=10)	
	Mean±SD	Mean±SD	Mean±SD	
Age (years)	54.70±4.62	50.20±10.69	56.50±6.39	0.318[a]
Sex, n (%)				0.749[b]
Male	8 (80.0)	9 (90.0)	9 (90.0)	
Female	2 (20.0)	1 (10.0)	1 (10.0)	
Body mass index (kg/m²)	26.09±3.88	27.50±3.97	25.76±4.95	0.638[a]
Hemodynamic profile				
Systolic blood pressure (mmHg)	130.80±27.95	123.10±28.50	118.20±14.31	0.591[a]
Diastolic blood pressure (mmHg)	88.90±21.78	79.30±19.82	76.50±8.78	0.278[a]
Heart rate (beats/min)	74.20±16.32	71.70±16.74	76.70±12.78	0.770[a]
Cardiovascular risk factors, n (%)				
Current or former smoking	6 (60.0)	8 (80.0)	8 (80.0)	0.506[b]
Hypertension	7 (70.0)	8 (80.0)	5 (50.0)	0.350[b]
Diabetes mellitus	4 (40.0)	2 (20.0)	4 (40.0)	0.549[b]
Dyslipidemia	8 (80.0)	2 (20.0)	5 (50.0)	0.027[b*]
Baseline DASS-42 scores				
Depression	3.70±3.09	3.50±3.13	3.10±0.73	0.796[a]
Anxiety	7.10±4.22	5.30±2.79	7.40±2.79	0.330[a]
Stress	6.90±5.95	5.40±5.25	6.40±6.46	0.835[a]

DASS-42: Depression Anxiety Stress Scales-42
[a] Analyzed using one-way ANOVA
[b] Analyzed using chi-squared test
[*] Statistically significant at $p<0.05$

Baseline laboratory and inflammatory parameters were comparable among the three study groups (**Table 2**). No significant differences were observed in hematological indices, including hemoglobin, hematocrit, erythrocyte count, leukocyte count, platelet count, neutrophil percentage, and lymphocyte percentage (all $p>0.05$). Similarly, inflammatory markers, including

erythrocyte sedimentation rate, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and systemic inflammation index, did not differ significantly among groups (all $p>0.05$).

Table 2. Baseline laboratory and inflammatory parameters in the one-juz recitation, half-juz recitation, and control groups

Laboratory parameters	Study group			*p*-value
	One-juz recitation (n=10)	Half-juz recitation (n=10)	Control (n=10)	
	Mean±SD	Mean±SD	Mean±SD	
Hemoglobin (g/dL)	13.98±1.45	13.95±2.00	13.41±1.62	0.706[a]
Hematocrit (%)	41.79±3.50	41.73±5.80	40.66±5.25	0.849[a]
Erythrocyte sedimentation rate (mm/h)	21.80±32.84	20.60±17.37	16.80±16.18	0.566[b]
Erythrocytes (10^6/µL)	4.75±0.56	4.86±0.65	4.88±0.83	0.908[a]
Leukocytes (10^3/µL)	8.10±1.60	7.59±1.36	7.77±2.26	0.812[a]
Platelets (10^3/µL)	260.80±107.54	256.50±61.62	256.60±67.43	0.991[a]
Neutrophils (%)	57.69±8.67	58.13±8.67	62.14±4.75	0.367[a]
Lymphocytes (%)	29.59±6.54	30.09±8.47	24.97±7.38	0.261[a]
Neutrophil-to-lymphocyte ratio	2.08±0.72	2.18±1.01	2.79±1.22	0.272[b]
Platelet-to-lymphocyte ratio	9.29±5.50	9.01±2.83	10.92±3.61	0.308[b]
Systemic inflammation index	645.75±452.64	542.98±235.31	687.80±251.14	0.369[b]

[a] Analyzed using one-way ANOVA
[b] Analyzed using Kruskal-Wallis test

Baseline echocardiographic parameters were also comparable among the three study groups (**Table 3**). No significant between-group differences were observed in cardiac chamber dimensions, including LVEDD, LVESD, IVSD, and IVSS (all $p>0.05$). Measures of left ventricular systolic function, including Teichholz ejection fraction, biplane ejection fraction, LVOT-VTI, and LVOT Vmax, were also similar across groups (all $p>0.05$). Likewise, right ventricular systolic function assessed by tricuspid annular plane systolic excursion did not differ significantly among groups ($p=0.433$). The prevalence of moderate-to-severe diastolic dysfunction (grade II–III) ranged from 80% to 100% across groups, with no significant difference among groups ($p=0.329$).

Table 3. Baseline echocardiographic parameters in the one-juz recitation, half-juz recitation, and control groups

Echocardiographic parameters	Study group			*p*-value
	One-juz recitation (n=10)	Half-juz recitation (n=10)	Control group (n=10)	
	Mean±SD	Mean±SD	Mean±SD	
Left ventricular end-diastolic diameter (mm)	52.80±8.02	55.80±8.59	55.20±6.90	0.670[a]
Left ventricular end-systolic diameter (mm)	44.50±7.21	47.90±8.25	47.70±6.86	0.529[a]
Interventricular septum diastole (mm)	9.20±3.32	9.50±2.63	8.20±1.93	0.535[a]
Interventricular septum systole (mm)	10.70±3.56	10.90±3.03	10.00±1.94	0.772[a]
Left ventricular contractility				
Teichholz ejection fraction (%)	33.30±4.42	28.80±6.77	27.90±6.33	0.112[a]
Biplane ejection fraction (%)	33.80±5.73	30.40±5.54	27.40±5.56	0.054[a]
LVOT velocity–time integral (cm)	16.61±5.13	16.90±4.82	15.49±6.29	0.831[a]
LVOT Vmax (cm/s)	81.85±14.49	98.13±26.22	86.30±21.46	0.228[a]
Right ventricular contractility				
TAPSE (cm)	2.01±0.34	1.98±0.30	1.83±0.33	0.433[a]
Diastolic dysfunction, n (%)				0.329[b]
Normal to grade I	2 (20.0)	1 (10.0)	0 (0.0)	
Grade II to grade III	8 (80.0)	9 (90.0)	10 (100.0)	

LVOT: left ventricular outflow tract; TAPSE: tricuspid annular plane systolic excursion
[a] Analyzed using one-way ANOVA
[b] Analyzed using chi-squared test

Baseline *SERCA2a* and *PIEZO1* mRNA expression levels were comparable among the three study groups (**Table 4**). Mean *SERCA2a* mRNA expression ranged from 7.63±6.51 to 9.02±8.49 ΔCt, with no significant between-group difference ($p=0.945$). Similarly, baseline *PIEZO1* mRNA expression ranged from 16.76±5.49 to 19.73±6.94 ΔCt and did not differ significantly across groups ($p=0.650$).

Table 4. Baseline *SERCA2a* and *PIEZO1* mRNA expression in the one-juz recitation, half-juz recitation, and control groups

Baseline gene expression	Study group			*p*-value
	One-juz recitation (n=10)	Half-juz recitation (n=10)	Control (n=10)	
	Mean±SD	Mean±SD	Mean±SD	
SERCA2a mRNA expression (ΔCt)	7.63±6.51	8.88±8.33	9.02±8.49	0.945[a]
PIEZO1 mRNA expression (ΔCt)	16.76±5.49	19.73±6.94	17.56±7.10	0.650[a]

[a] Analyzed using one-way ANOVA

Effects of Quranic recitation on depression, anxiety, and stress

Both Quranic recitation groups demonstrated significant improvements in psychological outcomes over the 30-day study period (**Table 5**). In the one-juz recitation group, depression, anxiety, and stress scores decreased significantly from baseline to day 30 (all $p<0.05$). Similarly, the half-juz recitation group had significant reductions in depression ($p=0.039$) and anxiety ($p=0.012$), whereas the reduction in stress did not reach statistical significance ($p=0.277$). In contrast, no significant changes in depression, anxiety, or stress scores were observed in the control group (all $p>0.05$). Between-group comparisons revealed a significant difference in depression scores at day 15 ($p=0.044$) and anxiety scores at day 30 ($p=0.015$), with lower scores observed in both intervention groups. No significant between-group differences were detected for stress scores at any assessment time point (all $p>0.05$) (**Table 5**).

Post hoc analyses revealed that both recitation interventions significantly improved depression scores over time (**Table 5**). In the one-juz group, depression decreased significantly by day 15 and remained reduced at day 30, whereas the half-juz group showed a significant reduction only at day 30. For anxiety, significant reductions were observed at both follow-up assessments in the one-juz group, while the half-juz group had a stepwise decline across all time points. Stress scores decreased significantly at day 15 in the one-juz group; however, the day 30 score was not significantly different from either baseline or day 15. No significant temporal changes were detected in the control group across any DASS-42 domain.

Table 5. Longitudinal changes in depression, anxiety, and stress scores measured by the Depression Anxiety Stress Scales–42 (DASS-42) among the one-juz recitation, half-juz recitation, and control groups

DASS-42 domain	Day 0	Day 15	Day 30	*p*-value
	Mean±SD	Mean±SD	Mean±SD	
Depression				
One-juz recitation group	3.70±3.09[c]	2.20±2.61[d]	1.40±1.89[d]	0.006[a*]
Half-juz recitation group	3.50±3.13[c]	1.70±2.11[c,d]	1.40±1.34[d]	0.039[a*]
Control group	3.10±0.73	5.50±6.83	5.10±8.04	0.412[a]
p-value	0.796[b]	0.044[b*]	0.188[b]	
Anxiety				
One-juz recitation group	7.10±4.22[c]	3.50±2.79[d]	2.40±3.30[d]	0.002[a*]
Half-juz recitation group	5.30±2.79[c]	3.30±2.00[d]	1.80±1.54[e]	0.012[a*]
Control group	7.40±2.79	6.30±3.71	6.70±4.69	0.564[a]
p-value	0.330[b]	0.053[b]	0.015[b*]	
Stress				
One-juz recitation group	6.90±5.95[c]	3.10±3.03[d]	2.10±3.31[c,d]	0.003[a*]
Half-juz recitation group	5.40±5.25	2.80±2.85	2.90±2.92	0.277[a]
Control group	6.40±6.46	6.70±6.54	6.10±7.07	0.428[a]
p-value	0.835[b]	0.115[b]	0.251[b]	

[a] Within-group comparisons were performed using repeated-measures ANOVA
[b] Analyzed using one-way ANOVA
[c-e] Different superscript letters indicate significant differences between time points according to post hoc pairwise comparisons ($p<0.05$)
[*] Statistically significant at $p<0.05$

Effects of Quranic recitation on left ventricular systolic function

Longitudinal echocardiographic assessment demonstrated significant improvements in several measures of cardiac contractility among participants within Quranic recitation groups (**Table 6**). In the one-juz recitation group, LVOT-VTI increased significantly from 16.61±5.13 cm at baseline to 20.53±6.56 cm at day 30 ($p=0.019$), followed by significant increases in LVOT Vmax

(81.85±14.49 to 98.80±17.44 cm/s; p=0.001) and Teichholz ejection fraction (33.30±4.42% to 39.40±6.38%; p=0.011). Similarly, the half-juz recitation group demonstrated significant improvements in LVOT-VTI (16.90±4.82 to 20.47±3.47 cm; p=0.044) and Teichholz ejection fraction (28.80±6.77% to 36.00±9.55%; p=0.012), whereas changes in LVOT Vmax were not significant (p=0.783). In contrast, no significant changes were observed in the control group for LVOT-VTI, LVOT Vmax, or ejection fraction (all p>0.05). Between-group comparisons revealed significant differences in LVOT-VTI at day 15 (p=0.045) and day 30 (p=0.004), as well as in LVOT Vmax at day 15 (p=0.024), while no significant differences were observed for ejection fraction at any assessment time point (all p>0.05) (**Table 6**).

Post hoc comparisons revealed that the one-juz recitation group experienced significant increases in LVOT-VTI and LVOT Vmax by day 15, which were maintained through day 30 (**Table 6**). Teichholz ejection fraction increased significantly only at day 30. In the half-juz recitation group, Teichholz ejection fraction was significantly higher at day 30 than at baseline and day 15, whereas LVOT-VTI and LVOT Vmax showed no significant pairwise differences. No significant temporal changes were detected in the control group.

Table 6. Longitudinal changes of left ventricular systolic function assessed by echocardiography among the one-juz recitation, half-juz recitation, and control groups

Echocardiographic metrics	Day 0	Day 15	Day 30	p-value
	Mean±SD	Mean±SD	Mean±SD	
LVOT-VTI (cm)				
One-juz recitation group	16.61±5.13^{c}	19.88±5.51^{d}	20.53±6.56^{d}	0.019^{a*}
Half-juz recitation group	16.90±4.82^{c}	18.39±4.57^{c}	20.47±3.47^{c}	0.044^{a*}
Control group	15.49±6.29	14.78±2.76	15.44±2.39	0.484^{a}
p-value	0.831^{b}	0.045^{b*}	0.004^{b*}	
LVOT Vmax (cm/s)				
One-juz recitation group	81.85±14.49^{c}	96.60±13.75^{d}	98.80±17.44^{d}	0.001^{a*}
Half-juz recitation group	98.13±26.22	100.70±20.51	103.60±16.50	0.783^{a}
Control group	86.30±21.46	80.36±13.94	89.82±6.08	0.178^{a}
p-value	0.228^{b}	0.024^{b*}	0.050^{b}	
Teichholz ejection fraction (%)				
One-juz recitation group	33.30±4.42^{c}	36.20±8.49^{cd}	39.40±6.38^{d}	0.011^{a*}
Half-juz recitation group	28.80±6.77^{c}	30.70±7.84^{c}	36.00±9.55^{d}	0.012^{a*}
Control group	27.90±6.33	34.90±9.29	32.00±8.03	0.171^{a}
p-value	0.112^{b}	0.339^{b}	0.143^{b}	

LVOT: left ventricular outflow tract; VTI: velocity time integral
[a] Within-group comparisons were performed using repeated-measures ANOVA
[b] Analyzed using one-way ANOVA
[c-e] Different superscript letters indicate significant differences between time points according to post hoc pairwise comparisons (p<0.05)
[*] Statistically significant at p<0.05

Effects of Quranic recitation on *SERCA2a* and *PIEZO1* mRNA expression

Longitudinal assessment of *SERCA2a* and *PIEZO1* mRNA expression revealed no significant changes within or between groups throughout the 30-day study period (**Table 7**). In the one-juz recitation group, *SERCA2a* mRNA expression remained relatively stable from baseline to day 30 (7.63±6.51 vs 6.51±6.55; p=0.741), with similar nonsignificant findings observed in the half-juz recitation group (8.88±8.33 vs 9.01±6.55; p=0.368) and control group (9.02±8.49 vs 10.56±9.88; p=0.097). Likewise, *PIEZO1* mRNA expression did not change significantly in the one-juz recitation group (16.76±5.49 vs 16.43±6.48; p=0.789), half-juz recitation group (19.73±6.94 vs 18.46±6.63; p=0.961), or control group (17.56±7.10 vs 22.37±5.17; p=0.337). No significant between-group differences were observed for either *SERCA2a* or *PIEZO1* expression at baseline, day 15, or day 30 (all p>0.05).

Table 7. Longitudinal changes in *SERCA2a* and *PIEZO1* mRNA expression among the one-juz recitation, half-juz recitation, and control groups

Gene expression	Day 0	Day 15	Day 30	p-value
	Mean±SD	Mean±SD	Mean±SD	
SERCA2a mRNA expression (ΔCt)				
One-juz recitation group	7.63±6.51	7.69±7.29	6.51±6.55	0.741^{a}

Gene expression	Day 0	Day 15	Day 30	*p*-value
	Mean±SD	Mean±SD	Mean±SD	
Half-juz recitation group	8.88±8.33	6.12±2.67	9.01±6.55	0.368[a]
Control group	9.02±8.49	5.85±3.18	10.56±9.88	0.097[a]
p-value	0.945[b]	0.727[b]	0.262[b]	
PIEZO1 mRNA expression (ΔCt)				
One-juz recitation group	16.76±5.49	17.58±6.12	16.43±6.48	0.789[a]
Half-juz recitation group	19.73±6.94	19.89±5.87	18.46±6.63	0.961[a]
Control group	17.56±7.10	20.89±5.07	22.37±5.17	0.337[a]
p-value	0.650[b]	0.240[b]	0.074[b]	

[a] Within-group comparisons were performed using repeated-measures ANOVA
[b] Analyzed using one-way ANOVA

Discussion

Psychological distress is highly prevalent among patients with HFrEF and contributes substantially to impaired functional status, reduced quality of life, and adverse clinical outcomes. The present study evaluated the effects of structured Quranic recitation on psychological outcomes, cardiac contractility, and *SERCA2a* and *PIEZO1* mRNA expression in patients with HFrEF. Regular Quranic recitation was associated with significant reductions in depression and anxiety scores, with improvements becoming evident by day 15 and sustained through day 30. Post hoc analyses showed that the one-juz recitation group experienced early and sustained improvements in depression, anxiety, LVOT-VTI, and LVOT Vmax, with significant changes observed by day 15 and maintained through day 30. Teichholz ejection fraction increased significantly only at day 30. In the half-juz recitation group, anxiety decreased progressively across all time points, while significant improvements in depression and Teichholz ejection fraction were observed only at day 30. No significant pairwise changes were detected for LVOT-VTI or LVOT Vmax.

The significant reduction in depression, anxiety, and stress observed in the present study is consistent with previous evidence demonstrating the psychological benefits of Quranic recitation [19,20,25]. Quranic recitation may alleviate psychological distress through an integrated neurospiritual mechanism that links spiritual engagement with physiological regulation [19]. Neurophysiological studies suggest that listening to or reciting the Quran promotes alpha-wave activity, a brain state associated with relaxation, emotional stability, and increased stress tolerance [20,25]. This response is accompanied by enhanced release of serotonin and endorphins, which contribute to improved mood and psychological well-being [20,25]. In addition, Quranic recitation has been shown to reduce anxiety levels in various clinical populations, including patients undergoing hemodialysis, while also alleviating depressive symptoms through the promotion of spiritual peace, positive coping, and greater life satisfaction [25]. Regular engagement with the Quran may further strengthen emotional resilience and facilitate adaptive responses to chronic illness and psychological stress [20,21].

The temporal pattern observed in the present study is biologically plausible. Acute physiological responses may occur within a single recitation session of 15–30 minutes, during which increased alpha-wave activity and parasympathetic activation contribute to reductions in heart rate and cortisol levels [25,26]. More sustained improvements generally require consistent daily practice. A systematic review of the previous intervention studies employing 15–20 minutes of Quranic recitation or listening per day found significant reductions in anxiety and depression scores after 2–4 weeks of intervention [25], supporting the progressive improvements observed at days 15 and 30 in the present study. Longer-term practice extending beyond eight weeks may produce more durable cognitive and emotional adaptations, transforming Quranic recitation into an established coping mechanism that enhances psychological resilience [25]. Collectively, these findings suggest that Quranic recitation may serve as a complementary non-pharmacological intervention capable of improving psychological well-being in patients with HFrEF, with measurable benefits becoming apparent within the first month of regular practice.

The observed improvement in echocardiographic parameters despite the absence of significant changes in *SERCA2a* mRNA expression is biologically plausible. The observed improvements in LVOT-VTI and LVOT Vmax may be mechanistically linked to enhanced calcium handling mediated by *SERCA2a* [9,27]. Increased *SERCA2a* expression promotes more efficient

reuptake of cytosolic calcium into the sarcoplasmic reticulum during diastole, replenishing intracellular calcium stores that are typically depleted in HFrEF [27,28]. As a result, greater amounts of calcium become available for release through ryanodine receptors during systole, leading to increased actin–myosin cross-bridge formation and enhanced myocardial contractility [27,28]. This improvement in both contractile force (positive inotropy) and relaxation efficiency (lusitropy) could increase peak systolic flow velocity across the LVOT Vmax and augment stroke volume, reflected by higher LVOT-VTI values [28].

In contrast, improvements in LVEF generally require a longer period of molecular and structural reverse remodeling [28]. Restoration of *SERCA2a* expression alone may be insufficient to produce immediate changes in LVEF, as a critical threshold of *SERCA2a* activity must first be achieved to overcome chronic sarcoplasmic reticulum calcium leakage and restore calcium homeostasis [28]. Previous studies suggested that clinically meaningful improvements in LVEF typically became evident after 3–6 months of therapy and might continue to evolve over 6–12 months as ventricular dimensions progressively normalize [29,30]. Such recovery depends not only on adequate *SERCA2a* mRNA expression but also on effective inflammatory control and continued adherence to guideline-directed medical therapy, which together provide a favorable environment for myocardial reverse remodeling [28-30].

Although no statistically significant differences in *SERCA2a* mRNA expression were observed among the three groups at day 30, a favorable trend was noted in the one-juz recitation group, which demonstrated lower ΔCt values than the half-juz recitation and control groups (6.51±6.55, 9.01±6.55, and 10.56±9.88, respectively). Because ΔCt values are inversely related to transcript abundance, lower values indicate relatively higher *SERCA2a* mRNA expression. The absence of statistical significance is biologically plausible, as molecular adaptations generally require a longer period to become detectable. Evidence from mind–body intervention studies suggests that reductions in stress-related biomarkers such as cortisol and pro-inflammatory cytokines may occur within 2–4 weeks, whereas significant epigenetic and transcriptional changes typically emerge after 4–8 weeks of sustained practice, with functional cardiac remodeling often requiring 3–6 months of intervention–which may explain the absence of significant changes in *SERCA2a* mRNA expression after only 30 days of follow-up [31,32].

Because lower ΔCt values indicate higher gene expression, the trend toward lower *SERCA2a* ΔCt values observed in the one-juz recitation group may suggest the initiation of a favorable molecular response. A plausible mechanism involves activation of the relaxation response, resulting in reduced circulating catecholamines and cortisol levels [33,34]. This neurohormonal shift may suppress NF-κB signaling, a known negative regulator of ATP2A2 transcription, while simultaneously reducing oxidative stress and pro-inflammatory cytokine activity [35-37]. In addition, lower oxidative stress may enhance the activity of positive transcription factors, including myocyte enhancer factor-2 (MEF2), thereby promoting ATP2A2 transcription and increasing *SERCA2a* mRNA synthesis [38,39]. Improved autonomic balance may also facilitate phospholamban phosphorylation, indirectly enhancing *SERCA2a* function [36].

Despite significant improvements in psychological status and cardiac function, no significant changes in *PIEZO1* mRNA expression were observed after 30 days of intervention. In patients with HFrEF, *PIEZO1* mRNA expression is generally upregulated in response to chronic mechanical stress and ventricular remodeling [11,40,41]. Experimental studies in animal models and human cardiac tissues have demonstrated increased *PIEZO1* mRNA expression in cardiomyocytes exposed to persistent pressure or volume overload [11,40,41]. As a mechanosensitive ion channel, PIEZO1 functions as a cellular sensor of mechanical stretch, and its expression increases as an adaptive response to excessive ventricular wall stress [40]. However, sustained activation of PIEZO1 may contribute to pathological remodeling through several mechanisms. Increased PIEZO1 activity promotes pro-inflammatory cytokine release, including interleukin-6, stimulates fibroblast-to-myofibroblast differentiation leading to myocardial fibrosis, and enhances calcium influx into cardiomyocytes, which may impair contractile function and promote apoptosis [11,12,41]. Furthermore, previous studies have reported a positive correlation between *PIEZO1* mRNA expression and the severity of left ventricular dysfunction, with higher expression levels observed in patients and experimental models exhibiting lower ejection fraction and more advanced ventricular dilatation [11,12,40,41].

These findings suggest that *PIEZO1* is not only a marker of mechanical stress but may also play an active role in the progression of HF.

The present study found no significant change in *PIEZO1* mRNA expression after 30 days in either intervention group. To date, no studies have directly evaluated the effects of spiritual interventions on *PIEZO1* mRNA expression in patients with HFrEF. Previous studies have primarily focused on the role of PIEZO1 in cardiac mechanotransduction and ventricular remodeling rather than on interventions targeting its expression. However, no clinical studies have investigated whether behavioral, psychological, or spiritual interventions can modulate *PIEZO1* mRNA expression. Consequently, the absence of significant changes in *PIEZO1* mRNA expression observed in the present study may reflect the relatively short intervention duration and highlights an important gap in the current literature regarding the interaction between psychological well-being, mechanotransduction pathways, and myocardial remodeling in HFrEF.

A major strength of this study is its randomized, parallel-group design, which enabled evaluation of a novel translational link between a culturally embedded spiritual intervention and psychological, molecular, and hemodynamic outcomes in patients with HFrEF within a relatively homogeneous Muslim population. Excellent adherence to the prescribed Quranic recitation protocol, with no participant withdrawals, further supports the feasibility of integrating structured spiritual practices into cardiovascular care. Several limitations should be acknowledged. The 30-day intervention period may have been insufficient to induce significant changes in *SERCA2a* and *PIEZO1* gene expression or substantial cardiac reverse remodeling, processes that typically require longer durations to manifest. The relatively small sample size may have limited the ability to detect modest between-group differences, particularly for molecular outcomes. Larger multicenter studies with longer follow-up periods are needed to determine whether the observed psychological and hemodynamic improvements translate into sustained molecular adaptations and long-term clinical benefits.

Conclusion

In patients with HFrEF, daily Quranic recitation for 30 days significantly reduced depression, anxiety, and stress scores and improved echocardiographic indices of cardiac contractility, including LVOT-VTI and within-group ejection fraction. Although changes in *SERCA2a* and *PIEZO1* gene expression did not reach statistical significance, the trend toward increased expression of *SERCA2a* was observed in the one-juz recitation group. These findings support the potential role of Quranic recitation as a complementary intervention to improve psychological well-being and early cardiac functional outcomes in Muslim patients with HFrEF. Larger multicenter studies with longer follow-up are warranted to confirm these findings and determine whether Quranic recitation produces sustained cardiac and molecular effects.

Ethics approval

The protocol of the present study was reviewed and approved by the Ethics Committee for Health Research, Dr. Zainoel Abidin Hospital, Banda Aceh, Indonesia (Approval number: 049/ETIK-RSUDZA/2024). All participants received information about the study objectives, procedures, potential benefits and risks, and their rights as research participants before enrollment. Written informed consent was obtained from each participant prior to participation. Participation was voluntary, and participants were free to withdraw from the study at any time without any effect on their medical care. Participant confidentiality was maintained throughout the study by using coded identifiers and restricting access to identifiable information to the research team. Data were analyzed and reported in anonymized form. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

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Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

Declaration of artificial intelligence use

This study used an artificial intelligence (AI) tool, ChatGPT, for language refinement (improving grammar, sentence structure, and readability of the manuscript). Authors confirm that all AI-assisted processes were critically reviewed by the authors to ensure the integrity and reliability of the results. The final decisions and interpretations presented in this article were solely made by the authors.

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