

Effects of coenzyme Q10 supplementation on diastolic function in patients with heart failure with preserved ejection fraction

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Summary

Heart failure with preserved ejection fraction (HFpEF) is a leading cause of morbidity and mortality without an established treatment. Diastolic dysfunction, the hallmark of HFpEF, is associated with altered myocardial bioenergetics. No previous study has examined the effects of coenzyme Q10 (CoQ10) on left ventricle (LV) diastolic function in patients with HFpEF. We investigated whether CoQ10 could improve LV diastolic function in patients with HFpEF. We performed a randomized controlled trial (RCT) using pretest and posttest control groups of 30 patients with HFpEF. The patients received either CoQ10 100 mg three times a day or no CoQ10 in addition to routine treatment for 30 days. Echocardiographic study was performed at baseline and follow-up. LV diastolic function was evaluated by two dimensional and Doppler echocardiography as follows; average E/e', septal and lateral e' velocity, and left atrium volume index (LAVI). A total of 28 patients completed the study. A statistically significant improvement was observed in the CoQ10 treatment group in terms of average E/e' (18.9 (3.8) vs. 15.1 (4.3); $p < 0.01$) and LAVI (32 (9) mL/m² vs. 26 (7) mL/m²; $p < 0.05$) and in the control group (18.4 (3.1) vs. 15.8 (5.6); $p < 0.05$) and (33 (7) mL/m² vs. 30 (8) mL/m²; $p < 0.05$, respectively). However, there was no difference in change reduction between groups (Δ E/e' - 3.6 vs. - 2.4; $p = 0.28$) and (Δ LAVI - 5.4 vs. - 4.4; $p = 0.83$). Short term CoQ10 supplementation provided no additional benefits in improving LV diastolic function in patients with HFpEF.

Keywords: Heart failure with preserved ejection fraction (HFpEF), LV diastolic function, coenzyme Q10

1. Introduction

The prevalence of heart failure with preserved ejection fraction (HFpEF) accounts for more than 50% of patients with heart failure (HF) and tends to increase with a prognosis as bad as that of HF with reduced ejection fraction (HFrEF) (1-6). Till date, no therapy has been demonstrated to improve mortality in patients with HFpEF including several large prospective, randomized controlled trial such as angiotensin

converting enzyme inhibitor (ACE-I) perindopril (PEP-CHF) (7), angiotensin II receptor blockers (ARBs) candesartan (CHARM-Preserved) (8) and irbesartan (I-PRESERVE) (9), aldosterone receptor blockers spironolactone (TOPCAT (10) and Aldo-DHF (11)), and beta blocker (SENIORS) (12).

Recent studies have shown that bioenergetic deficiency is involved in the pathophysiology of HFpEF and that these changes lead to myocardial remodeling and dysfunction (13). Patients with HFpEF show abnormalities in myocardial energetics in the formation of adenosine triphosphate (ATP) and movement between phosphocreatine and ATP through creatine kinase reactions. Phan *et al.* (14,15) found a significant reduction in the phosphocreatine/ATP ratio of patients with HFpEF compared to that in controls.

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Coenzyme Q10 (CoQ10) or ubiquinone is a cofactor that plays a critical role in facilitating the production of ATP by participating in redox reactions within the electron transport chain in the mitochondria. In addition, CoQ10 is a potent antioxidant (16). Previous studies reported that CoQ10 increased left ventricular ejection fraction (LVEF), improved proinflammatory mediators, reduced oxidative stress, and increased myocardial bioenergetics (17,18). However, to our knowledge, no previous study has evaluated the effect of CoQ10 supplementation on the diastolic function in patients with HFpEF. Only one clinical trial evaluated the use of CoQ10 in patients with hypertrophic cardiomyopathy with diastolic dysfunction (19). The aim of this study was to determine whether CoQ10 could improve LV diastolic function in patients with HFpEF.

2. Materials and Methods

2.1. Trial design

This study was a single-center, unblinded, randomized controlled clinical trial, that enrolled patients from Dr. Kariadi Hospital, Semarang, Indonesia. The trial was conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and local and national regulations. Written informed consent was provided by all patients before any study-related procedures were performed.

2.2. Participants

The complete eligibility criteria for participants are described in Table 1.

2.3. Study drug administration and study procedures

Eligible patients were randomly assigned to receive

either CoQ10 100 mg three times a day or no coenzyme Q10 in addition to routine treatment for 30 days. The randomization ratio according to permuted blocks was 1:1 for CoQ10 or without CoQ10. Use of standard therapies for controlling the risk factors and symptoms control was at the discretion of treating physicians and required to be unchanged within the 4 weeks prior to randomization.

Echocardiography. A detailed echocardiography was performed as described previously (20,21). Diastolic dysfunction was prospectively identified and graded by a prespecified algorithm defined in the study protocol and diagnostic criteria for HF with normal EF were used according to current guidelines of the American Society of Echocardiography (ASE) or the European Association of Cardiovascular Imaging (EACVI).

All patients underwent physical examination, echocardiography, and blood sampling at baseline and 1-month follow-up visits.

2.4. Study objectives and end points

The primary objective of this trial was to determine whether CoQ10 is superior to routine treatment in improving the diastolic function in patients with HFpEF. The diastolic function was assessed by the changes in septal and lateral e' , ratio E/e' mitral, and LAVI at 1 month. Additional secondary endpoints included changes in echocardiographic measures of cardiac function and remodelling. Clinical tolerability was assessed as the safety endpoint.

2.5. Statistical analysis

The Kolmogorov-Smirnov test was used to assess normality. For continuous variables with normal distribution, the data are presented as mean \pm standard deviation, and variables without normal distribution, are reported as median and interquartile range (IQR). The

Table 1. Eligibility criteria for study participants

Inclusion Criteria:

1. Men or women aged ≥ 45 years old;
2. Typical symptoms and signs of chronic heart failure (CHF) (New York Heart Association Class 2-3);
3. Left ventricular ejection fraction on echocardiography (LVEF $\geq 50\%$);
4. Evidence of diastolic dysfunction on non-invasive imaging based on ASE/EACVI guideline (diastolic dysfunction of at least grade 1 ($E/A \leq 0.8 + E > 50$ cm/s or $E/A > 0.8 < 2$) with "requirement of at least one of the following criteria: (1) septal $e' < 7$ cm/sec or lateral $e' < 10$ cm/s, (2) average $E/e' > 14$, (3) LA volume index > 34 mL/m², and (4) TR velocity > 2.8 m/s;
5. Stable medical therapy for 4 weeks prior to randomization;
6. Informed consent available.

Exclusion Criteria:

1. Chronic atrial fibrillation;
2. Acute coronary syndrome or coronary revascularization within 60 days;
3. Clinically significant valvular disease;
4. Significantly low systolic blood pressure (< 100 mmHg) or high blood pressure;
5. Patients with a prior LVEF $< 40\%$;
6. Known infiltrative cardiomyopathy (e.g. amyloidosis), hypertrophic cardiomyopathy or chronic pericardial disease;
7. Dyspnea or edema due to non-cardiac causes such as pulmonary disease, and anemia (Hb < 8.0 g/dL);
11. Inability or refusal to provide informed consent;
12. Poor echocardiographic recordings.

categorical variables are presented as absolute numbers and percentages. The groups were compared using two-tailed unpaired Student's *t* test for variables with normal distribution and Wilcoxon test for variables without normal distribution. *P* values < 0.05 were considered as statistically significant.

3. Results

3.1. Basic demographic and clinical characteristics

A total 51 subjects met the inclusion criteria, of whom 21 patients were excluded due to moderate or severe mitral regurgitation (10 patients), chronic renal failure with Hb < 8 g/dL (4 patients), moderate or severe pericardial effusion (3 patients), atrial fibrillation (2 patients), and post-treatment of acute coronary syndrome within 2 months (2 patients). The remaining 30 patients were randomized by permuted blocks and divided into two groups, which included 15 patients in the treatment group receiving routine therapy plus CoQ10 100 mg three times a day (CoQ10 group), and 15 patients in the control group receiving routine

therapy without CoQ10. One patient each from the control group and the treatment group dropped out due to exacerbations of heart failure and acute coronary syndrome (Figure 1).

Among the 30 study patients analyzed, there was no difference in the demographic characteristics between the two groups in terms of sex, age, and body mass index (BMI). Eight patients (53.3%) were females in the CoQ10 group, and the control group had 7 female patients (46.7%) (*p* = 0.71). The mean age was 64 ± 10 years in the CoQ10 group and 61 ± 7 years in the control group (*p* = 0.31).

As shown in Table 2, there were no differences in baseline clinical characteristics between the control and CoQ10 groups, which included a history of comorbid disease, symptoms and signs of heart failure, physical examination, laboratory parameters, and prescribed medical therapy. The frequency of hypertension history was extremely high (93.3%) in all samples. Blood pressure measured at the time of recruitment was fairly controlled (mean systolic/diastolic pressure was 133/79 mmHg) with no difference between the two groups. Shortness of breath during activity (DOE = dyspnea on

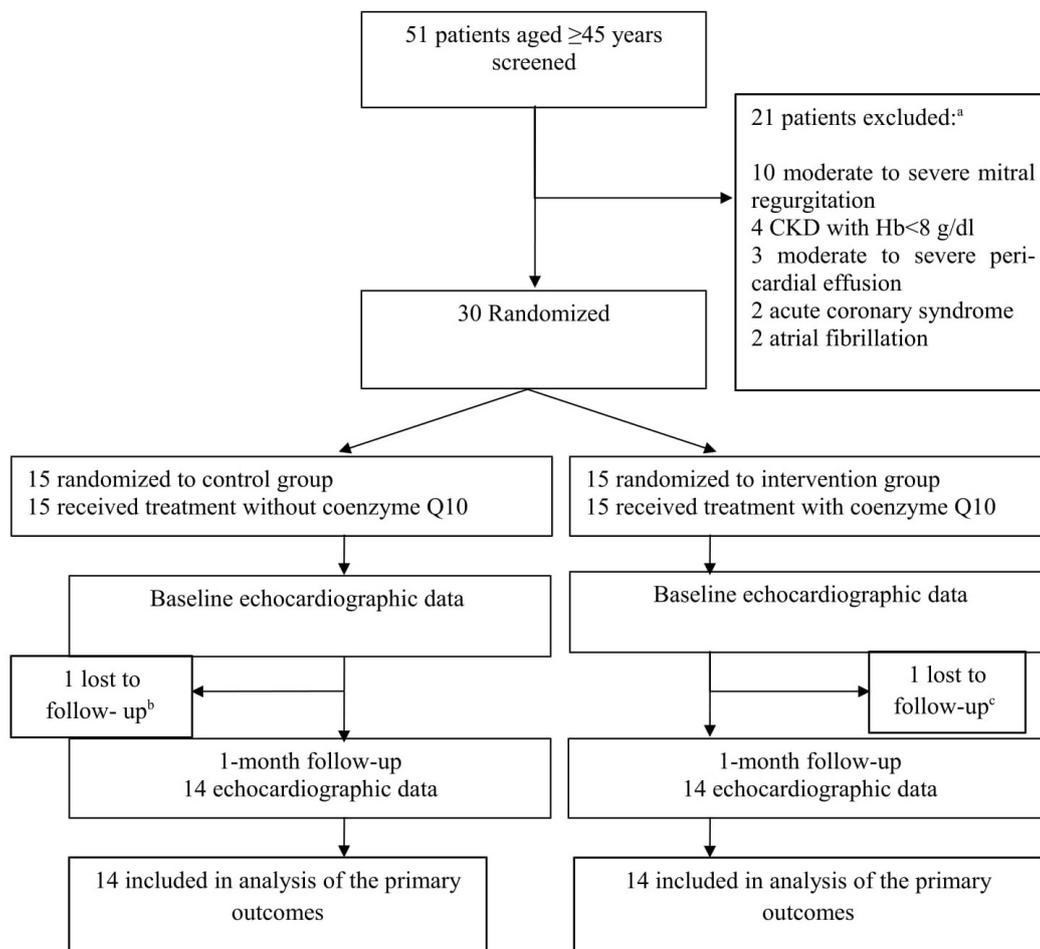


Figure 1. Participant Flow. Flow diagram showing participant flow in the study. The study is a before-and-after study with a comparison group (control group). ^aExcluded according to exclusion criteria listed in Table 1; ^{b,c}Dropped-out due to exacerbation of heart failure and acute coronary syndrome events.

Table 2. Demographic and clinical baseline characteristics

Characteristics	Total (n = 30)	Control Group (n = 15)	Coenzyme Q10 (n = 15)	P value
Demographics				
Age, mean (SD), y	62 (8)	61 (7)	64 (10)	0.31 ^a
Female, %	50.0	46.7	53.3	0.71 ^c
Medical history, %				
Hypertension	93.3	100.0	86.7	0.48 ^d
Diabetes mellitus	73.3	66.7	80.0	0.68 ^d
CAD	63.3	53.3	73.3	0.25 ^c
Sign and symptom, %				
DOE	86.7	73.3	100.0	0.10 ^d
PND	23.3	26.7	20.0	1.00 ^d
Fatigue	66.7	73.3	60.0	0.43 ^c
Peripheral edema	36.7	40.0	33.3	0.70 ^c
Physical examination, Mean (SD)				
BMI	24.8 (2.8)	24.3 (2.4)	25.3 (3.2)	0.34 ^a
Heart rate	75 (11)	76 (13)	74 (10)	0.68 ^a
Systolic BP	133(11)	129 (12)	137(8)	0.08 ^b
Diastolic BP	79(9)	78 (9)	81 (10)	0.38 ^b
Laboratory measurement Mean (SD)				
Hemoglobin, g/dL	12.5 (1.6)	12.1 (1.5)	12.9(1.6)	0.19 ^a
Creatinine, mg/dL	1.8(1.7)	2.0(2.2)	1.6 (0.8)	0.90 ^b
Creatinine clearance	47(22)	47(22)	46(23)	0.88 ^a
Total Cholesterol	185(39)	181(36)	187(43)	0.68 ^a
HbA1c	7.8(2.0)	7.7 (2.2)	7.9(1.9)	0.46 ^b
Current medications, %				
ACE-I	6.7	6.7	6.7	1.00 ^d
ARB	93.3	93.3	93.3	1.00 ^d
Beta blockers	80.0	80.0	80.0	1.00 ^d
Spirolactone	26.7	26.7	26.7	1.00 ^d
CCB	43.3	40.0	46.7	0.71 ^c
Antiplatelets	70.0	66.7	73.3	1.00 ^d
Statin	76.7	80.0	73.3	0.42 ^d

*Significance value $p < 0.05$; ^aun-paired *t*-test; ^bNon-parametric Mann-Whitney test; ^cchi-square test; ^dFisher's-exact test; SD: standard deviation; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; BMI: body mass index; BP: blood pressure; CCB: calcium channel blocker; CAD: coronary artery disease; DOE: dyspnea on exertion; PND: paroxysmal nocturnal dyspnea.

effort) was the most commonly complained symptom (86.7%).

Basic blood laboratory parameters showed no difference between the groups in terms of hemoglobin concentration, creatinine, total cholesterol and HbA1c levels. The mean hemoglobin concentration was 12.1 ± 1.5 g/dL in the CoQ10 group and 12.9 ± 1.6 g/dL in the control group ($p = 0.19$), while the mean total cholesterol levels were 181 ± 36 and 187 ± 43 mg/dL ($p = 0.68$), respectively. Renal function assessed by creatinine levels was similar between the CoQ10 group (1.6 ± 0.88) mg/dL and the control group (2.0 ± 2.2) ($p = 0.90$). Regarding medical therapy prescription, the majority of patients received ACE-I or ARBs (100%), beta-blockers (80%), and spironolactone (26.7%). Other drugs that were administered included calcium antagonists (43.3%), antiplatelets (70%), statins (70%) and antidiabetic (56.7%). There was no significant difference in medical therapy prescription between the two groups.

3.2. Basic echocardiogram characteristics

Echocardiographic examination showed no significant differences between groups (Table 3). The mean LVEF did not differ between the CoQ10 group ($55\% \pm 5\%$)

and the control group ($58\% \pm 8\%$) ($p = 0.32$). Regarding left ventricular structure, all patients had normal left ventricular diameter (mean LVIDd 49 ± 8 mm and LVIDs 33 ± 8 mm), with concentric remodeling or increased left ventricular mass in male (143 ± 37 g/m²) and female (145 ± 34 g/m²) patients of the CoQ10 group and in male (135 ± 27 g/m²) and female (129 ± 32) g/m²) patients of the control group.

Left ventricular diastolic function showed a lower E/A ratio in the CoQ10 group than that in control group (0.94 ± 0.3 vs. 1.24 ± 0.4), however, the difference was not significant ($p = 0.06$). Tissue Doppler imaging (TDI) E' showed a similar decrease in either septal (4.2 ± 1.2 vs. 4.8 ± 1.0) cm/s; $p = 0.13$) or lateral (5.5 ± 1.2 cm/s vs. 6.6 ± 1.8 cm/s; $p = 0.08$) in the CoQ10 and control groups. The increase in left ventricular filling pressure was indicated by an increased the E/e' ratio in the CoQ10 group (18.9 ± 3.8) and in the control group (18.4 ± 3.1), however, the difference was not significant ($p = 0.67$). Left atrium volume index (LAVI) was increased by ≥ 34 mL/m² among 50% of patients, with a mean LAVI of 32 ± 9 mL/m² in the CoQ10 group and 33 ± 7 mL/m² in the control group.

Among 10 patients (33.3%), out of 30 studied patients, the speed of tricuspid regurgitation could be

Table 3. Baseline echocardiographic characteristics

Characteristics	Total (n = 30)	Control Group (n = 15)	Coenzyme Q10 (n = 15)	P value
LV diastolic function				
E/e' ratio	18.6 (3.4)	18.4 (3.1)	18.9 (3.8)	0.67 ^a
Medial e', cm/s	4.5 (1.1)	4.8 (1.0)	4.2 (1.2)	0.13 ^a
Lateral e', cm/s	6.0 (1.6)	6.5 (1.8)	5.5 (1.2)	0.08 ^a
E velocity, m/s	87 (22)	92 (23)	82 (21)	0.15 ^a
E/A velocity ratio	1.09 (0.5)	1.24 (0.4)	0.94 (0.3)	0.06 ^a
Deceleration t, ms	186 (50)	182 (47)	190 (55)	1.00 ^a
LAVI, mL/m ²	33 (8)	33 (7)	32 (9)	0.88 ^a
LV systolic function				
LVEF biplane, %	56 (7)	58(8)	55 (4)	0.32 ^b
LVIDd, mm	49 (8)	49 (9)	48 (8)	0.27 ^a
LVIDs, mm	33 (8)	33 (9)	33 (6)	0.42 ^a
LV structure				
LVMI, g/m ²	138 (31)	132 (29)	144 (34)	0.33 ^a
Men	139 (31)	135 (27)	143 (37)	
Women	137 (33)	129 (32)	145 (34)	

*Significance value $p < 0.05$; ^aun-paired *t*-test; ^bNon-parametric Mann-Whitney test; SD: standard deviation; LV: left ventricle; LAVI: left atrium volume index; LVEF: left ventricular ejection fraction; LVIDd: left ventricle internal diameter diastolic; LVIDs: left ventricle internal diameter systolic; LVMI: left ventricle mass index.

Table 4. Echocardiography results after 1 month

Measurements	Control			Coenzyme Q10		
	Pre (n = 15)	Post (n = 14)	P value	Pre (n = 15)	Post (n = 14)	P value
Diastolic Function						
E/e' ratio	18.4 (3.1)	15.8 (5.6)	0.04 ^{a*}	18.9 (3.8)	15.1 (4.3)	0.00 ^{b*}
Medial e', cm/s	4.8 (1.0)	4.8 (1.6)	0.70 ^b	4.2 (1.2)	4.3 (1.1)	0.61 ^b
Lateral e', cm/s	6.5 (1.8)	5.5 (1.7)	0.06 ^b	5.5 (1.2)	5.1 (1.0)	0.23 ^b
E velocity, m/s	92 (23)	75 (18)	0.01 ^{b*}	82 (21)	71 (20)	0.12 ^a
E/A velocity	1.24 (0.5)	1.08 (0.5)	0.46 ^a	0.94 (0.3)	0.82(0.3)	0.55 ^b
Deceleration t, ms	182 (47)	197 (46)	0.17 ^b	190 (55)	169 (45)	0.66 ^a
LAVI, mL/m ²	33 (7)	30 (8)	0.02 ^{b*}	32 (9)	26 (7)	0.04 ^{b*}
Systolic Function						
LVEF, %	58(8)	57 (7)	0.82 ^a	55 (4)	56 (8)	0.73 ^a
LVIDd, mm	49 (9)	49 (8)	0.53 ^b	47 (7)	48 (9)	0.37 ^b
LVIDs, mm	33 (9)	32 (8)	0.26 ^b	33 (8)	33 (8)	0.27 ^b
GLS		16.0 (3.3)			16.5 (4.4)	
Other Variable						
LVMI, g/m ²	132 (29)	131 (43)	0.71 ^a	144 (34)	129 (37)	0.08 ^b
Men	135 (27)	121 (33)		143 (37)	117 (35)	
Women	129 (32)	145 (54)		145 (34)	140 (38)	

*Significance value $p < 0.05$; ^anon-parametric Wilcoxon test; ^bpaired *t*-test. SD: standard deviation; LV: left ventricle; LAVI: left atrium volume index; LVEF: left ventricular ejection fraction; LVIDd: left ventricle internal diameter diastolic; LVIDs: left ventricle internal diameter systolic; LVMI: left ventricle mass index.

measured and only 4 patients (13.3%) with a TR Vmax of > 2.8 m/s. Other valvular abnormalities found among patients were mild mitral regurgitation (46.7%) and mild aortic regurgitation (13.3%).

3.3. Comparison of pre versus post echocardiography findings between the groups

Pre and post-echocardiographic studies revealed no significant differences in left ventricular function and structure in either CoQ10 or control group. The mean LV ejection fraction was not significantly different between the initial value: ($55\% \pm 4\%$ compared to the final value $56\% \pm 8\%$; $p = 0.73$). Left ventricular mass index (LVMI)

also showed no significant differences (144 ± 34 vs. 129 ± 31 g/m²; $p = 0.08$).

As for left ventricular diastolic function, CoQ10 administration decreased E/e' ratio from 18.9 ± 3.8 to 15.1 ± 4.3 ($p = 0.002$) and left atrial volume index (LAVI) from 32 ± 9 to 26 ± 7 mL/m² ($p = 0.049$). Regarding other diastolic function parameters, CoQ10 administration did not significantly increase the TDI e' septal value (4.2 ± 1.2 vs. 4.3 ± 1.1 ; $p = 0.61$), and even the lateral TDI value tended to decrease (5.5 ± 1.2 vs. 5.1 ± 1.0 cm/s; $p = 0.23$). As in the control group, left ventricular diastolic function improved as characterized by a decrease in the E/e', and the LAVI index and a significant decrease in E velocity (Table 4).

Table 5. Post echocardiographic and Δ changes between control and coenzyme Q10 groups

Parameter	Post			Coenzyme Q10-Control	
	Control (14)	Coenzyme Q10 (14)	P value	Δ changes	P value
Diastolic function					
E/e' ratio	15.8 (5.6)	15.1 (4.3)	0.85 ^a	-1.14	0.28 ^a
Medial e', cm/s	4.8 (1.6)	4.3 (1.1)	0.36 ^b	0.05	0.88 ^b
Lateral e', cm/s	5.5 (1.7)	5.1 (1.0)	0.42 ^b	0.48	0.39 ^b
E velocity, m/s	75 (18)	71 (20)	0.61 ^b	0.05	0.58 ^b
E/A velocity ratio	1.08 (0.5)	0.82(0.3)	0.10 ^a	0.07	0.94 ^a
Deceleration t, ms	197 (46)	169 (45)	0.11 ^b	-30.9	0.37 ^a
LAVI, mL/m ²	30 (8)	26 (7)	0.18 ^b	-1.07	0.72 ^b
Systolic function					
LVEF,%	57 (7)	56 (8)	0.54 ^a	1.99	1.00 ^a
LVIDD, mm	49 (8)	48 (9)	0.76 ^b	0.03	1.00 ^b
LVIDs, mm	32 (8)	33 (8)	0.76 ^b	1.59	0.43 ^b
Other variable					
LVMI, g/m ²	131 (43)	129 (37)	0.76 ^a	-12.4	0.78 ^a
Men	121 (33)	117 (35)	0.77 ^a		
Women	145 (54)	140 (38)	0.94 ^a		

*Significance value $p < 0.05$; ^anon-parametric Mann-Whitney test; ^bun-paired *t*-test. SD: standard deviation; LV: left ventricle; LAVI: left atrium volume index; LVEF: left ventricular ejection fraction; LVIDD: left ventricle internal diameter diastolic; LVIDs: left ventricle internal diameter systolic; LVMI: left ventricle mass index.

3.4. Differences and changes in echocardiographic findings of the CoQ10 and control groups

Administration of CoQ10 improved two parameters of left ventricular diastolic function, but the difference was not significant compared with those in the control group (Table 5). The E/e' ratio was also not significantly different between the CoQ10 and control groups (15.1 ± 4.3 vs. 15.8 ± 5.6 ; $p = 0.85$). Similarly, there was no significant difference in LAVI between the two groups (26 ± 7 vs. 30 ± 8) mL/m², $p = 0.72$). TDI e' septal and e' lateral showed no differences between the two groups, respectively (4.3 ± 1.1 vs. 4.8 ± 1.6 cm/s; $p = 0.36$) and (5.1 ± 1.0 vs. 5.5 ± 1.7 cm/s; $p = 0.42$, respectively) after 1 month of treatment. Administration of CoQ10 also did not affect left ventricular function parameters as assessed by LVEF and LVMI, which showed no differences between the groups. Although CoQ10 reduced the E/e' ratio by 1.14 ($\Delta -3.6$ vs. -2.4 ; $p = 0.28$) and LAVI by 1.07 mL/m² ($\Delta -5.4$ vs. -4.4 ; $p = 0.83$), and increased e' septal by 0.05 ($\Delta 0.2$ vs. 0.1 , $p = 0.88$), the difference was not statistically significant when compared with the values in the control group (Figure 2).

4. Discussion

In this study, the baseline characteristics of patients with HFpEF were a mean age ≥ 60 years, an equal number of men and women, and the dominant risk factors being hypertension $\geq 90\%$ of patients, followed by diabetes mellitus and coronary artery disease (CAD). Compared with major studies such as TOPCAT (10), I-PRESERVE (9), CHARM-Preserved (8), PEP-CHF (7) and SENIORS (12); the patients in this study tended to be younger and had a higher frequency of diabetes

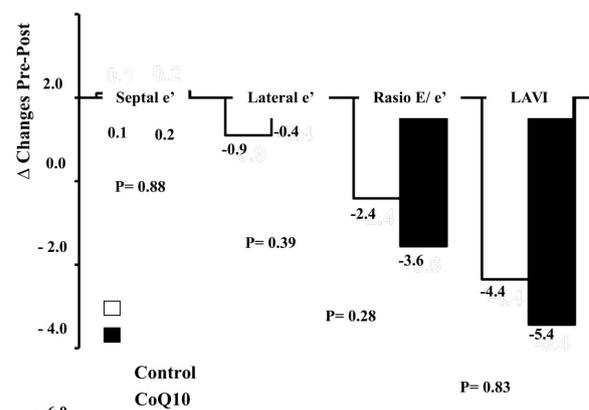


Figure 2. Comparisons of pre-post Δ changes of diastolic function between groups. P values describe comparisons of the changes of diastolic function the control or CoQ10 group. No additional improvement by CoQ10 after 1 month treatment.

mellitus.

Compared with the characteristics of patients with HFpEF in Southeast Asian countries as reported by MacDonald *et al.* (22), among Singaporean citizens with a variety of ethnic or racial backgrounds, a similar trend of slightly younger patients and slightly higher prevalence of CAD and diabetes was observed also in the present study. Another tendency of difference was found in medicine use, wherein more ACE-I or ARBs were administered in this study. Diastolic dysfunction evaluated using echocardiographic parameters also showed higher baseline data in terms of E/e' ratio (18.6 ± 3.4) than that reported by other studies that also used echocardiographic parameters to assess the effect of tested drugs, such as the Aldo-DHF study (mean medial E/e' 12.8 ± 4) (11).

In this study, plasma CoQ10 levels were not measured during the study; therefore, the initial level and the level after treatment could not be confirmed. However, using the same dosage and a coenzyme preparation of Q10 in a soft gel capsule form, Hosoe *et al.* (23) showed that daily administration of CoQ10 300 mg for 4 weeks to healthy individuals increased plasma CoQ10 levels by seven-fold from 0.66 to 7.28 $\mu\text{mol/L}$. Similarly, Belardinelli *et al.* (24) reported that administration of CoQ10 300 mg per/day for 4 weeks to patients with heart failure increased plasma CoQ10 from 0.95 to 3.764 $\mu\text{mol/L}$. Although the administered dose is the same, the probability of a lower response of CoQ10 levels may occur due to the influence of the factors of older age, the degree of severity of heart failure, and the use of statin drugs. Mortensen *et al.* (25) found that administration of pravastatin and lovastatin decreased the levels of CoQ10 from week 6, while the CORONA study evaluating CoQ10 levels by administering statins simultaneously showed a significant decrease in CoQ10 levels, however, the clinical outcomes were not affected (26). In addition, the CORONA study showed that serum concentrations of CoQ10 were lower in older patients and patients with more severe degree of heart failure. In the present study, the mean age of the CoQ10 group tended to be older (64 ± 10 vs. 61 ± 7 years) than that of the control group, but there was no difference in the percentage of use and the type of statin administered.

In this study, administration of CoQ10 to patients with HFpEF within 1 month showed improved diastolic function, but it was not significantly different from the control group. There were no significant differences in the echocardiographic parameters such as E/e', e' septal, e' lateral, and LAVI. To date, no studies have assessed the effects of CoQ10 administration on left ventricular diastolic function in patients with HFpEF. Adarsh *et al.* (19) evaluated patients with hypertrophic cardiomyopathy with diastolic heart failure and without history of prolonged hypertension, showed that co-administration of CoQ10 may improve diastolic function and decrease the severity of mitral regurgitation due to reduced LVOT gradient and left ventricular and posterior left ventricular mass index. This difference in outcomes might be due to the different samples characteristics, wherein the present study did not include patients with hypertrophic cardiomyopathy, and a shorter time of CoQ10 administration (1 month vs. 14 months). Different results were also reported in the Q-SYMBIO study involving 7% among a total of 420 patients with LVEF $\geq 45\%$, suggesting a lower trend of major adverse cardiovascular events (MACE) in patients with LVEF $\geq 30\%$ (27). Interestingly, although there was no significant difference between the control group and the CoQ10 after 1 month of treatment in the present study, there was an improvement in the E/e', E velocity,

and LAVI parameters at the end of the study (post). These results can be interpreted as follows; CoQ10 administration does not provide additional benefits of improvement in diastolic function and there are other factors that provide a major contribution, including possibly the influence of routine medication received by the study patients. This study showed that patients in each study group received ACE-I or ARB, beta-blockers and spironolactone. Previous studies confirmed that ARB (28,29), beta blockers (30,31) and spironolactone (11); improved diastolic dysfunction. Valsartan may decrease isovolumic relaxation time (IVRT) (28) while azilsartan decreases the E/e' ratio (29). In the Swedish Doppler-echocardiographic study (SWEDIC), Bergstrom *et al.* (30) demonstrated that administration of carvedilol improved the E/A ratio, especially in patients with a heart rate more than 71 times per minute. Long-term beta-blocker use can also play an important role in delaying the development of HFpEF in hypertensive patients with diastolic dysfunction as reported by Gu *et al.* (31) who observed that in 7 years, only 6.0% of patients using beta-blockers developed HFpEF, whereas 13.2% of those not using beta-blocker developed HFpEF. Edelman *et al.* (11) in the Aldo-DHF study revealed that spironolactone decreased the E/e' ratio and induced reverse remodeling by lowering the left ventricular mass index. Another drug that can ameliorate diastolic dysfunction is metformin. Metformin use in diabetic patients with a mean LVEF of 45% improved left ventricular relaxation by decreasing IVRT and increasing e' velocity compared to those by insulin and sulfonylurea drugs (32).

CoQ10 administration was found to be relatively safe and well tolerated in patients with HFpEF. This can be observed from the level of adherence in taking CoQ10 (94% of patients along with medication for an average of 28.2 days). During this study period, no allergies or severe side effects of CoQ10 were found. Three patients each complained of nausea, diarrhea, and palpitation at the beginning but then the complaints were not felt anymore. However, none of these patients stopped taking CoQ10. This is relevant to previous studies that CoQ10 was safe enough to be administered to patients with heart failure even for longer periods (27).

In conclusion, short-term CoQ10 supplementation provided no additional benefit to the improvement of left ventricular diastolic function in patients with HFpEF.

Limitations

There are several potential limitations to be acknowledged in this study. First, no blood plasma CoQ10 measurements were taken to assess the changes or increased level of CoQ10. Second, the short duration of administration of CoQ10, 30 days in this study, may indicate that the treatment response was not maximal and an optimal effect could not be obtained.

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