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Choir singing improves respiratory muscle strength and quality of life in patients with structural heart disease – HeartChoir: a randomised clinical trial

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Summary

AIMS OF THE STUDY: Most patients with reduced exercise capacity and acquired or congenital structural heart disease also have a reduced respiratory muscle strength. The aim of this pilot study was to investigate whether choir singing in combination with respiratory muscle training positively influences respiratory muscle strength, exercise capacity and quality of life in this population.

METHODS: In this single-centre, randomised and open-label interventional study we compared respiratory muscle strength, exercise capacity and quality of life in patients with acquired or congenital structural heart disease who received either standard of care and a 12-week intervention (weekly choir rehearsal and daily breathing exercises) or standard of care alone. The primary endpoint was the difference in change in maximum inspiratory pressure (ΔMIP%predicted). Secondary endpoints included the difference in change in maximum expiratory pressure (ΔMEP%predicted), exercise capacity quantified as maximal oxygen uptake during exercise (ΔMVO_2%predicted) and quality of life quantified by the Minnesota living with heart failure questionnaire (ΔMLHFQ score).

RESULTS: Overall 24 patients (mean age 65, standard deviation [SD] 19 years, 46% male) were randomised after exclusion. ΔMIP%predicted was significantly higher in the intervention group (ΔMIP%predicted +14, SD 21% vs −14, SD 23%; p = 0.008) and quality of life improved significantly (ΔMLHFQ score −5, SD 6 vs 3, SD 5; p = 0.006) after 12 weeks. ΔMEP%predicted and ΔMVO_2%predicted did not differ between both groups (ΔMEP%predicted −3, SD 26% vs −3, SD 16%; p = 1.0 and ΔMVO_2%predicted 18, SD 12% vs 10, SD 15%; p = 0.2).

CONCLUSIONS: Choir singing in combination with respiratory muscle training improved respiratory muscle strength and quality of life in patients with structural heart disease and may therefore be valuable supplements in cardiac rehabilitation. (Clinical trial registration number: NCT03297918)

Keywords: *breathing exercises, heart failure, congenital heart defects, cardiac rehabilitation, quality of life*

Introduction

Exercise intolerance is a substantial limiting factor in the life of patients with acquired or congenital structural heart disease. Cardiac causes, including ventricular and valvular dysfunction, chronotropic incompetence and factors related to previous cardiac surgery, contribute to an impaired exercise tolerance. However, there are many other extracardiac factors related to exercise intolerance, such as parenchymal and vascular lung disease, pulmonary arterial hypertension, anaemia and iron-deficiency [1–3]. Patients with structural heard disease and chronic heart failure often have generalised myopathy involving the peripheral skeletal muscles as well as the respiratory muscles, which influences exercise capacity [4–6]. Moreover, inspiratory muscle strength expressed as maximum inspiratory pressure (MIP) is an independent predictor of prognosis [7] and is closely related to the sensation of dyspnoea [8]. In patients with complex congenital heart disease, respiratory muscle weakness is common and similar in extent to that in elderly patients with chronic heart failure from acquired heart disease. It is also associated with reduced exercise capacity [9]. Therefore, it appears obvious that in training the skeletal muscles, a particular attention should also be paid to the respiratory muscles and should be a therapy target to improve exercise capacity in patients with structural heart disease and heart failure. Structural physical training has shown beneficial effects on exercise capacity and respiratory muscle strength as well [10–13]. However, many patients with structural heart disease and heart failure do not participate in regular physical exercise for several reasons, such as physical disability, frailty and lack of motivation. Specific respiratory muscle training could be an addition or an alternative to the standardised cardiac rehabilitation to

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enhance exercise capacity without strenuous physical exertion [14]. The aim of this study was to investigate if regular singing in combination with structural breathing exercises would improve respiratory muscle strength, exercise capacity and quality of life in patients with acquired or congenital structural heart disease.

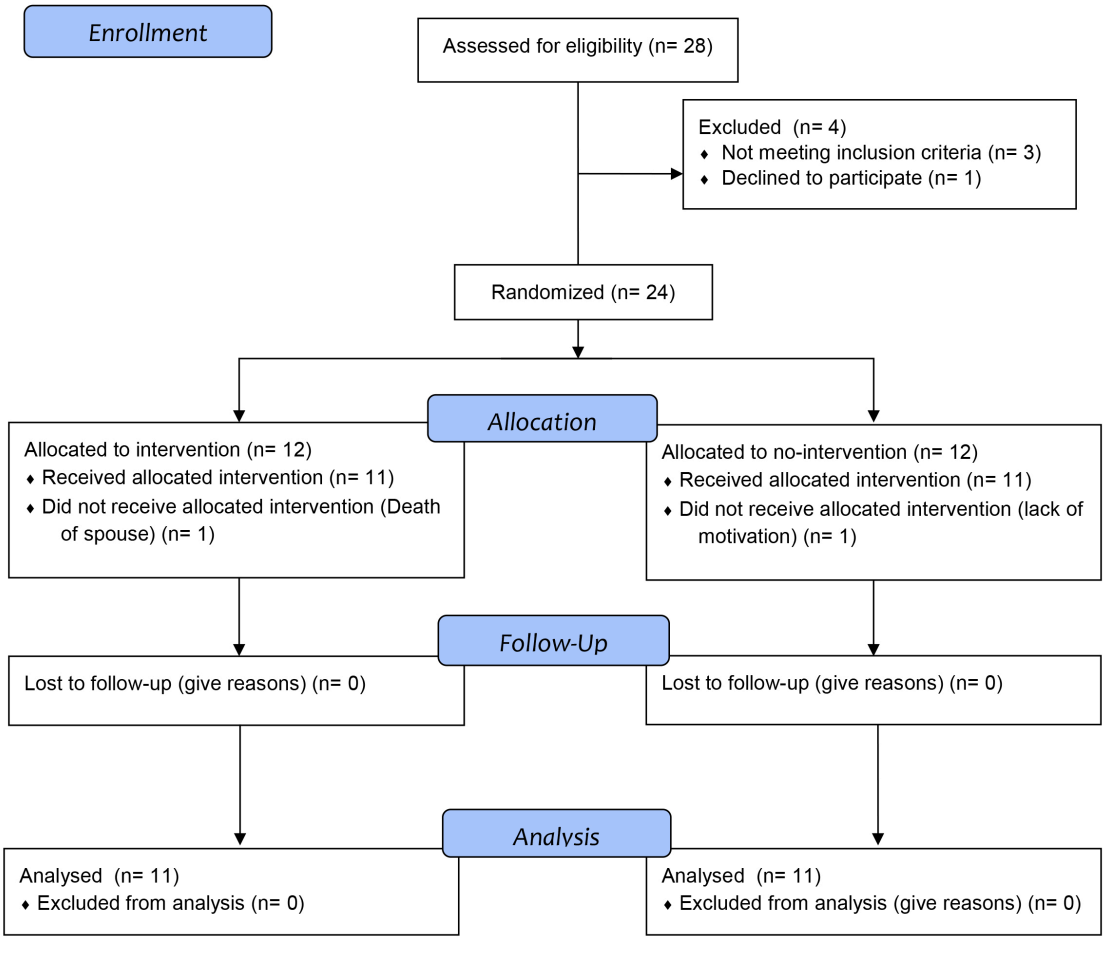
Materials and methods

Participants and design

This single-centre, randomised and open-label interventional study was conducted in patients with known cardiomyopathy from acquired heart disease (ischaemic, valvular or dilated) or in patients with complex congenital heart disease (cyanotic congenital heart disease, Fontan palliation, subaortic right ventricle or repaired tetralogy of Fallot). This study was intended to be a pilot study. Patients were recruited at the outpatient Heart Failure Clinic and Congenital Heart Disease Clinic at the University Hospital Basel by the attending cardiologists. Entry criteria for the study were age ≥18 years and a previous history of symptomatic heart failure or complex congenital heart disease as described above. Exclusion criteria were acute coronary syndrome, cardiac surgery or heart failure hospitalisation within the previous 6 months; chronic metabolic, orthopaedic, or infectious disease; treatment with steroids, hormones, or cancer chemotherapy; severe exercise-induced asthma, being a professional singer or professionally playing a wind instrument, and enrolment in a cardiac rehabilitation programme. The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees (EKNZ 2017-02008). Written informed consent was obtained from all patients. The authors designed the study, gathered and analysed the data according to the CONSORT statement for reporting randomised controlled trials [15] (fig. 1 and supplementary table S1 in appendix 1), vouched for the data and analysis, wrote the paper and decided to submit it for publication.

Participants were randomised in a 1:1 ratio to the intervention or standard therapy group using electronically concealed randomisation lists. The randomisation was carried out block-wise by the Clinical Trial Unit of the Department of Clinical Research in Basel. Beside the standard treatment, patients in the interventional group participated in singing and breathing exercises conducted by a professional choir instructor for 12 weeks. The intervention consisted of weekly singing lessons for 90 minutes in a choir and additional instructions for daily breathing exercises at home (description of breathing exercises: videos "straw-breathing" and "pranayamabreathing"), which they should perform for 20 minutes daily. The control group received standard treatment alone without any specific physical exercise. Respiratory muscle strength (expressed as maxi-

Figure 1: CONSORT 2010 flow diagram.



mum inspiratory pressure [MIP] and maximum expiratory pressure [MEP]), exercise capacity (expressed as maximal oxygen uptake during exercise [MVO_2]) and quality of life (quantified by the Minnesota living with heart failure questionnaire [MLHFQ] score) were assessed at baseline and after 12 weeks in all patients. The compliance with the breathing exercises at home was self-reported (numbers of days with breathing exercises of at least 20 minutes), whereas the participation in the choir rehearsals was recorded by the choir instructor.

Baseline characteristics including cardiac history, ejection fraction of the systemic ventricle measured by the modified Simpson method, presence of pulmonary hypertension defined as end-systolic pulmonary arterial pressure ≥40 mm Hg assessed by echocardiography and New York Heart Association (NYHA) functional class were collected from the available medical records. N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and kidney function were measured, and pulmonary function was assessed in all participants at baseline.

Outcome measures

The primary endpoint was the difference in change of MIP (% of predicted) between both groups (ΔMIP%predicted). Secondary endpoints were the difference in change in MEP (% predicted), MVO_2 (% predicted) and MLHFQ score between both groups (ΔMEP%predicted, ΔMVO_2%predicted and ΔMLHFQ)

Study procedures

Respiratory muscle strength

MIP and MEP were measured by experienced respiratory technicians at the Department of Pneumology, University Hospital Basel. The technicians were blinded to the randomisation. According to the clinical standard and recommended by the literature [16], MIP was measured after maximum expiration and MEP after maximum inspiration. A flanged mouthpiece was used and participants were asked to seal the mouthpiece with their hands during the manoeuvre to avoid air leak. Out of three valid measurements with a <10% variability, the highest measurement was used for analysis.

Patient and public involvement

The study was substantially supported by a professional soprano singer, herself a cardiac patient with complex congenital heart disease regularly seen in our outpatient clinic. She played a major role in designing the intervention plan, the information material to support the intervention and the burden of the intervention from the patient's perspective. She established the training plan for the breathing exercises, instructed study participants and lead the choir rehearsals. As a culmination of the choir rehearsals, a benefit concert was given with the support of 60 volunteers recruited from various lay choirs in the region of Basel, Switzerland.

The results of the study have been communicated to all study participants personally. Further impact of the study results and publication will be equally communicated with all participants, volunteers and other interested persons such as colleagues from different rehabilitation programmes in Switzerland and abroad.

Cardiopulmonary exercise testing

All patients underwent symptom-limited cardiopulmonary exercise testing on a cycle ergometer (Schiller Reomed BP 200 Plus) in accordance with published guidelines [17]. Testing was done by three different standardised protocols according to the patients' estimated capacity. The chosen protocol for an individual patient was the same for the entry test and the end of study testing. Participants were advised to interrupt the test at their individual maximum physical capacity. Expired gas was analysed breath by breath (Power Cube Electronic Gas analyser). In addition to heart rate and blood pressure, the following parameters were recorded at rest, at ventilator threshold (derived by the slope method) and at peak exercise by averaging five out of seven cycles: oxygen uptake (VO_2), carbon dioxide output (VCO_2) and minute ventilation (VE). The respiratory exchange ratio (VCO_2 divided by VO_2) at peak exercise was calculated in all participants and a value of >1.05 was a marker for maximum physical effort. Measurements were normalised for age, gender and height, and expressed as percentage of the predicted value. All participants underwent spirometry before exercise testing: forced vital capacity (FVC) and forced expiratory volume during the first second of expiration (FEV_1) were measured.

Quality of life assessment

Quality of life was assessed by the Minnesota Living with Heart Failure Questionnaire (MLHFQ) [18, 19]. This is a validated and widely used tool to assess quality of life in patients with chronic heart failure. It is a multidimensional questionnaire assessing the impact of heart failure on overall quality of life by the mean of 21 questions with a six-point rating scale, with 0 = none/not applicable to 5 = very much applicable, focusing on physical, socioeconomic and psychological/emotional aspects of life with heart failure. A score of <24 points is estimated to represent a good quality of life, a score of 24–45 points a moderate quality of life and a score of >45 points a poor quality of life [18, 20].

Statistical analysis

Data were analysed using SPSS® for Windows (version 23, SPSS, Chicago) and tested for normality with the Kolmogorov-Smirnov test. Descriptive data for continuous variables were presented as means with standard deviations (SDs) or as medians with interquartile ranges (IQRs) as appropriate.

For comparison between groups, continuous variables were evaluated using the independent Student t-test and proportions were evaluated using chi-square or Fischer-exact tests as appropriate. Linear univariate regression was used to determine relationships in the intervention group between ΔMIP%predicted and the baseline measurements of MIP % predicted and MVO_2 % predicted. The Pearson correlation coefficient was used to determine the relationship between ΔMIP%predicted in the intervention group and the number of days of fulfilled breathing exercises at home. The sample size calculation was based on the primary endpoint – change of MIP in % predicted between patients with and without the intervention. Based on previous data [14], we estimated that a sample size of 11 individuals

in each group would have a power of 80% to detect a 10% difference in MIP % predicted for a two-sided alpha set at 0.05.

Results

Participants

Between January and March 2018, 24 patients were included in the study and randomised equally in two groups after their eligibility was confirmed. In each group one patient dropped out during the intervention period (fig. 1). Twenty-two patients were included in the analysis. Age and gender were well balanced. Baseline characteristics are described in table 1.

Of the five patients with coronary heart disease, two had prior surgical revascularisation and four had prior myocardial infarction. Of the five patients with valvular heart disease, three had prior aortic valve surgery and two had prior mitral valve surgery. Patients with congenital heart diseases included two patients with unoperated cyanotic heart disease (tricuspid atresia and double inlet left ventricle), one patient with a Fontan palliation and two patients with repaired tetralogy of Fallot and residual pulmonary regurgitation. The remaining two patients were diagnosed with hypertrophic obstructive cardiomyopathy, repaired atrial myxoma and hypertensive cardiopathy with reduced ejection fraction. All patients were in stable functional class NYHA I or II. None of the patients had evidence of obstructive lung disease.

Patient compliance in the intervention group was as follows: on average, they took part in 13 of 14 weekly choir rehearsals and completed 86% (SD 14%) of the daily breathing exercises at home (72 [SD 12] of a total of 84 possible exercise days). None of the patients suffered any harm or unintended effects.

Respiratory muscle function test

After 12 weeks, ΔMIP%predicted was significantly higher in the intervention group (ΔMIP%predicted mean difference −27.5, 95% CI −46.9 to −8.14; p = 0.008; fig. 2a). ΔMIP in the intervention group was inversely correlated with baseline MIP (β = −0.611; p = 0.042), but did not correlate with baseline MVO_2 (β = −0.428; p = 0.088). There was no significant correlation between ΔMIP %predicted in the intervention group and the number of days with fulfilled breathing exercise (Pearson correlation 0.42; p = 0.2). MEP % predicted did not change after 12 weeks (ΔMEP%predicted mean difference −0.182, 95% CI −19.2 to 18.9; p = 1.0; fig. 2b). Detailed results of the respiratory muscle strength tests are described in table 2.

Cardiopulmonary exercise testing

All patients in the intervention group were able to complete the cardiopulmonary exercise test, whereas three patients in the control group had to terminate prematurely owing to back pain (two patients) or general discomfort (one patient). After 12 weeks, ΔMVO_2 %predicted did not differ between both groups (ΔMVO_2%predicted 18 [SD 12%] vs 10 [SD 15%], p = 0.2, fig. 2c). Detailed results of the cardiopulmonary exercise tests are described in table 2 and supplementary table S2 in appendix 1.

Quality of life

After 12 weeks, quality of life score was significantly better in the intervention group than in the control group (ΔMLHFQ score −5 [SD 6] vs 3 [SD 5], p = 0.006, fig. 2d and table 2).

Table 1: Baseline characteristics.

	All (n = 22)	Intervention (n = 11)	Control (n = 11)
Age, years (SD)	65 (19)	64 (19)	65 (19)
Male gender, n (%)	10 (45)	5 (45)	5 (45)
BMI, kg/m^2 (SD)	25 (4)	25 (4)	26 (4)
Left ventricular ejection fraction in %, (SD)	48 (13)	47 (12)	49 (14)
Cardiomyopathy, n (%)			
– Coronary cardiomyopathy	5 (23)	2 (18)	3 (27)
– Dilated cardiomyopathy	4 (18)	0	4 (36)
– Valvular cardiomyopathy	5 (23)	4 (36)	1 (9)
– Congenital heart disease	5 (23)	3 (27)	2 (18)
- Other	3 (14)	2 (18)	1 (9)
Severe valvular disease, n (%)	3 (14)	2 (18)	1 (9)
Pulmonary hypertension, n (%	2 (9)	2 (18)	0
Medication, n (%)			
– ACE-inhibitors/ARBs	14 (64)	7 (64)	7 (64)
– Diuretics	9 (41)	4 (36)	5 (45)
– Beta-blockers	14 (64)	6 (55)	8 (73)
– Aldactone	8 (36)	6 (55)	2 (18)
Sinus rhythm, n (%)	17 (75)	9 (82)	8 (73)
NT-proBNP, ng/l (IQR)	560 (278-1272)	443 (299–1011)	572 (206–1824)
FEV_1, % predicted, (SD)	85 (20)	85 (22)	86 (19)
FVC, % predicted, (SD)	82 (17)	81 (20)	82 (14)
FEV_1/FVC in %, (SD)	77 (18)	75 (23)	80 (10)

ACE = angiotensin-converting-enzyme; ARB = angiotensin receptor blocker; BMI = body mass index; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; IQR = interquartile range; NT-proBNP = N-terminal prohormone of brain natriuretic peptide; SD = standard deviation

Discussion

This randomised clinical study in patients with acquired or congenital structural heart disease showed an increase in inspiratory muscle strength after a 12-week intervention with weekly choir singing rehearsals in combination with structured daily breathing exercises at home. We report seven major findings:

The effect of breathing exercise on respiratory muscle function and exercise capacity

First, structured breathing exercises combined with regular singing rehearsals improved significantly the inspiratory muscle strength expressed as MIP. Exercise training is widely recognised as nonpharmacological intervention to improve exercise tolerance and quality of life in patients with chronic heart failure [13]. However, conventional physical exercise as instructed in many cardiac rehabilitation programmes does not specifically train the respiratory muscles. A previous randomised study in patients with

Figure 2: Primary and secondary endpoints. The figure shows the results at baseline (black bar) and after 12 weeks (grey bar) in the intervention (left bars) and in the control group (right bars). * marks the p-value of the mean change between both groups. Panel A (primary endpoint): maximum inspiratory pressure (MIP, %predicted). Panels B–D (secondary endpoints): maximum expiratory pressure (MEP, %predicted), maximum oxygen uptake during exercise (MVO_2, %predicted), Minnesota living with heart failure questionnaire (MLFQ) scores.

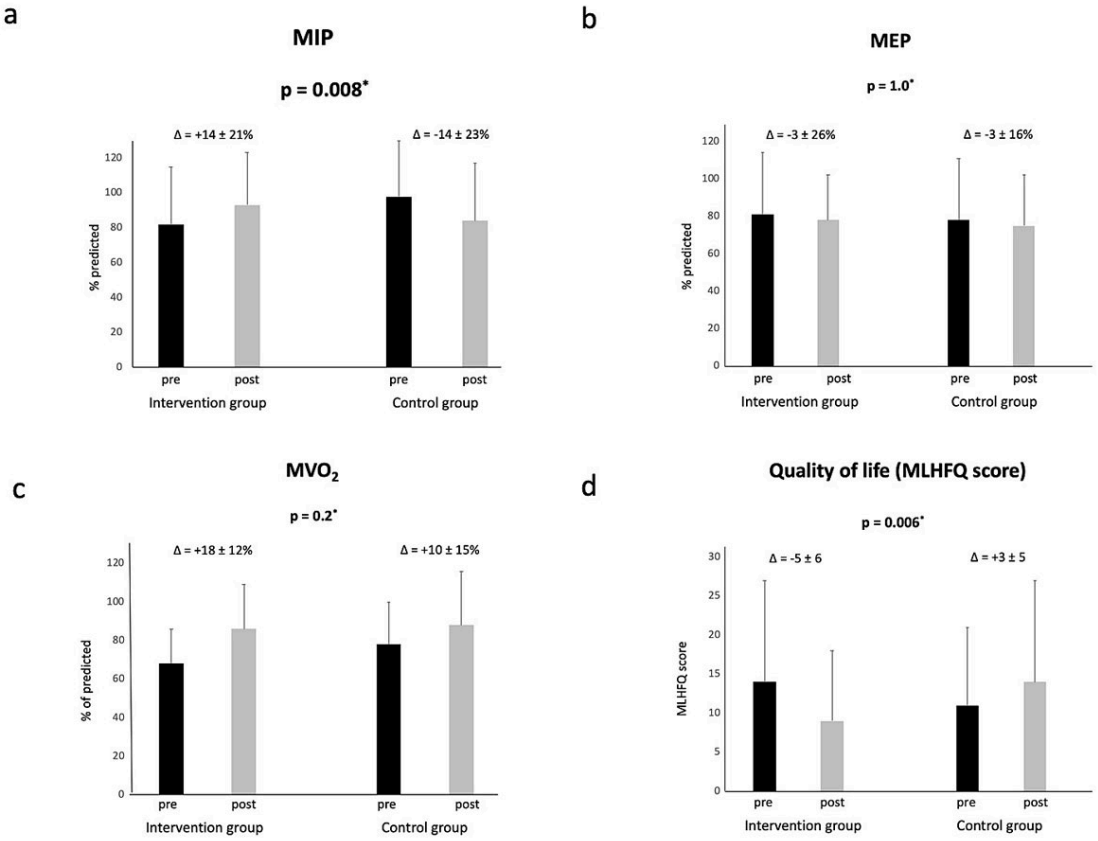


Table 2: Indices of respiratory muscle strength, cardiopulmonary exercise testing and quality of life score

	Intervention (n = 11)				Control (n = 11)				Intervention versus control	
	BL	FU 12	Change	p-value	BL	FU 12	Change	p-value	Mean change	p-value
MIP, kPa (SD)	5.2 (2.0	6.2 (2.2)	0.9 (2.3)	0.02	6.2 (2.3)	5.4 (2.6)	−0.9 (1.3)	0.04	1.8 (0.5)	0.002
MIP, % predicted (SD)	82 (33)	96 (30)	14 (21)	0.05	98 (32)	84 (33)	−14 (23)	0.07	27.5 (9.3)	0.008
MEP, kPa (SD)	7.6 (3.9)	7.6 (4.0)	−0.06 (2.4)	0.9	6.8 (2.7)	6.6 (2.4)	−0.2 (1.2)	0.6	0.3 (0.8	0.8
MEP, % predicted (SD)	81 (33)	78 (24)	−3 (26)	0.7	78 (33)	75 (27)		3 (16)	0.5	0.2 (9.1)
Respiratory exchange ratio (SD)*	1.16 (0.05)	1.14 (0.05)	0.02 (0.04)	0.12	1.16 (0.08)	1.10 (0.08)	0.06 (0.07)	0.048	0.04 (0.03)	0.15
MVO_2, ml/min/kg (SD)*	15.6 (5.7)	19.6 (6.9)	4.1 (2.2)	<0.001	16.8 (7.7)	19.4 (11.0)	2.6 (4.1)	0.1	1.5 (1.5)	0.3
MVO_2, % predicted (SD)	68 (18)	86 (23)	18 (12)	0.001	78 (22)	88 (28)	10 (15)	0.1	8 (6)	0.2
QoL Minnesota score (SD)	14 (13)	9 (9)	−5 (6)	0.026	11 (10)	14 (13)	3 (5)	0.1	8 (3)	0.006

BL = baseline; FU12 = follow-up after 12 weeks; MIP = maximum inspiratory pressure; MEP = maximal expiratory pressure; MVO_2= maximum oxygen uptake during exercise; QoL = quality of life; SD = standard deviation * 3 patients in the control group had to terminate prematurely and were excluded from the analysis.

chronic heart failure showed an even stronger increase of inspiratory muscle strength after a 12-week programme of inspiratory muscle training using an inspiratory muscle training device [14]. In another clinical trial comparing aerobic exercise alone and aerobic exercise plus inspiratory training showed a positive impact of inspiratory muscle training on physical capacity [21].

Second, there was no difference in the expiratory muscle strength expressed as MEP. In contrast to training with a handheld device, which strengthens the diaphragm muscles, breathing exercises such as in yoga-breathing strengthen the intercostal muscles. Therefore, breathing exercises such as those in our study focus less on the expiratory process, a fact that could be an explanation to why the MEP did not improve in our study.

Third, delta ΔMVO_2 did not improve in our study because of the small sample size. Breathing exercises (yoga breathing) are a relaxation and meditation technique based on postures, exercises and breathing techniques, and has demonstrated beneficial effects in patients with chronic heart failure. In another trial, 19 patients were randomised to yoga breathing or standard medical therapy alone. After 8 weeks of training, MVO_2 and quality of life significantly improved in the yoga group versus the control group [22]. The same research group demonstrated benefits of adding yoga to standard medical care in a small cohort of African American patients with heart failure by improving MVO, quality of life and inflammatory markers [23].

Fourth, baseline MIP showed a reverse correlation with the increase of MIP after 12 weeks of inspiratory muscle training. Therefore, baseline MIP might serve as a possible factor to predict the success of respiratory therapy.

Fifth, regular breathing exercise is an affordable intervention and can be performed by almost all patients, even in the frailest ones, the elderly and those with very advanced heart disease. These patients frequently are not capable of participating in regular physical exercise or cardiac rehabilitation programmes. Therefore, even minor changes in respiratory muscle strength and maximum oxygen uptake are difficult to obtain, and respiratory muscle training could be an available option to improve exercise capacity in these patients.

The effect of group singing on quality of life and respiratory muscle strength

Sixth, there was a high compliance rate with the daily respiratory training due to the study concept, with additional weekly choir rehearsals. On average, patients fulfilled their daily breathing exercise programme on about six of seven days per week. Nevertheless, no correlation could be found between compliance with performing breathing exercises at home with an increase of inspiratory muscle strength in the intervention group. The weekly choir rehearsals became an entertaining and enjoyable moment of social interaction and they seem to enhance the motivation of performing daily yoga breathing exercises at home.

To our knowledge, group singing is a new therapy concept for patients with chronic heart failure and so far, no study has analysed beneficial effects of singing in a choir in this population. *Seventh*, we found an improved quality of life in the intervention group compared with patients who did not receive the intervention and did not participate in the choir. Singing is associated with a number of physiological changes. Studies have shown that singing can cause changes in neurotransmitters and hormones, including the upregulation of oxytocin, immunoglobulin A and endorphins, which improves immune function and increases happiness [24]. Additionally, in older patients, a group-singing programme with deep breathing training and song-learning can have a positive effect on memory, language, speech information processing, executive function and respiratory muscle strength [25]. The cardiorespiratory system is utilised during continuous singing training, resulting in improved respiratory muscles and an optimised breathing mode [24]. This improvement could also be demonstrated in patients with lung disease: a beneficial effect of singing during pulmonary rehabilitation was shown in patients suffering from chronic obstructive pulmonary disease (COPD) and other chronic respiratory disorders [26], as well as in children with cystic fibrosis [27].

Implications for future projects

Patients with generalised myopathy and reduced exercise capacity due to underlying cardiac disease and/or chronic heart failure benefit from physical activity and, as shown in our study, from respiratory therapy. However, it is unclear whether respiratory therapy has an additional effect in patients undergoing conventional cardiac rehabilitation. We are planning to investigate this question in a larger randomised multicentre trial.

Since our study showed that choir singing in combination with breathing exercises improved quality of life in patients with heart disease, we will continue the "HeartChoir" independently of the study, and will include other patient groups with exercise intolerance (patients with pulmonary disease) and, thus, contribute to public health.

Limitations

The study was powered to analyse the improvement of inspiratory muscle strength. Whether respiratory muscle training also leads to an improvement in exercise capacity in patients with structural heart disease could not be determined owing to the low number of patients in the study. We included patients with various types of cardiomyopathies and the patients' characteristics were heterogeneous. The small sample size and the heterogeneity of the underlying cardiac disease limit the interpretation of the secondary endpoints. Larger studies are needed to analyse specific subgroups of cardiac diseases. A project with weekly rehearsals of choir singing limits the number of patients because it excludes patients from outer areas and patients who were not able to participate a result of mobility issues. Thus, a selection bias may be possible. The choir was led by only one instructor, so the effect of different instructors with different background and motivation is not shown. Lastly, given that our study was not blinded, the interpretation of the quality of life is limited.

Conclusion

Regular choir singing and respiratory muscle training improved respiratory muscle strength and quality of life in patients with chronic structural heart disease. Larger stud-

ies are needed to evaluate the effect of respiratory muscle training on exercise capacity and cardiac outcomes.

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Potential competing interests

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Appendix 1

Supplementary information

Table S1: CONSORT 2010 checklist of information to include when reporting a randomised trial.

Section/topic	Item no.	Checklist item	Reported on page no.*
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	-
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5–6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6
	6b	Any changes to trial outcomes after the trial commenced, with reasons	–
Sample size	7a	How sample size was determined	9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	–
Randomisation:			
– Sequence generation	8a	Method used to generate the random allocation sequence	5–6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	5–6
– Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	5–6
– Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5–6
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	–
	11b	If relevant, description of the similarity of interventions	–
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	–
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	10
	14b	Why the trial ended or was stopped	–
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	9/table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	10
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	10–11
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	–
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	–
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	10
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	15
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	12–15
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	12–15
Other information			
Registration	23	Registration number and name of trial registry	3
Protocol	24	Where the full trial protocol can be accessed, if available	–
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	16

* Page numbers refer to the original manuscript

Table S2: Remaining indices of respiratory muscle strength and cardiopulmonary exercise testing.

	Intervention (n = 11)				Control (n = 8)				Intervention versus control	
	BL	FU12	Change	p-value	BL	FU12	Change	p-value	Mean change	p-value
T50MIP, seconds	2.0 ± 1.6	2.4 ± 1.2	0.4 ± 0.6	0.07	2.2 ± 0.8	2.3 ± 0.8	0.06 ± 0.6	0.7	0.3 ± 0.2	0.3
T50MEP, seconds	1.6 ± 1.4	2.5 ± 1.2	0.9 ± 1.8	0.1	2.2 ± 1.3	2.4 ± 1.5	0.3 ±1.7	0.6	0.6 ± 0.7	0.4
Watt, (SD)	91 (32)	95 (40)	4 (11)	0.3	116 (60)	112 (65)	−4 (12)	0.4	8 (5)	0.2
Watt, % predicted, (SD)	70 (20)	72 (24)	2 (7)	0.3	78 (26)	75 (33)	−3 (10)	0.4	5 (4)	0.2
METS, (SD)	4.4 (1.6)	5.6 (2.0)	1.1 (0.7)	<0.001	4.8 (2.2)	5.5 (3.1)	0.8 (1.2)	0.1	0.4 (0.4)	0.4
VO_2 at AT, % of MVO_2, (SD)	52 (14)	73 (26)	21 (17)	0.002	71 (11)	83 (12)	12 (7)	0.003	9 (7)	0.2
O_2 pulse, ml/beat	8.9 (2.5)	10.5 (3.7)	1.6 (1.8)	0.016	9.3 (4.0)	12.1 (5.5)	2.8 (2.6)	0.17	−1.2 (1.0)	0.3
O_2 pulse, % predicted, (SD)	86 (17)	102 (29)	16 (19)	0.019	83 (26)	108 (31)	25 (18)	0.006	−9 (9)	0.3
VE/VCO_2 slope, (SD)	32.7 (8.1)	31.9 (6.5)	−0.9 (4.3)	0.5	33.7 (5.0)	29.8 (4.7)	−3.9 (5.1)	0.09	−3.0 (2.2)	0.2
Heart rate rest, bpm, (SD)	83 (15)	82 (20)	0 (14)	1.0	84 (18)	77 (16)	−7 (8)	0.5	−7 (6)	0.2
Heart rate max, bpm, (SD)	126 (29)	131 (25)	6 (13)	0.2	141 (18)	122 (15)	−18 (15)	0.01	−24 (6)	0.002
Blood pressure rest, mm Hg, (SD)	128 (33)	120 (27)	−9 (16)	0.1	140 (26)	133 (16)	−7 (16)	0.2	1 (7)	0.9
Blood pressure max, mm Hg, (SD)	168 (39)	165 (29)	-2 (17)	0.7	189 (24)	188 (19)	1 (16)	0.8	−8 (16)	0.9
SpO_2 rest in %, (SD)	93 (6)	93 (4)	0.1 (2.3)	0.9	93 (5)	92 (5)	0.5 (1.5)	0.4	1 (3)	0.6
SpO_2 max in %, (SD)	90 (11)	90 (11)	0.1 (4.4)	0.9	90 (14)	90 (11)	0.1 (3)	0.9	0 (2)	1.0
VE max, % predicted, (SD)	57 (17)	76 (17)	19 (19)	0.007	69 (8)	74 (22)	4 (22)	0.6	15 (10)	0.1
VT max, % predicted, (SD)	76 (26)	83 (26)	8 (13)	0.077	88 (18)	84 (23)	−4 (17)	0.5	12 (7)	0.1
RR max, % predicted, (SD)	113 (15)	121 (17)	9 (13)	0.061	119 (19)	121 (19)	2 (13)	0.7	7 (20)	0.3

AT = anaerobic threshold; BL = baseline; FU12 = follow-up after 12 weeks; MET = metabolic equivalent of task; MVO_2 = maximum oxygen uptake during exercise; RR = respiratory rate; SD = standard deviation; SpO_2 = oxygen saturation; VE max = maximum ventilation; VE/VCO_2 = ventilatory equivalent for carbon dioxide; VT = tidal volume