A RANDOMIZED CONTROLLED TRIAL OF LISTENING TO RECORDED MUSIC FOR HEART FAILURE PATIENTS: STUDY PROTOCOL

Francesco Burrai, Ph.D.
Adjunct Professor of Complementary and Alternative Medicine
School of Medicine
University of Bologna
Viale GB Ercolani 6, 40138, Bologna, Italy
francesco.burrai2@unibo.it
+39 051 636 3 053

Wohaib Hasan, Ph.D
Research Assistant Professor
Knight Cardiovascular Institute
Oregon Health and Science University
MC: UHN62, 3181 S.W. Sam Jackson Park Road,
Portland, OR 97239-3098, USA
hasan@ohsu.edu.
+1 503 494 4873

Daisy Fancourt, Ph.D.
Research Associate in Performance Science
Centre for Performance Science,
Royal College of Music, Prince Consort Road, London SW7 2BS, UK
daisy.fancourt@rcm.ac.uk
+44 07958 065 563

Marco Luppi, Ph.D.
Assistant Professor of Neurophysiology
Department of Biomedical and Neuromotor Sciences
University of Bologna
Via Zamboni, 33 - 40126 Bologna, Italy
marco.luppi@unibo.it
+39 051 20 9 1731

Salvatore Di Somma, Ph.D.
Professor of Medicine
Director Emergency Medicine
Chairman Postgraduate School of Emergency Medicine
Department of Medical-Surgery Sciences and
Translational Medicine
University La Sapienza Rome
Sant'Andrea Hospital
Rome, Italy
+39 063 37 7 5581

Abstract

Aims. To describe a conceptual framework and to test the effectiveness of a recorded music listening protocol on symptom burden and quality of life in heart failure patients. **Background**. Heart failure is an important public health problem. Many heart failure patients experience symptoms burden and poor quality of life, even with current improvements in pharmacological treatments. Recorded music listening has been shown to improve outcomes in cardiovascular patients, but it has never been tested on heart failure patients and with a specific music protocol and a randomized controlled trial methodology. **Methods.** This study is a multi-center blinded randomized controlled trial that will involve 150 patients. Eligible patients will have a diagnosis of heart failure, in NYHA functional classification of I to III, and will be recruited from three large hospitals in Northern Italy. Patients will be randomly allocated in a 1:1 ratio to receive recorded music listening intervention with or without standard care for 3 months. Data will be collected at baseline and at the end of the first, second and third month during the intervention, and at six months for follow-up. The following variables will be collected from heart failure patients with validated protocols: quality of life (primary endpoint), use of emergency services, re-hospitalization rates, all cause mortality, self-care, somatic symptoms, quality of sleep, anxiety and depression symptoms, and cognitive function. **Discussion.** This study will examine the effect of recorded music listening on heart failure patients and will inform clinical practice. If the findings are found to be positive, the protocol could be used as a tool for evidence-based applications of recorded music in HF patients. The framework developed in this study may be helpful for future research focused on the effects of music in heart failure patients.

Keywords: heart failure, music therapy, quality of life, conceptual framework, study protocol, randomized controlled trial.

Introduction

Heart failure (HF) is a chronic clinical syndrome that occurs when the heart is unable to pump blood within the circulation system and organs do not receive sufficient oxygen and nutrients (1). It is estimated that 1-2% of the general population has HF with an increase to 20% in people over 70 years of age (2). More recent statistics have shown that 15 and 5 million people are affected by HF in Europe and United States, respectively (2-3). Approximately 40% of HF patients die or are re-hospitalized one year after diagnosis (4). In Italy, HF is the second leading cause of hospitalization, with a hospitalization rate of 4-5 admissions per 1,000 population and a progressive increase in the number of hospitalizations (5). It has been estimated that hospitalizations for HF represent 2.0% of the total cost of hospital expenditures (6). Although treatments for HF have advanced in the last 20 years, and longer survival rates have been reached, symptom burden and decreased QOL due to HF, can continue to be a problem. Some of the secondary problems that result from HF include ankle swelling, shortness of breath, fatigue and mood disturbances. All of these can have a negative impact on the patients' quality of life (QOL) (7-8). It has been shown that QOL in HF patients is even worse than in cancer patients (9). In fact, a large proportion of HF patients, between 50% to 85%, remain in the more severe functional classification within the New York Heart Association (NYHA) class, even after progressive improvements in pharmacological treatments (10-12).

Therefore while pharmacological therapies may improve heart function, they may be only partially effective at reducing symptoms. Persistence of HF symptoms are not only a criteria for hospitalization or discharge (13) and an important predictor of survival (14), but can also reduce quality of life (15) and influence decision making related to treatment (8). Current guidelines regarding symptom relief in HF suggest that the introduction of non-pharmacological treatments to decrease severity of symptoms and improve quality of life is urgently required for these patients (7).

An important non-pharmacological treatment already used for cardiovascular patients, and other patient populations, is music listening. Music has been used as a therapeutic tool for populations with cardiovascular diseases including coronary heart disease (CHD) (16), heart failure (17), hypertension (18), cardiac rehabilitation (19), cardiac surgery (20) and during cardiac diagnostic procedures (21). Several investigators have found that listening to music influences QOL (22), psychological distress (23) , anxiety (24), depression (25), mood (26), blood pressure (27), heart rate (28) and quality of sleep (29). However, these studies have used differing research designs and different methods for music exposure.

So far no rigorous randomized controlled trials (RCTs) have been conducted to test the effect of listening to music on symptoms and quality of life in HF patients. Also, no studies, even in other patient populations, have shown if listening to music can improve self-care, the use of emergency services, re-hospitalitation rates, and mortality. The psycho-neuro-immuno-endocrinology (PNIE) framework that describes the connections among mental, neurological, hormonal and immunological functions, supports the hypothesis that listening to music may have beneficial effects on the variables outlined above (30).

Background

Several studies have been conducted in clinical settings to explore the effect of listening to music on cardiac patients, but only a limited number of randomized controlled trials had the aim of testing the effectiveness of music therapy specifically in cardiac health care (22). Only one study has been attempted on music’s therapy's effects on the incidence of heart failure events in elderly patients with cerebrovascular disease and dementia (17), but no trials have been carried out on HF patients. It has been shown in several studies that listening to music can improve several outcomes in cardiac patients, specifically blood pressure, heart rate, somatic symptoms, sleep, anxiety, and depression. However, most of these studies have not specifically targeted HF patients.

A first Cochrane Review of 23 RCTs (1461 participants) showed that listening to music significantly reduced systolic blood pressure (SBP) by 5.34 mmHg (95% IC effect size -7.20 to -3.48, p<0.00001) (31). These results were confirmed in an update of this systematic review that included 26 RCTs (1369 participants) with a mean reduction in SBP of 5.52 mmHg (95% IC effect size -7.43, -3.60,P < 0.00001) (29). The effect of listening to music on SBP was also demonstrated in cardiac rehabilitation patients, where listening to music plus cardiac rehabilitation showed significantly greater changes in SBP than cardiac rehabilitation alone (−9.7 mmHg vs. −0.07 mmHg, P = 0.03) (19). A reduction of SBP over a 24-hour period was also shown in patients undergoing breathing exercises accompanied by listening to music (32).

Regarding diastolic blood pressure (DBP), the first Cochrane Review on patients with CHD showed a reduction on DBP of -1.84 mmHg (95% CI effect size -3.53 to -0.14, P = 0.03) (31). In the updated Cochrane Review in the same population, the results showed a reduction of -1.12 mmHg (95% IC effect size -2.57, 0.34), but this difference was not statistically significant (P = 0.13) (29).

Listening to music also has effects on heart rate (HR) as demonstrated in the first Cochrane Review on patients with CHD (mean difference of -3.92, 95% CI -6.84 to -1.00, P = 0.009) (31). This finding was confirmed also in the update of the Cochrane Review (MD = -3.40, 95% CI effect size -6.12 to -0.69, P = 0.01) (29).

In addition, listening to music can also improve somatic symptoms in cardiac patients; indeed Mandel et al (2007) have shown that cardiac rehabilitation patients who listened to music had better control of unpleasant symptoms.

In patients who underwent to a cardiac procedure or cardiac surgery, listening to music improved sleep (MD = 0.91, 95% CI effect size 0.03 to 1.79, P = 0.04) (29). Similarly, Ryu et al (33) showed that listening to music improved quality of sleep in patients after a percutaneous trans luminal coronary angiography.

Listening to music has also been shown to reduce anxiety in a number of conditions including prior to cardiac surgery (34-35), in patients awaiting cardiac catheterization examination (36), in patients undergoing a C-clamp procedure after percutaneous coronary interventions (37-38), in older adults undergoing cardiovascular surgery (39), and in adults with coronary heart disease (16). The updated Cochrane Review on patients with CHD showed moderate effects on anxiety, but the results were inconsistent across studies (MD = -0.70, 95% CI effect size -1.17 to -0.22, P = 0.004). In contrast, for people with myocardial infarction, a more consistent reduction of anxiety from listening to music has been observed, with an average anxiety reduction of 5.87 units on a 20 to 80 point score range (95% CI effect size -7.99 to -3.75, P < 0.00001) (29).

For depression, in the first Cochrane Review on a CHD population, music was not shown to alter results significantly (MD = -0.12, 95% CI effect size

-0.42 to 0.18, P = 0.44) (31), a result found again in the updated Cochrane Review (MD = - 0.11, 95% CI effect size -0.38 to 0.16, P = 0.42) (29). Other studies have shown that music can reduce depression in patients enrolled in cardiac rehabilitation programs (19, 40) and in adults with CHD (16).

The effect of music on quality of life has yielded important results. Hanser (22) showed that music could contribute to improve QOL in cardiac rehabilitation patients (22) and represents a coping strategy over the long-term (41). Patients in cardiac rehabilitation after 4 months of music therapy intervention showed significantly greater improvement in QOL (19), but the loss of patients at follow-up reduced the usefulness of this data set (29). Also, music improves QOL during cardiac surgery (34), in patients after coronary angiographic procedures (42) and during cardiac rehabilitation (19). In the latter population music has been shown to be an effective tool of self-management to improve QOL (43).

Regarding the effects of music over time, the best randomized controlled trials show a duration of treatment of 3 months (12 weeks) and follow up at 3 months (44).

Conceptual Framework

The conceptual framework that will guide this study is the PNIE framework developed by Fancourt and colleagues (30); Figure 1 shows the system interactions involved (45-59).In the Fancourt's study the collected data on music therapy demonstrating changes in 37 biomarkers from 63 studies carried out in 22 countries involving over 8,000 participants. In this study, the hypothesis was that music could influence health via a combination of personal, social, aural and physical factors. Listening to recorded music involves two of these factors: aural (i.e. the dimensions of the music itself, such as its tempo, tonality, mood) and personal (i.e. how an individual responds to the music, whether they like or dislike it, and whether they are familiar with it or not). The PNIE model suggests that these factors then interact to affect psycho physiological systems within the body including mental wellbeing, cardiovascular measures, stress hormones and biomarkers of the immune system in bidirectional pathways. This model shows that responses to music are interconnected among psycho-neuro-immuno-endocrinological systems. As such, music is capable of influencing a broad range of psychological and physiological systems, showing its potential as a therapeutic agent and a strategy over the long-term (41).

At the level of the auditory system, sound is perceived by the hearing system and the neural signals triggered by cochlear vibrations follow the auditory nerves and come initially into the brainstem (60). Neural signals then travel to both the primary (Brodmann areas 41 and 42) and secondary (Brodmann area 22) cortical areas within the temporal lobes which are involved in the final cognitive processing (61).

Centrally, relaxing music actives autonomic parasympathetic outflow that inhibits sympathetic outflow; as a consequence a reduction in heart rate (HR) and attenuation of the Low Frequency/High-Frequency ratio (HFr:LFr) of the heart rate variability (HRV) occurs (17). A decrease of epinephrine and norepinephrine plasma levels (62), and an increase of μ-opiate receptor functionality (63), has been shown after listening to relaxing music. In contrast to classical music reducing sympathetic outflow to the heart and HFr:LFr ratio (64), listening to heavy metal music has an opposite effect on these parameters (65).

Looking at the endocrine system, music may reduce the plasma levels of catecholamines (66) with a reduction of sympathetic outflow, a reduction in tachycardia, and in anxiety levels (17). The amygdala, hippocampus, the para-hippocampal gyrus, and the temporal lobes are all influenced by relaxing music which reduces activity in these brain structures and thereby promotes reductions in both circulating cortisol levels (67-72) and in markers of physical and psychological stressors (73). Listening to relaxing music can also reduce circulating adrenaline levels (62) and increase plasma levels of oxytocin and growth hormone (74). A reduction of circulating cortisol levels will likely have beneficial effects on arterial function and blood pressure control via inhibition of the hypothalamic-pituitary-adrenal axis (75).

In relation to the immunological system, listening to relaxing music can modulate the immune system through reductions in pro-inflammatory signals, associated with increased IgA and IgG levels (73, 76-77), reduce the plasma levels of interleukins -4, -6, -10, -13 and TNF (62-63, 78), increase natural killer cells (79) and CD8+ T cell expression (80-81), and decrease circulating histamine levels (82).

At the level of cognition, relaxing music positively influences perceptual information, declarative memory learning, memory recall and motor learning (86), and may improve verbal learning and memory through its influence over the chunking mechanism and perceptual information processing (87). Listening to music also promotes brain plasticity allowing the recovery of verbal learning and memory function after traumatic brain injury (88), and can also influence brain plasticity during general speech perception and learning (89). As such, listening to music influences the neuronal networks connecting verbal memory function, chunking and plasticity (90-92). In addition, listening to music enhances deep encoding in memory processes, improves memory retrieval (93), and evokes autobiographical recall (94-95). In particular, short-term memory is influenced by rhythmic music characteristics because this music parameter influences brain oscillations (91). Classical music can develop the learning of three-dimensional mental rotation tasks (96) and can improve cognitive performance in intelligence tests (97), and classical music with a pattern of 60 beats per minutes, activates both the left and right brain. The simultaneous left and right brain activation maximizes learning and retention of information (98). A wealth of scientific data therefore supports a positive impact of relaxing music on a broad range of physical and psychological parameters within the body.

The study

Aims

The purpose of this study is to investigate the effect of listening to music on specific HF outcomes such as: quality of life, somatic symptoms, quality of sleep, anxiety, depression, cognition, self-care, use of emergency services, re-hospitalization rates, and all-cause mortality.

Research hypothesis

The following hypothesis was generated from the conceptual framework:
HF patients participating in the intervention group will have better quality of life, fewer somatic symptoms, better quality of sleep, lower anxiety and depression levels, enhanced cognition, better self-care, fewer uses of emergency services, lower re-hospitalization rates, and lower all-cause mortality.

Design/methodology

A multi-center (n=3) randomized controlled trial with two parallel arms will be conducted. The experimental arm of the study will involve participants in listening to music in addition to receiving standard care. The control arm will receive standard care. To determine the effects of the listening to music intervention the trial will include assessments at the end of the 1st 2nd and 3rd month of the intervention, and a follow-up assessment at 6 months after enrollment.

Participants

This study is in line with the Declaration of Helsinki. Ethical approval has been granted by the Ethics Committee of the Local Health Unit of Bologna (local protocol no.1063/CE). Ethical approval was gained on December 22, 2014. One hundred fifty HF patients will be enrolled in this study. Participants will be recruited from the outpatient cardiology units of three major cardiology centers in Northern Italy. The eligibility criteria for participants' enrolment will be:

A) Inclusion criteria

1) a confirmed diagnosis of HF according to the guidelines specified by the European Society of Cardiology (3); 2) NYHA functional classification I to III, including patients with preserved ejection fraction (HFPEF) and with a reduced ejection fraction (HFREF); 3) the presence of a formal or informal caregiver; 4) signed informed consent.

B) Exclusion criteria

1) deafness; 2) severe neurological disorder (Parkinson, multiple sclerosis, Alzheimer's disease; 3) severe psychiatric disorder; 4) obvious dementia, 5) reduced level of consciousness.

Recruitment of patients
Nurses trained in music therapy protocol will be divided into two different groups: data collectors and outcome assessors. HF patients will be approached to participate by data collectors during routine cardiology outpatient visits. Data collectors will screen HF patients for eligibility, and after consideration of the exclusion and inclusion criteria will enrol the HF patients, giving full information about the trial to both patients and caregivers.
Data collectors will explain to HF patients that they will be randomized into the study groups; they will be educated on recorded music listening and will be trained on how to use tools for recorded music listening through the use of an Mp3 player and volume controls for headphones . After explaining the study design and parameters, if eligible, HF patients that are interested in the study will have informed written consent obtained by the data collectors. Once obtained, socio-demographic, clinical data and baseline questionnaires will be completed. After this phase, participants will be randomized and allocated to the two arms with anonymous IDs. For HF patients in the music therapy group, the data collector will evaluate the patient's ability to use an Mp3 player and volume controls for headphones, and will instruct the caregiver on how to supervise the patient in listening to music. Patients will be educated to listen to the playlist daily for at least 30 minutes a day. Outcomes assessors will collect data at the 1^{st} 2^{nd}, 3^{rd} month during the intervention, and at the 6^{th} month after enrolment.

Intervention
Patients will be randomly assigned to one of two following groups:

Experimental group
In addition to the standard care, HF patients assigned to the music group will listen to recorded classical music. Nurses trained in music therapy protocol will educate HF patients on recorded music listening. Patients will be trained during the enrollment phase and every two weeks they will be called to strengthen their adherence to listening to the playlist. The training is the explanation of how to use the MP3, choose the music tracks, use of the headphones, volume control, timing the period of listening, how to fix problems, the type of musical pieces, and who and when to call to get help during the three months of music listening therapy.

The use of headphones gives a detailed, pure and natural sound and a fairly 'flat' accurate response with isolation from environmental noises. The headphones allow excellent fidelity and high quality audio for listening to music, greatly limiting extraneous sounds.
Music will be listened to by the patient in his/her home, in a resting position and in a bed or armchair. The music playlist will consist of a classical repertoire that has been structured in accordance to the PNIE framework outlined previously. This playlist is designed to avoid music that erroneously can negatively stimulate catecholamines, or that may result in increased

circulating cortisol (99-100), adrenocorticotropic hormone, norepinephrine, and growth hormone levels (101).

The playlist will avoid music with an emphatic trait (high emotional impact), or a crescendo that can generate skin vasoconstriction, and an increased heart rate and blood pressure (102), or high arousal music that may decrease activation of the parasympathetic nervous system, decrease the LF component of HRV, and thereby stimulate the cardiovascular system (103-104).

The pre-selected music list will include 80 different music tracks. Allowing HF patients to choose the music to listen to from a large pre-selected playlist may enhance a patient's motivation as other investigators have already shown (105). During the intervention, HF patients will agree to listen to the recorded music for a minimum of 3 months, once or more than once per day at any time, at least a total of 30 minutes per day, as suggested by previous studies (106-110). During the enrollment phase, the listening parameters outlined here will be emphasized to study participants and caregivers, with an emphasis on achieving these benchmarks every day in order to obtain optimal benefits for the patient's health and wellbeing.

According to the intention-to-treat principle, patients who will listen to music for less than 30 minutes per day will not be excluded from data analysis. To check how long participants listen to the music playlist, HF patients will keep a detailed diary. To ensure the completion of the diary, in the enrollment phase participants and caregivers will be educated on the importance of this task. In addition, every two weeks a nurse will call the patient to ratify and encourage the HF patient to complete this task.

Music will be listened to at 50-60 decibels below the threshold of 85 db established for listening to portable media devices such as compact disc and Mp3 players (111). This sound level is optimal for listening to music over long periods of time without causing hearing problems (111).

Music used in this protocol has a tempo/rhythm in a range of 60-80 beats per minute (bpm). This range mirrors the human heart rate and facilitates relaxation (35). Tempo/Rhythm factors are fundamental to creating a coherent state; a synchronization between music and the cardiovascular system (102). Indeed, an increase in the tempo/rhythm of the listened music may increase the rate of cardiovascular parameters (73, 112).

Therefore, music that will be chosen for the play list will be classical music, with meditative ambient sounds, played in a relaxing atmosphere. These soft, soothing, and calming sounds are designed to evoke tranquility and joy. Many studies have shown that soft musical sounds with a slow tempo decrease plasma cortisol (34, 67, 70, 72), epinephrine and norepinephrine levels (17, 62). In contrast, stimulating music styles with beat ranges of 130-200 beats/min increase plasma cortisol, ACTH, prolactin, growth hormone and norepinephrine levels (101). Soothing music can decrease autonomic sympathetic activation, with consequent reductions in anxiety levels, tachycardia, and tachypnea; this occurs via vagal nerve (17, 34) increases in R-R intervals (112). Despite these studies showing clear benefits of relaxing music, a few studies, however, have shown no significant effects on plasma cortisol (105, 113) and epinephrine and norepinephrine levels (105, 113) following music therapy. We have decided to offer classical music because this music shows the clearest beneficial effects on the cardiovascular system and cardiovascular health (114)(98). In addition, autonomic responses have been well studied with classical music with marked synchronization between classical music and cardiovascular parameters (102, 112).

The most stable tonic pitch in the Western major scale commonly occurs at the beginning and endings of phrases on strong metrical positions (115) that are typical in classical music. The perception of 'calm' or 'happy' is linked primarily by major intervals while the perception of 'tense' or 'sad' emotions is characterized by minor intervals (116). The listening of classical music pieces in a major key mode causes a more positive mood, whereas the minor mode causes negative shifts in mood (117). Music in major keys reduces the levels of cortisol in the salivary glands during mental fatigue, whereas minor keys are mostly ineffective (97). In accordance with these findings our playlist for most of the pieces will be in a major key.

Control group

HF patients assigned to the control group will receive standard care only. The standard care will consist of nursing and medical counseling, self-care education and medication. These patients will not have access to the playlist but will of course be free to listen to music of their choice during the three months of the study. In Italy, the majority of HF patients for cultural reasons and advanced age do not listen to classical music or specific sedative music every day. However, popular music is generally heard on the radio and this remains very popular in this demographic as opposed to digital music sources in younger age groups. These socio-cultural characteristics could prevent the introduction of confounding factors in this study.

Outcomes

The measuring tools for the primary and secondary endpoints are shown in Table 1.

*Primary outcome*s

This RCT has two primary endpoints: HF specific and generic QOL.

The HF specific quality of life will be measured with the Minnesota Living with Heart Failure Questionnaire (MLHFQ) (118). The MLHFQ measures the impact of HF on patient’s health-related quality of life. It consists of 21 items that use a 6-point Likert scale, from 0 (no impact) to 5 (very high impact). The MLHFQ total score ranges from 0 to 105, and higher score indicates a poorer quality of life. From the MLHFQ, two scores can be obtained that reflect the physical and the emotional impact of HF on the patient’s QOL. The MLHFQ is the most commonly used questionnaire in HF research and clinical practice (119-121) and its psychometric properties have been shown to be adequate in several studies (122). In a recent systematic review the MLHFQ has been shown to have good reliability with supportive Cronbach's alpha coefficients (ranging from 0.81 to 0.95) and test–retest reliability for both the physical (0.91) and emotional (0.92) subscales (123).

Generic QOL will be measured with the Short Form -12 (SF-12) a multi-item generic tool that measures QOL (124). The SF-12 consists of 12 items that are grouped in two dimensions: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). The total scale score of each SF-12 dimension ranges from 0–100, with higher scores indicating better QOL. The SF-12 has demonstrated supportive psychometric properties of validity, reliability and sensitivity in measuring the perception of the state of health of the patient (124-126) .

Secondary outcomes

Use of emergency services, hospitalization and mortality. These three variables will be evaluated with telephone interviews at the 1st 2nd, and 3rd month during the intervention, and a follow-up assessment at the 6th month after enrolment. Patients and caregivers at enrollment will be asked to keep a diary of any of the above events. (127).

Self-care. Patient's self-care will be measured with the Self-Care of Heart Failure Index version 6.2 (SCHFI V.6.2). (128). The SCHFI v.6.2 is a questionnaire consisting of three scales that measure self-care maintenance, self-care management and self-care confidence. The self-care maintenance scale has 10 items and measures how frequently a HF patient checks his/her symptoms (e.g., ankle edema) and adheres to the recommended pharmacological and non-pharmacologic treatments (e.g., take medicines and exercise). The six items of the self-care management scale evaluate patient's symptom recognition, symptom evaluation, treatment implementation and treatment evaluation. The self-care confidence scale, with 6 items, evaluates patient's confidence in engaging in self-care. Each SCHFI v.6.2 item uses a 4-point Likert format for responses. Each scale has a 0-100 standardized score with higher scores meaning better self-care. Psychometric properties of the SCHFI v.6.2 have been tested in several studies and have been found adequate also in the Italian population (129-130).

Somatic perception of HF symptoms. They will be evaluated with the Heart Failure Somatic Perception Scale (HFSPS) (12). The HFSPS is a questionnaire consisting of 18 items that measure how much specific HF symptoms were bothersome for a patient during the last week. Each item corresponds to a symptom (e.g., breathing problems or fatigue). The 18 considered symptoms are measures with a 6-point Likert scale that ranges from 0 that corresponds to "I did not have symptom" to 5 that correspond to "Extremely bothersome". The HFSPS score range from 0 to 90, with higher scores that indicating higher symptom burden. Psychometric testing of the HFSPS have shown adequate validity, reliability and sensitivity in measuring somatic perceptions of HF symptoms (12).

Sleep quality. Sleep quality will be measured with the Pittsburgh Sleep Quality Index (PSQI) (131). The PSQI is an instrument used to measure the quality and patterns of sleep in the adult population. The PSQI is composed of seven domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction over the last month. The PSQI has 9 items; 1 to four are open questions, these are not scored. Items 5 to 8 are scored with a 4-point Likert scale from 0 (not during past month), 1 (less than 1 week), 2 (once or twice a week), 3 (three or more times). Item 9 about sleep quality overall is scored with a 4-point Likert scale from 0 (very good), 1 (fairly good), 2 (fairly bad), 3 (very bad). A total sum of “5”or greater indicates a “poor” sleeper. The PSQI has demonstrated adequate validity and reliability (131).

Anxiety and depression. These will be measured with the Hospital Anxiety and Depression Scale (HADS) (132).The HADS is a screening tool for anxiety and depression for a non-psychiatric clinical population. The scale consists of 14 items strategy over the long-term (41). Patients in cardiac rehabilitation after 4 months of music therapy intervention showed significantly greater improvement in QOL (19), but the loss of patients at follow-up reduced the usefulness of this data set (29). Also, music improves QOL during cardiac surgery (34), in patients after coronary angiographic procedures (42) and during cardiac rehabilitation (19). In the latter population music has been shown to be an effective tool of self-management to improve QOL (43). Regarding the effects of music over time, the best randomized controlled trials show a duration; 7 for anxiety and 7 for depression. Each item describes a feeling or behavior that characterizes anxiety and depression (e.g., feeling nervous) and are scored on a 0 – 3 Likert scale from “not at all” (0) to “very often” (3). Responses are based on the frequency of symptoms over the preceding week. Possible scores range from 0 to 21 for each subscale. An analysis of scores on the two subscales support the differentiation of each mood state into four ranges; ‘mild cases’ (scores 8-10), ‘moderate cases’ (scores 11-15), and ‘severe cases’ (scores 16 or higher). The PSQI has demonstrated good validity and reliability (133).

Cognition. The Montreal Cognitive Assessment (MOCA) (134) will be used to measure patient’s cognition. It consists of 30 items and assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. The total possible score ranges from 0 to 30 points; a score of 26 or above is considered normal cognition, and scores lower than 26 are considered cognitive impairment. The cognitive domains are assessed with these modalities: 1. Alternating Trail Making (0 - 1 points); 2. Visuo-constructional Skills, Cylinder (0-6 points); 3. Visuo-constructional Skills, Clock (0 -3 points); 4. Naming (0-3 points); 5. Memory (0-5 points); 6. Attention (0-2 points); 7. Vigilance (0-1 points); 8. Serial 7s (0-3 points); 9. Sentence repetition (0-2 points); 10. Verbal fluency (0-1 points); 11. Abstraction (0-2 points); 12. Delayed recall (0-5 points); 13. Orientation (0-6 points). The MOCA has demonstrated adequate validity and reliability (134) and it is more sensitive to mild cognitive impairment than the Mini Mental State Exam (135).

Comorbidity. The Charlson Comorbidity Index (CCI) (136) will be used to measure comorbid conditions. It consists of 12 items each one of which identifies a specific illness. Scores for each item (illness) can be 1, 2, 3 or 6 depending on the risk of mortality from having that illness (137). CCI total score ranges from 0 to 24. All patients enrolled in this study will have at least 2 points at the CCI since 2 points is the score given to HF.

Socio-demographic and clinical data. A tool already successfully used in a prior study (138) will be used to collect socio-demographic and clinical variables such as sex, age, marital status, level of education, city of residence, nationality, occupation, number of people living with the patient, income, blood pressure, heart rate, ejection fraction, NYHA functional class illness duration, etiology of HF, and pharmacological treatment; Table 1 shows dependent variables and measurements. For monitoring music listening with the Mp3 player, at every monthly visit patients will be asked if they listened to the music on the Mp3 player every day. They will also be asked if they were sitting in a chair just listening to the music or were doing other tasks at the same time; on a scale from 1-10 how much did they like the music and how much attention did they pay to it.

Sample size calculation

The sample size will be based on the primary endpoint of quality of life measured with the MLHFQ. Considering two balanced groups (n1 = n2), a medium effect size (d = 0.5), α error of 5% and with a power of 80% to detect differences between groups, it will be necessary to enroll a total of 128 (n1 = n2 = 64) patients. A medium effect size d = 0.5 implies a sample difference expectation of 10 points at the MLHFQ, in accordance with a study by Parati and colleges (139). Given the ordinal nature of the variables, and assuming a normal distribution of scores, to maintain power to the expected value (80%), we should multiply by π / 3 (asymptotic relative efficiency value), obtaining a total of 134 subjects. Finally, assuming a drop-out of 10% for the study group (140), we will need to enroll a total of 150 patients; 75 subjects per group.

Randomization

A randomization list will be generated by the statistical software SPSS version 19 (IBM Corporation, Armonk,NY), with a ratio of 1:1 allocation. Randomization will be carried out by an independent statistician. To ensure allocation concealment, the randomization list will be centralized and stored in a University server, with access by username and password permission only to an independent statistician, so that it cannot be subverted by investigators and it will not be possible for the investigators to know the allocation sequence in advance.

While patients' assignment to the study groups will be not blinded to data collectors, as this is not possible for this music interventions (29), the outcome assessors will be blinded to the study group assignment. Also, outcome assessors will be instructed not to ask patients if they listened to the music, and HF patients and their caregivers will be asked not to reveal their group allocation to outcome assessors during follow-up data collection appointments.

Data analysis

Data from patients will be entered into spreadsheet files and checked for data errors independently by another researcher. Analyses will be conducted using SPSS 19.0 (IBM Corporation, Armonk,NY). Descriptive statistics, mean, standard deviation, frequencies, median and interquartile ranges will be used to describe scale scores and socio-demographic and clinical data. All tests will be two-tailed. A probability value <0.05 will be considered the minimum level for statistical significance. To test the means differences between groups at baseline and at the 1st 2nd, and 3rd month, and at the 6th month after enrolment, repeated measures ANOVAs with Bonferroni post-hoc tests will be used. If repeated measures ANOVA show an effect of treatment, MANCOVA analysis will be used to verify possible associations between the outcome and continuous predictor variables. To calculate the correlations between the scores of the different questionnaires the correlation coefficient of Pearson or Spearman will be used. Fisher's exact test or χ^2 test will be used to identify differences in use of emergency services, hospitalization and mortality between the intervention and control group.

Discussion

The aim of this study will be to investigate the effect of listening to music on specific HF outcomes such as: somatic symptoms, quality of sleep, anxiety, depression, cognition, self-care, quality of life, use of emergency services, re-hospitalization rates, and all-cause mortality.

This study addresses a research gap in the development of research protocols for music medicine interventions (22) thereby introducing a music intervention protocol for HF patients. To our knowledge this is the first RCT that will evaluate the effect of a non-pharmacological intervention with such a specific recorded music playlist for HF patients. This trial is designed to compare the effect of recorded music listening in addition to standard care, with standard care alone in HF patients, with measurements at the 1st 2nd, and 3rd month during the intervention, and at a follow-up visit at the 6th month. This broad time interval during and following the music intervention, will allow us to evaluate how the HF outcomes considered in this study change over time.

For the purpose of this study, a PNIE conceptual framework has been designed based on the work of Fancourt and colleagues (30). This PNIE framework suggests that aural and personal responses to recorded music can lead to psycho physiological changes that could alter mental health, physical health and health behaviors with implications for QOL, self-care, HF progression, and use of health services (Figure 2).

This framework will be tested in this research study to assess its validity. It is hoped that, if supported by the data, this framework will provide enhanced understanding of how music-based interventions may impact individual health and the wider healthcare system. The music intervention delivered in this trial is based on a PNIE framework, where the music therapy could improve not only somatic aspects of heart failure, but could also improve the holistic needs of patients (141).

In the holistic view of the human being, music can gain, sustain or maintain this human dimension (142). Music can yield positive experiences, a sense of wholeness and coherence, and can be linked to the patients' inner dimension: many pieces of music may speak directly to us recalling positive emotions and peace (143).

Within many societies, music is an integral part of life (144), and this existential condition may provide resources for the recovery of self-identity (145). Music may also contribute to the quality of life through the awareness of feelings and providing vitality, developing empowerment, and building social networks (146). Music can thus be regarded as a kind of 'immunogen' behavior; a health enhancing practice (147).

The results of this study may show evidence for benefits of this music protocol intervention in HF patients, and if the hypothesis is supported, this music intervention may be integrated into the normal care protocol of HF patients, with a very low cost burden and a very simple protocol for use by HF patients.

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Conflict of interest
No conflicts of interest have been declared by the authors.

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Figure and Table legend

Figure 1. The conceptual framework
Figure 2. Psychophysiological changes and HF outcomes
Table 1. Measuring tools for the primary and secondary endpoints