Original Article

Trajectories of Terminally Ill Patients' Cardiovascular Response to Receptive Music Therapy in Palliative Care

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Abstract

Context. Relaxation interventions are frequently used to promote symptom relief in palliative care settings, but little is known about the underlying mechanisms.

Objectives. The present analysis aimed at examining the psychophysiological pathways of terminally ill patients' cardiovascular response to a live music therapy vs. prerecorded mindfulness exercise.

Methods. Eighty-four patients of a palliative care unit were randomly assigned to either of the two interventions. Multilevel modeling was used to analyze trajectories of physiological change. Vagally mediated heart rate variability (VM-HRV) and blood volume pulse amplitude (BVP-A) served as indices of autonomic nervous system response. Participants' gender, age, baseline scores, self-rated pain, and assignment to treatment were entered to the models as predictors.

Results. Both VM-HRV and BVP-A showed significant linear and quadratic trends over time, as well as substantial heterogeneity among individuals' trajectories. Baseline scores, pain, and treatment significantly accounted for random variation in VM-HRV intercepts. BVP-A levels were significantly higher in women than in men. Moreover, assignment to treatment significantly accounted for differences in the linear slopes of peripheral blood flow.

Conclusion. Higher levels of VM-HRV in the music therapy group highlight the importance of a therapeutic relationship for the effectiveness of relaxation interventions in end-of-life care settings. Music therapy caused significantly stronger reductions of vascular sympathetic tone and, therefore, may be indicated in the treatment of pain and stress-related symptoms in palliative care. Initial self-ratings of pain moderated patients' physiological response and need to be taken into account in clinical practice and future theory building. J Pain Symptom Manage 2016;52:196–204.

Key Words
Music therapy, mindfulness, palliative care, randomized controlled trial, multilevel analysis, cancer, pain

Introduction

Over the past several years, the benefits of complementary and alternative therapies have been increasingly recognized in the treatment of advanced malignancies.[1–3] In particular, mindfulness-based (MB) relaxation interventions with and without the use of creative elements such as music and arts showed promising results in improving symptom distress and quality of life.[4–7] However, little is known about the underlying psychophysiological mechanisms that may elicit a relaxation response in terminally ill patients.

The World Health Organization defines palliative care as a multidisciplinary approach "[…] that improves the quality of life of patients and their families facing the problem associated with life-threatening illness."[8] The German classification of procedures recommends the use of music therapy (MT) as an adjunct treatment in palliative care.[9] In contrast to music

The trial was registered by German Clinical Trials Register—DRKS00006137.
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Accepted for publication: January 29, 2016.

0885-3924/$ - see front matter
http://dx.doi.org/10.1016/j.jpainsymman.2016.01.008

medicine or music listening interventions, the definition of MT highlights the importance of the therapeutic relationship and dynamic interactions between patient and therapist.[10] In end-of-life care, MT interventions aim at improving the patients' quality of life by supporting symptom management, enhancing emotion regulation, and communication skills, as well as facilitating spiritual experiences.[11] Today, MT is among the most frequently provided complementary treatments in U.S. hospices[3,12] and receives high acceptance by other health care professionals in the U.K.[13] Interventions typically encompass the use of active techniques (e.g., songs or improvization), as well as receptive techniques such as relaxation or imagery.[14] The latter do not require active physical or musical participation of the patient and, therefore, are very common in work with terminally ill patients.

Although the complementary application of MT has formed an inherent part of palliative cancer care for more than 35 years,[15] to date, only limited evidence on its specific effects is available.[6,16] Empirical investigations showed that MT may improve quality of life[17] and alleviate pain in palliative care patients.[18–21] Furthermore, previous studies reported significant effects on anxiety,[22,23] stress,[24] communication,[25] and spirituality.[26] A recent retrospective analysis suggests that MT may be associated with spiritual support and a decrease of breathing problems.[27] However, the majority of the reported findings stem from studies with high risks of bias.[6,16,28]

Although certain aspects of the concept of mindfulness may be inherent in receptive MT techniques and have been subject to a recent pilot study with breast cancer patients,[29] more research exists on verbal MB interventions. Mindfulness is defined as to pay attention "on purpose, in the present moment, and nonjudgmentally."[30] MB interventions have shown to generally improve health in clinical and nonclinical populations[31,32] and to reduce anxiety, depression, sexual difficulties, stress, and sleep disturbances in various oncological conditions.[4,33,34] However, only few studies included advanced cancer patients or end-of-life care settings. One quasi-randomized study used a prerecorded body scan meditation and found significant improvements in mental and physical health over a period of one month.[5] In a qualitative pilot study, hospice patients reported beneficial effects after participating in mindfulness groups.[35]

The physiological correlates of both short-term MB and receptive MT interventions in resting positions are most likely to be represented by a relaxation response,[36] which is mainly modulated by a shift in the activation patterns of the autonomic nervous system. Contrasting the stress response, a relaxation response is expected to manifest in a reduction in sympathetic arousal and increase in parasympathetic activity.[36,37] Study outcomes that have been commonly used for the operationalization of autonomic nervous system activity were 1) high-frequent (HF) oscillations in the beat-to-beat-intervals of successive heartbeats (i.e., heart rate variability [HRV]) as an index of vagally mediated (VM) cardiac outflow, and 2) the amplitude of peripheral blood flow (blood volume pulse amplitude [BVP-A]) as a measure of sympathetic tone.

Low HRV has proven to be a risk factor for oncological and cardiac diseases[38,39] and is associated with emotional dysregulation.[40–42] In accordance with Porges's polyvagal theory, which emphasizes the role of myelinated vagus fibers in engaging in adaptive, prosocial behavior and in suppressing automated fear and stress responses, high VM-HRV seems to be positively correlated with resilience, social engagement, well-being, and psychological flexibility.[43–45]

Previous studies on apparently healthy participants' cardiovascular response to MB interventions showed significant reductions in heart rate[46–48] and increases in VM-HRV[46–49] and BVP-A.[46] An observational study found evidence for a positive association between HRV and the ability to mindfully regulate one's attention.[50] Fewer studies evaluated the cardiovascular effects of MB interventions for clinical populations. Significant decreases in heart rate and increases in the HF spectrum were reported for chronic pain patients[51] but were not found in myocardial infarction patients.[52]

Evidence on the effects of music on HRV is inconsistent. Clinical trials revealed significant increases in HF variation among preoperative patients undergoing a music listening intervention[53] and in elderly patients with cerebral vascular disease and dementia exposed to live music therapy sessions.[54] A pilot study with female cancer survivors replicated the pattern of decreased heart rate and increased VM-HRV after 2 hours of participating in MT.[55] In female cancer patients undergoing chemotherapy, however, listening to prerecorded monochord sounds led to a significant increase in the LF, but not in the HF spectrum.[56] To our knowledge, no study has yet examined the physiological response of terminally ill cancer patients to music or MT.

The present study was designed to evaluate the efficacy of an MT relaxation intervention in palliative care patients. A prerecorded verbal mindfulness exercise served as an active control group condition.[28] Pre-to-post changes in self-report data and physiological outcomes have been addressed in a previously published article,[57] identifying significant between-group effects on self-reported relaxation, well-being, and fatigue, as well as changes in subjects' physiological state before versus after the intervention. However, preliminary analyses on the individual trajectories revealed significant

heterogeneity in both baseline values and slopes among patients' cardiovascular response, raising the question of how to explain this between-subject variation.

Hence, the present analysis aimed at investigating both individual- and group-level effects of terminally ill patients' cardiovascular response to short-term MT and MB interventions and at examining mechanisms underlying these trajectories of physiological change. Because of the design of the interventions, we hypothesized U- or inverted U-shaped quadratic trends over time for both groups. Because of the personal presence of a therapist and the soothing live music sounds, we predicted a stronger relaxation response to occur in the MT group.

Methods

Study Design and Procedures

The study received institutional review board approval, was entered into the German Clinical Trials Register, and was carried out at St. Vincentius Hospital, Heidelberg between May 2013 and March 2015. A two-arm parallel randomized controlled trial was designed to evaluate and compare the effects of two different relaxation exercises for hospitalized patients in a palliative care unit. Patients were eligible for study participation if they met the following criteria: 1) receiving palliative care, 2) not in the final phase, 3) no cognitive or hearing impairments, 4) no signs of restlessness and agitation, and 5) sufficient understanding of the German or English language.

Patients who were eligible and willing to participate signed informed consent and were randomly assigned to either two sessions of live MT or two sessions of a prerecorded MB exercise, each lasting for a total of 20 minutes. Both a five-minute preintervention and postintervention recording in a resting state enveloped all sessions. During the entire duration (30 minutes), patients lay in a supine position while continuous physiological data were recorded. We used a computer-based, permutated block randomization sequence, which was concealed by use of sequentially numbered, opaque-sealed envelopes. A study assistant who was not involved in providing the interventions carried out randomization and outcome assessment.

The receptive MT intervention was carried out by a professional music therapist and included a brief body scan exercise (3 minutes), a vocal improvization (12 minutes), and a feedback conversation on the patient's experiences (5 minutes). The first 15 minutes were accompanied by improvised musical play on the monochord. The control group (CG) intervention comprised a 20-minute recording of a mindfulness exercise consisting of a standardized body scan and meditation for supine positions,[58] which was provided via headphones. In contrast to the MT session, a study assistant remained silently inside the room. Both interventions did not differ between Sessions 1 and 2. The interventions are fully described in the study protocol.[11]

Outcomes

For purpose of the present analysis, physiological data obtained from photoplethysmography served as a dependent variable. For noninvasive, continuous recordings of participants' physiological response during the interventions, a NeXus blood volume pulse sensor (128sps) was placed on the index fingertip of the nondominant hand, detecting changes in relative peripheral blood flow.[59] The time point of the R-wave was used to extract interbeat intervals between successive heartbeats in milliseconds. HRV parameters were derived for six consecutive time segments of five minutes each.[60] Because of the relatively fast response times of parasympathetic fibers and their close linkage to respiratory rhythms, HF oscillations in interbeat intervals (0.15−0.4 Hz) are mainly attributed to vagal modulation of cardiac outflow.[61] The HF power density in ms^2, therefore, was used as a biomarker of parasympathetic activity.

The amount of peripheral blood flow in the fingertips' capillaries, on the other hand, is predominantly subject to adrenergic innervation by the sympathetic nervous system, leading to tonic vasoconstriction. An increase in BVP-A, therefore, is associated with a reduction in sympathetic arousal. Thus, the mean BVP-A of each five-minute segment was considered an inversely related index of vascular sympathetic tone.[59]

Statistical Analysis

Sample size calculations were adapted for the analysis of covariance models used within the primary analysis[57] and were presented in the study protocol.[11] Baseline characteristics were analyzed with means, standard deviations, frequencies, independent-samples *t*-tests, and χ^2-tests.

Multilevel modeling with the software package HLM 7[62] was used to analyze trajectories of patients' physiological response because different observations in the dependent variable were "nested" within participants, and preliminary analysis revealed substantial between-subject heterogeneity regarding the intercepts and slopes. Two models were calculated for each outcome independently: The first model (M1) included two repeated-measures factors only (TIME and $TIME^2$) and examined, whether mean data of the entire sample showed the expected linear and quadratic trend over time. In addition, HLM detected the amount of random variation between individuals' intercepts, linear, and quadratic slopes.

In case of significant heterogeneity, a second model (M2) was built, including the following set of predictors to account for random variance:

Baseline. Values from the 5-minute segment before the onset of the intervention were considered a covariate to account for between-subject variability in the subsequent trajectories of physiological change.[63,64]

Age and Gender. Previous findings identified a negative relationship between HRV and age. In addition, evidence suggests that HRV indexes are higher in men, whereas differences adapt with increasing age.[65–68] Therefore, participants' age and gender were added as control variables.

Pain. Although the underlying mechanisms are still subject to discussion, several studies showed an association between pain and autonomic arousal.[69–71] Hence, self-ratings of acute pain were assessed before each session via visual analogue scale, 0–10. Pain ratings were expected to moderate the effects.

Treatment. While controlling for the influence of the aforementioned variables, assignment to one of the two treatment groups was added to the model as a predictor. We expected an interaction between individual trajectories and treatment to manifest in stronger increases in parasympathetic activity and stronger decreases in sympathetic arousal in the MT group.

In accordance with procedures from similar studies, each predictor was tested for significant influences on the intercepts, linear, and quadratic trends and was deleted from the model in case of nonsignificant associations.[64,72] Categorical variables were dummy-coded (0/1) and continuous predictors were grand-mean centered.[73] The repeated-measures factors TIME and $TIME^2$ were coded so that "0" concurred with the first interval after the onset of the intervention (labeled in subsequent figures as "0–5 min."). Outcome variables were log-transformed because of skewed distributions in raw data. For each time segment and patient, data were averaged between Sessions 1 and 2. Restricted maximum likelihood was chosen to estimate the model parameters.[73] Type-I error probability was set on $\alpha = 0.05$ for all statistical tests.

Results

Eighty-four patients (60 female, mean age = 63.0 ± 13.4 years) with progressive, life-threatening disease participated in this study; 82 were diagnosed with advanced cancer. No significant differences occurred between treatment arms regarding gender, age, and diagnosis (all $P > 0.05$, Table 1). After removal of erroneous recordings from movement artifacts and low peripheral blood flow, physiological data from 80 (log_BVP-A) and 73 (log_HF) patients were available for statistical analysis. A patient flowchart for physiological outcomes is presented in Figure 1.

Table 1
Baseline Characteristics

Variable	MT ($N = 42$)	CG ($N = 42$)	P^a
Gender (female)[b]	28 (66.7%)	32 (76.2%)	0.33
Age[c]	63.8 (14.1)	62.2 (12.8)	0.59
Diagnosis (Cancer)[b]	41 (97.6%)	41 (97.6%)	1.00

MT = music therapy; CG = control group.
[a]Statistically significant if $P < 0.05$.
[b]Mean, SD, *t*-test.
[c]Frequency, χ^2 test.

First, M1 was built for the trajectories of parasympathetic modulation of heart rate (log_HF). Both a significant negative linear ($P = 0.02$) and positive quadratic fixed effect ($P < 0.001$) were found for the group mean development over time, indicating a U-shaped trajectory on average. Furthermore, as summarized in Table 2, HLM identified significant between-subjects variation regarding the intercepts ($P < 0.001$), linear ($P = 0.003$), and quadratic slopes ($P < 0.001$).

Hence, a second model was built including predictors that accounted for the observed heterogeneity. Regression coefficients and *P*-values are summarized in Table 3. Despite participants' baseline scores ($P < 0.001$), self-ratings of pain showed a marginally significant negative effect on the intercept ($P = 0.055$), and a significant positive effect on the linear slope ($P = 0.003$). Thus, log_HF was initially lower in patients reporting high levels of pain, but the increase in parasympathetic outflow over time was also stronger in these patients. While controlling for baseline and pain, assignment to either of the treatment arms significantly predicted the intercepts of log_HF scores ($P = 0.002$), indicating that log_HF was generally higher in the MT group than in the CG. Modulation of the patients' parasympathetic response by the factors pain and treatment is shown in Figure 2.

Similar model building procedures were applied to the analysis of sympathetic arousal (log_BVP-A). M1 identified a significant positive linear ($P < 0.001$) and negative quadratic trend over time ($P < 0.001$), resulting in an inversely U-shaped mean curve. The mean curve, again, did not adequately represent individual-level trajectories regarding intercepts ($P < 0.001$), linear ($P < 0.001$), and quadratic slopes ($P < 0.001$, Table 2).

Despite the baseline values (all $P < 0.001$), pain, gender, and treatment contributed to the explanation of between-subjects differences. Participants' subjective level of pain significantly affected the linear slopes of log_BVP-A ($P = 0.01$), implying that high ratings of pain led to a slower reduction of sympathetic arousal. Patients' gender explained substantial differences in

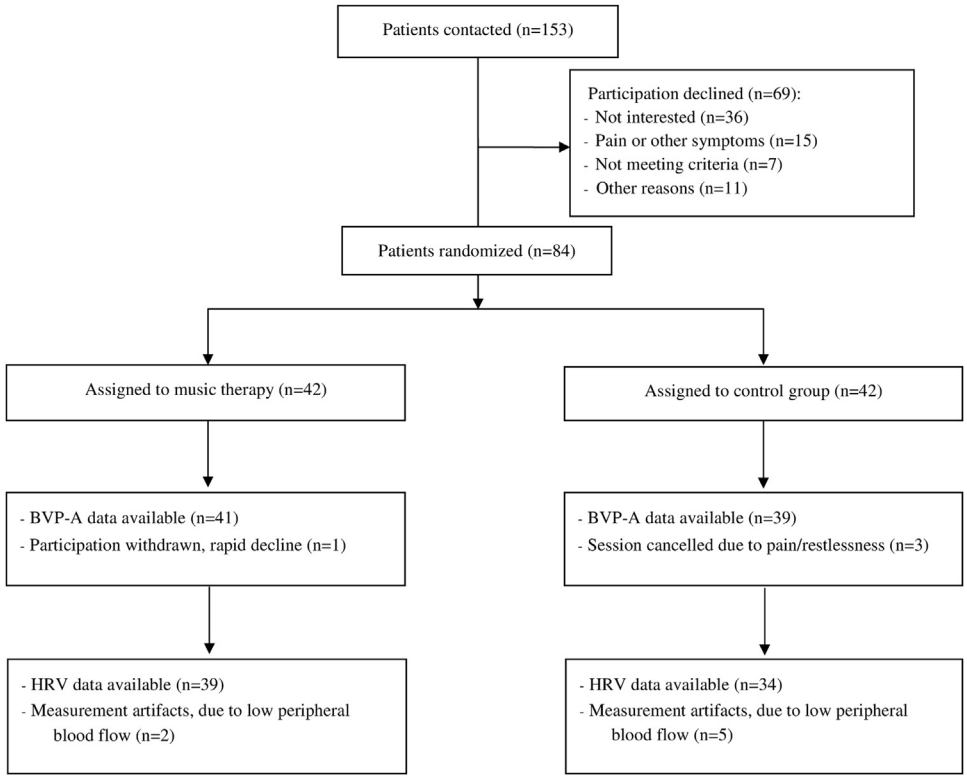

Fig. 1. Patient flowchart. BVP-A = blood volume pulse amplitude; HRV = heart rate variability.

the general intercept of sympathetic arousal ($P = 0.03$), with women showing generally more arousal than men. Allocation to MT vs. CG (treatment) significantly predicted the linear slopes of peripheral blood flow ($P = 0.03$) with stronger increases in the MT group. Figure 3 illustrates the influence of pain and treatment on participants' sympathetic response.

Discussion

Exceeding the scope of previous effectiveness research,[17,18,57] the present findings add important insights to the study of the underlying mechanisms of relaxation and mindfulness techniques for terminally ill patients.

Table 2
Final Estimation of Variance Components (Random Effects)

	Model 1 (M1)				Model 2 (M2)			
Random Effect	Var	χ^2	df	*P*-value	Var	χ^2	df	*P*-value
log_HF								
INTRCPT, r_0	2.812	1235.49	72	<0.001	0.808	395.78	69	<0.001
TIME, r_1	0.127	109.46	72	0.003	0.129	109.61	71	0.002
TIME^2, r_2	0.016	151.97	72	<0.001	0.016	152.29	72	<0.001
Residual, e	0.443				0.196			
log_BVP-A								
INTRCPT, r_0	0.547	7380.88	79	<0.001	0.051	728.17	75	<0.001
TIME, r_1	0.043	489.98	79	<0.001	0.027	333.82	76	<0.001
TIME^2, r_2	0.002	474.90	79	<0.001	0.002	408.80	78	<0.001
Residual, e	0.007				0.007			

Var = variance; df = degrees of freedom; log_BVP-A = log-transformed blood volume pulse amplitude; log_HF = log-transformed high frequency power.

Table 3
Final Estimation of Fixed Effects (M2)

Fixed Effect	Coefficient	SE	*t*-value	df	*P*-value
log_HF					
For INTRCPT, β_0:					
INTRCPT, γ_{00}	4.817	0.147	32.733	69	<0.001
Treatment, γ_{01}	**0.535**	**0.179**	**3.154**	**69**	**0.002**
Baseline, γ_{02}	0.860	0.057	15.141	69	<0.001
Pain, γ_{03}	−0.094	0.048	−1.953	69	0.055
For time, β_1:					
INTRCPT, γ_{10}	−0.168	0.071	−2.347	71	0.022
Pain, γ_{11}	0.030	0.010	3.022	71	0.003
For time^2, β_2:					
INTRCPT, γ_{20}	0.072	0.020	3.575	72	<0.001
log_BVP-A					
For INTRCPT, β_0:					
INTRCPT, γ_{00}	3.531	0.050	70.314	75	<0.001
Treatment, γ_{01}	−0.005	0.048	−0.100	75	0.921
Gender, γ_{02}	0.103	0.047	2.197	75	0.031
Baseline, γ_{03}	0.932	0.038	24.793	75	<0.001
Pain, γ_{04}	0.012	0.011	1.059	75	0.293
For time, β_1:					
INTRCPT, γ_{10}	0.088	0.022	3.963	76	<0.001
Treatment, γ_{11}	**0.030**	**0.014**	**2.227**	**76**	**0.029**
Baseline, γ_{12}	−0.164	0.029	−5.685	76	<0.001
Pain, γ_{13}	−0.008	0.003	−2.556	76	0.013
For time^2, β_2:					
INTRCPT, γ_{20}	−0.026	0.006	−4.628	78	<0.001
Baseline, γ_{21}	0.027	0.008	3.552	78	<0.001

M2 = model 2; SE = standard error; df = degrees of freedom; log_HF = log-transformed high frequency power.
Bold text indicates significant effects of treatment allocation.

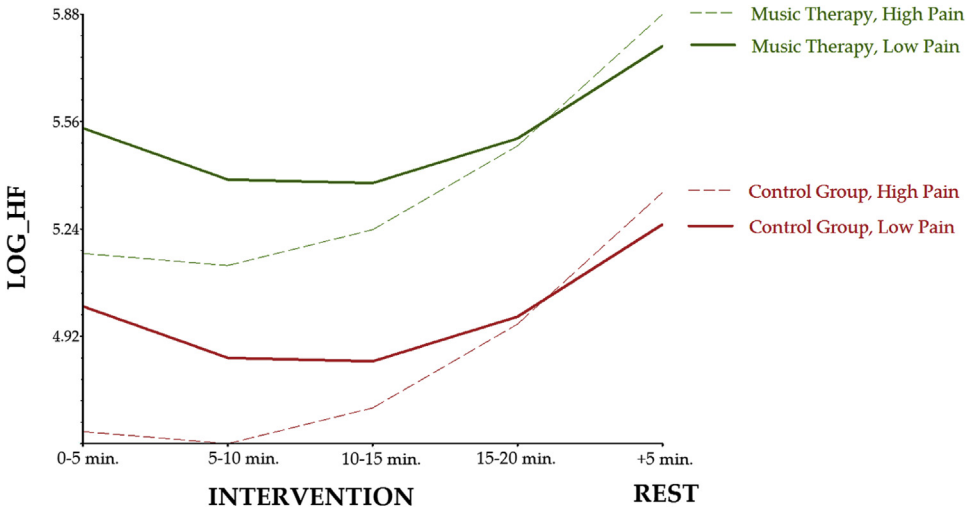

Fig. 2. Predicted values of log_HF modulated by treatment and pain (controlling for baseline scores). Group = treatment; High Pain = 2 points above average; log_HF = log-transformed high frequency power; Low Pain = 2 points below average.

VM-HRV was examined as a biomarker of parasympathetic cardiac outflow. Regarding the entire sample (M1), trajectories of change were not in the predicted direction, as with the beginning of the interventions, VM-HRV was initially reduced. With the progression of the treatment, the slopes became more positive, exceeding the initial values at the end of the session (Fig. 2). This finding contradicts the assumption of a simple, linear relation between the relaxation response and parasympathetic activity. Some authors argued that a state of subjective relaxation may rather be related to a general decrease in cardiac outflow with a relative shift toward parasympathetic dominance.[49,74] The psychophysiological interpretability of alternative HRV indices such as the frequency ratios, however, has been subject to controversial discourse.[49,63,75]

Clinically relevant inferences can be drawn from predictor analysis. Subjective ratings of acute pain significantly interacted with the linear slopes of VM-HRV. Interestingly, the positive linear slope over the entire duration of a session was more positive, if patients initially reported higher levels of pain (Fig. 2). This means that baseline differences in VM-HRV caused by pain can be compensated by use of MT and MB interventions.

The type of treatment did not affect the slopes of the parasympathetic response. However, the level of VM-HRV was generally higher during the MT than during MB sessions. This finding is consistent with Porges's polyvagal theory, as one major difference between the two interventions was the presence of a therapeutic interaction in the MT group. Although the number of persons inside the patient's room was held constant across conditions, the therapeutic skills and both verbal and nonverbal communication initiated by the music therapist may have driven the patients to engage in prosocial behavior, resulting in increased vagal modulation of cardiac activity.[45,61]

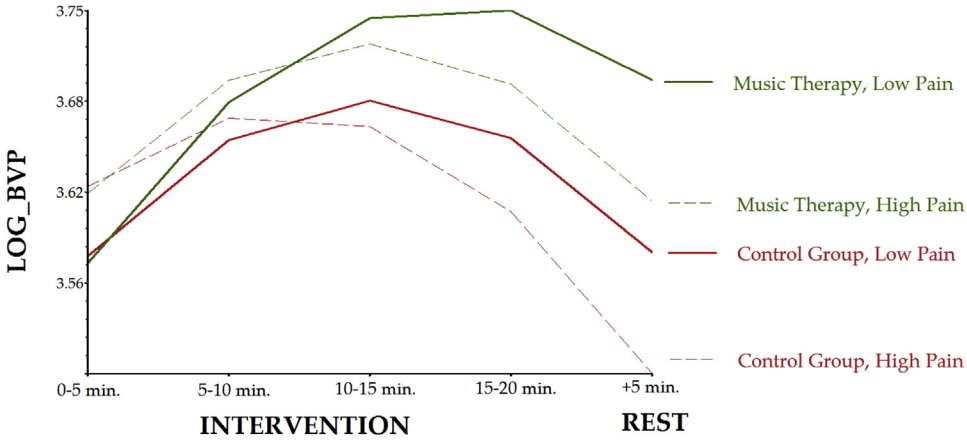

Fig. 3. Predicted values of log_BVP-A modulated by treatment and pain (controlling for baseline scores and gender). Group = treatment; High Pain = 2 points above average; log_BVP-A = log-transformed blood volume pulse amplitude; Low Pain = 2 points below average.

Regarding sympathetic vascular tone, baseline values had a strong influence on the entire shape of each individual's response curve. Furthermore, BVP-A intercepts differed by gender, with women's levels of sympathetic arousal being significantly higher throughout the entire session. This corresponds to previous metaanalytic findings of women reporting a higher level of distress in the course of a cancer progression.[76]

Self-ratings of acute pain moderated the trajectories of sympathetic tone. With higher scores on the visual analogue scale, the reduction of sympathetic tone was less pronounced. Hence, although even patients with high levels of pain showed the expected inversely U-shaped time course (Fig. 3), patients with lower levels benefited more from the interventions regarding the reduction of sympathetic arousal.

While controlling for baseline differences, gender, and pain, the linear slopes differed significantly between treatment arms. Confirming the hypothesis, the average increase in peripheral blood flow was significantly higher in the MT group compared to the CG. This difference in the patients' growth rate can be interpreted as direct evidence for the stress-reducing effect of the MT relaxation intervention, which differed from the MB intervention in the live played soothing sounds of the monochord, vocal improvization synchronized with the patients breathing, and the building of a therapeutic relationship.

Methodological limitations of the present study encompass the lack of outcome assessor blinding and the missing of a no-treatment condition. Furthermore, although the use of a photoplethysmography sensor causes significantly lower patient burden, it also carries the disadvantage of lower sampling rate compared to common electrocardiogram recordings. Hence, future studies may address these issues in subsequent designs making further use of the rapidly developing methods for minimally invasive, physiological measurements.

The present study presents results of hierarchical linear modeling of objective, physiological data from a randomized controlled trial on the effects of MT intervention in palliative care. First, results highlight the importance of a therapeutic relationship for both an increase in VM-HRV and a reduction of sympathetic arousal, and thus, speak in favor of the application of live MT over, for example, music listening or music medicine interventions in end-of-life-care settings. Second, specific characteristics of the receptive MT intervention used in this study caused significant reductions of vascular sympathetic tone. Hence, the study presents evidence for an indication of MT in the treatment of pain and stress-related symptoms in palliative care. Finally, self-rated levels of acute pain proved to be an important moderator in explaining individual differences in the physiological response to relaxation interventions.

Disclosures and Acknowledgments

No funding was received for this study and the authors declare no conflicts of interest.

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