Hemodynamic and stress response after sound intervention with different headphone systems: A double-blind randomized study in healthy volunteers

Anna Hohneck [1,2], Christina Reyser [3], Rimma Usselmann [3], Lara Heinemann [3], Simone Weingärtner [3], Hardy Reckling [4], Gerhard Schumacher [5], Iris Burkholder [6], Kirsten Merx [3], Wolf Karsten Hofmann [3], Ralf-Dieter Hofheinz [3]

[1] Department of Cardiology, Angiology, Haemostaseology and Medical Intensive Care, University Medical Centre Mannheim, Medical Faculty Mannheim, Heidelberg University, Germany
[2] European Center for AngioScience (ECAS) and German Center for Cardiovascular Research (DZHK) partner site Heidelberg/Mannheim, Mannheim, Germany
[3] Department of Hematology and Oncology, University Medical Centre Mannheim, Heidelberg University, Mannheim, Germany
[4] Corporate health management, University Medical Centre Mannheim, Medical Faculty Mannheim, Heidelberg University, Germany
[5] inmediQ GmbH, Butzbach, Germany
[6] StaBiL Statistical and Biometric Solutions, Zweibrücken, Germany

ABSTRACT

Aim The present double-blind randomized study investigates the effects of a sound intervention on cardiovascular parameters, indicators of stress and subjective feelings. Two headphone systems using different sound systems are compared within this trial.

Methods Hundred volunteers reporting elevated stress levels participated in the study between July and September 2020. Participants were randomized to a 12-minute sound intervention (classical music) with either conventional headphones (CH; "MEZE 99 Classic") or with the same – but internally modified – headphone (called *"Lautsaenger"*). Cardiovascular parameters were measured with the VascAssist2.0, both before (pre) and after (post) sound interventions. In addition, participants were asked to complete questionnaires on burnout risk (modified Maslach Burnout Inventory, MBI) and emotions /stress.

Results The study population consisted mainly of female participants (n=83), with the majority being students (42%). Median age was 32.5 years (range 21 – 71). According to the MBI, eight participants showed indices for an elevated burnout risk.

In terms of objective measurements with VascAssist 2.0, each treatment arm led to a significant reduction of aortic pulse wave velocity and heart rate, while heart rate variability remained unaffected. A significant reduction in resistance index (median reduction, -1.7, $p = 0.0008$) and vascular age as a combined variable (median reduction -2.3 years, $p = 0.02$) was only documented with Lautsaenger. Treatment groups were comparable in terms of subjective feedback by participants: a significant increase in emotional well-being was achieved with both headphone systems. Likewise, significant improvements were also noted for anxiety, sadness and the reduction of anger.

Conclusion

Healthy volunteers reporting subjective symptoms of stress achieved objective cardiovascular improvements after a single short term sound intervention, using two different headphone systems in this double-blind randomized trial. Moreover, significant emotional improvement was reported within both arms. Our results indicate additional benefit in terms of "vascular age" and resistance index with the "Lautsaenger" system.

INTRODUCTION

In a fast-moving, performance-driven world almost everyone faces some degree of stress. However, when stress becomes a permanent condition, it contributes to the onset and progression of a range of physical and emotional chronic disorders, such as cardiovascular diseases [1], anxiety [2], depression [3] or burnout [4]. Stress is not only a catalyst for psychological diseases and impacts emotional functions[5]. Hemodynamic parameters, such as heart rate variability (HRV) [6] or pulse wave velocity (PWV)[7], which are objectively measurable, can also be affected by mental stress.

In addition to conventional therapeutic approaches, such as psychotherapy or the administration of tranquillizers, integrative therapies are becoming more and more important to reduce the harmful effects of chronic stress [8]. For centuries, people have listened to music to regain energy and find relaxation. The stress reducing qualities of music and sound interventions are well documented [8–10] and are therefore increasingly being used to reduce stress and enhance emotional and physical well-being [11,12]. Generally, sound interventions are distinguished from classical music therapy, which represents an interaction of a music therapist and a client / patient using music or sound as a therapeutic measure [13]. The term sound intervention comprises a range of different methods from passive music listening to active practice such as singing or playing an instrument. While classical music therapy focuses not only on the music / sound, but also on the interaction with the therapist and reflective discussions, the advantage of passive interventions such as listening to music is the inherent standardization and thus better comparability, especially within the framework of clinical trials [14,15].

In the present randomized double-blind study we investigated the effects of a standardized sound intervention on cardiovascular parameters, indicators of stress and subjective feelings. We were especially interested in elucidating differential effects on hemodynamic and stress parameters using two identically shaped headphone systems with different sound generation systems.

METHODS

Study design and setting

This study was performed at the University Medical Centre Mannheim, University of Heidelberg, Germany. It was designed as a double-blind study randomizing healthy volunteers with subjective stress to a 12-minute sound intervention with either of two commercially available headphone systems. Recruitment started in July 2020 and ended in September 2020. Patients were not followed up.

The study was conducted according to the principles of the declaration of Helsinki and was approved by the local ethical committee, Medical Ethics Commission II, Faculty of Medicine Mannheim, University of Heidelberg, Germany (2019-736N). Data protection was in accordance with the EU Data Protection Directive.

Material and Methods

Study population

Hundred individuals > 18 years exposed to elevated stress levels consented to participate in this study between July 2020 and September 2020. The study was featured by the corporate health management at the University Medical Centre Mannheim and was primarily addressed to employees and students.

Exclusion criteria comprised serious hearing impairment, acute coronary syndrome or stroke within 4 weeks before study participation, planned bypass surgery, dependence on pacemaker, cardiac arrhythmia (e. g. atrial fibrillation, sick-sinus-syndrome, sinoatrial / atrioventricular block), uncontrolled hypertension or severely low blood pressure (< 90/50 mmHg) and breast cancer with bilateral axillary dissection.

Questionnaires

Baseline demographic characteristics (age, gender, weight, height, etc.) were collected from all study participants. In addition, participants were asked to fill in two questionnaires, of which one part was filled in before (pre) and another part after (post) the sound intervention. Using a numeric rating scale (NRS) information on emotions and stress were obtained *before* and *after* the sound intervention (emotional well-being, pain, anger, anxiety, sadness, stress, music for coping stress). The NRS indicates a continuum ranging from 0 to 100, where 0 represents no correlation and 100 the maximum extent. A modified Maslach Burnout

Inventory (MBI), which is an established tool to assess the burnout risk was completed *before* the sound intervention [16] .

Furthermore, a NRS was also used *after* the sound intervention to assess subjective sound perception and to what extent listening stimulated the imagination. In addition, dichotomous questions were used to evaluate the headphone systems in particular. Compare **Figure 1** "Study design".

Sound intervention

Patients were randomized to a sound intervention with either of two different commercially available headphones, one with conventional sound generation technique (conventional headphone, CH; "MEZE 99 Classic"), and one with an internally modified "MEZE 99 Classic" headphone. The latter called "Lautsaenger" uses a special technique generating centripetal force to generate sound. This underlying technique is based on research results from cymatics. Cymatics analyze sound by applying basic principles of wave mechanics [17]. According to the manufacturer, special cymatic organs are integrated into the "MEZE 99 Classic" headphone to produce a more vibrant sound [18].

The two headphone systems did not differ in appearance, and both, participants and investigators, were blinded to the type of headphone allocated after randomization. A 12-minute music compilation of relaxing music (Débussy – Clair de lune and Pyotr Tchaikovsky – Andate cantabile (arranged for Violoncello) from string Quartett No.1, Opp.11) was played through both headphone systems.

Cardiovascular parameters

Cardiovascular parameters were assessed non-invasively using the VascAssist2.0 device (inmediQ GmbH, Butzbach, Germany) after a 10-minute resting phase before and after the sound intervention and evaluated both for the total population and separately according to the type of headphones. The VascAssist2.0 is based on a refined multicompartment model of the arterial system, providing an individualized transfer function giving realistic pulse waveforms [19]. In addition to vital parameters (heart rate, brachial blood pressure), the VascAssist2.0 is able to determine PWV as direct measure of arterial stiffness and risk factor for cardiovascular disease, central (aortic) blood pressure and augmentation index (Aix; also a marker for arterial stiffness and determinant of central hemodynamics) through pulse wave

analysis [20–22]. Moreover, the root mean square of successive differences between normal heartbeats (RMSSD) as HRV metric and stress indicator is captured [23]. Beyond that, resistance index, compliance index and the vascular age, which is a combined variable (composed of the calendrical age, compliance and resistance) are provided, but have not yet been validated. The resistance and compliance index both reflect vascular properties. Compliance is the equivalent of vascular elasticity, whereas an increased resistance index indicates an increased arterial flow resistance.

Outcomes and Statistical analysis

This exploratory study tested no formal hypothesis. We sought to describe the subjective and objective impact of the 12-minute sound intervention on cardiovascular parameters and subjectively reported stress symptoms regarding the whole group of participants. Moreover, we were interested in comparing both arms / headphones with regard to potential different outcomes as a basis for further confirmatory comparative trials.

Quantitative characteristics were evaluated using statistical parameters (N, arithmetic mean, standard deviation, median, minimum and maximum) and qualitative characteristics were evaluated in the form of frequency tables. Demographic and other characteristics at baseline were analyzed descriptively both for the total population and separately by type of headphone. Data from the MBI were presented descriptively. In addition, the association with gender, profession, sleep problems, regular physical activity and age were examined. For this purpose, contingency tables were created and the chi-square test or Fisher's exact test was used for explorative analysis.

Cardiovascular parameters were measured before and after the sound intervention and evaluated both for the total population and separately according to the type of headphones.

Mann-Whitney-U test was used for quantitative characteristics and the chi-square test or Fisher's exact test for qualitative characteristics. The comparison between different measurements within the two groups was made using the Wilcoxon signed-rank test. The results were visualized with the help of grouped boxplots per parameter and measurement time.

All statistical analyses were performed with SAS 9.4. (SAS Institute Inc., North Carolina). Statistical significance was assumed at $p< 0.05$.

RESULTS

Baseline characteristics.

The study population consisted mainly of female participants (83 female, 17 male), with the majority of the participants being students (42 %). Median age was 32.5 years (range 21 – 71). 28 % were married and 34 % reported having children.

Only one person indicated hearing difficulties, while 29 of the study participants reported sleeping problems. Medication was taken by 39 patients and 72 respondents reported to exercise regularly. The preferred music genre was most often pop (66.0 %), followed by rock (37.0 %) and classical music (34.0 %).

In total, 8 patients were diagnosed with a burnout risk based on the MBI. The most frequent symptoms were reduced performance in 31 study participants, followed by emotional exhaustion in 22 respondents. Female patients were more likely to report symptoms of depersonalization.

Participant´s data were well balanced with the exception of a higher percentage of nursing staff in the Lautsaenger group ($p = 0.051$), and an imbalance in terms of increased risk for burnout (CH 2 % vs Lautsaenger 14 %, $p = 0.03$).

Complete baseline characteristics are shown in **Table 1**.

Cardiovascular parameters.

Cardiovascular parameters were assessed using the VascAssist before (pre) and after (post) the sound intervention (**Table 2**).

Heart rate was lowered by both headphone systems ($p < 0.001$), which resulted in an increase in Aix (%) (CH $p < 0.001$, Lautsaenger $p = 0.02$), while sound intervention with Lautsaenger additionally led to a slight but significant reduction in systolic blood pressure (median reduction -1.5 mmHg, $p < 0.01$). Moreover, Lautsaenger was able to reduce the resistance index (pre median 22.1 (range 6.6 – 74.0) vs post (median 19.0 (range 8.0 – 63.9), $p = 0.0008$). Sound intervention with both headphone systems led to a significant reduction of aortic PWV (CH $p < 0.001$, Lautsaenger $p = 0.0003$) (**Figure 2**). The vascular age as a combined variable was only influenced by Lautsaenger (median reduction -2.3 years, $p = 0.02$). No effects on RMSSD as HRV metric could be detected.

Emotions and stress.

An increase in emotional well-being could be achieved by sound intervention with both headphone systems ($p < 0.001$), whereas significantly fewer subjects reported anger (CH $p < 0.001$, Lautsaenger $p = 0.0001$). A significant improvement was also achieved for anxiety ($p < 0.001$) and sadness (CH $p = 0.0003$, Lautsaenger $p = 0.0007$). Median pain levels were low, considering the NRS range from 0–100, with 5 for CH and 6.5 for Lautsaenger, and consequently no effects could be demonstrated in either treatment arm on pain levels. Almost all subjects reported a reduction in stress after the sound intervention ($p < 0.001$), regardless of the headphone system (**Figure 3**). The study participants were asked to indicate whether music helps them to cope with stress. After the intervention, almost all participants marked higher values on the NRS ($p < 0.001$). This effect was also independent of the headphone system.

Detailed information on emotions and stress is depicted in **Table 3**.

Subjective sound perception and rating of the headphones.

The characteristics of the second part of the questionnaire were evaluated descriptively and are summarized in **Supplemental Table ST1**. Overall, only marginal differences between the two headphone systems were observed.

For fantasy stimulation and size of the room, the study participants reported median values above 60 (imagination median 65.0 (range 2 – 100); size of the room median 63.0 (range 9 – 100). A total of 5 patients stated that the sound was not natural and 3 patients did not find the sound pleasant. A total of 4 patients reported a feeling of pressure. The vast majority of paticipants indicated they would recommend the headphone systems with a slightly higher number in the Lautsänger group (90% vs 82%, n.s.). A total of 37 study participants were familiar with the piece of music.

DISCUSSION

Music listening and especially intended listening of relaxation music can reduce stress with affecting the endocrine and autonomic stress system [24]. Stress has the potential to be a major health threat and promote the development of mental illnesses such as burnout [25,26]. In the described cohort, consisting of healthy individuals, a high proportion of burnout symptoms was found (8 %). Compared to the prevalence in the general population, this was almost twice as high [27]. Besides the mental health burden and consequences for quality of life, burnout is associated with adverse physical health and an increased risk for cardiovascular events [28,29]. The underlying mechanism is thought to be a dysregulation of the autonomic nervous system, with sustained enhanced sympathetic activity and reduced parasympathetic activity [30]. HRV can serve as measure of autonomic function. While heart rate was lowered by both headphone systems, HRV remained unchanged. Other studies have shown positive effects of music therapy on stress reduction and HRV in healthy individuals [31–33] as well as in cancer patients [34–36]. One reason for this could be that cancer patients have a higher likelihood of pathological HRV and thus a higher potential for improvement than do stress patients. Furthermore, in the present study, the participants received only a single brief intervention. Another difference could be the type of intervention. We used recorded music, which was played over headphones, while in part of the mentioned studies live music with a monochord was applied. So far, there are only a few studies comparing live music and recorded music, with divergent findings [37–39]. A positive effect on HRV was described by Shoda et al. only for live performance [40]. One reason for this could be a direct response of the limbic system or the interaction between music therapist and patient, which allows a customization of the therapy to the individual needs [41,42]. Especially in times of social distancing with limited possibilities for musicians to perform live, these aspects become even more important.

We were able to demonstrate an increase in emotional well-being as well as stress reduction prompted by music intervention in our cohort. Similar to HRV, positive effects for pain reduction by music therapy in cancer patients have been described [43]. However, the median pain level in our cohort was low, so there is also little potential for improvement. In addition to heart rate, PWV, as marker for arterial stiffness, was lowered by both headphone systems. This is consistent with the findings of Vlachopoulos et al. [44]. An increased PWV is an independent marker of cardiovascular risk and thus has prognostic relevance [45]. The

resistance index, which measures arterial flow resistance on the other hand, and vascular age, as a combined variable, were only influenced by the Lautsaenger system. The relationship between flow, differential pressure and vascular resistance is described in physical terms by Ohm's law. The vascular resistance is dynamically controlled by the vascular smooth muscles. Relaxing of these muscle cells leads to vasodilation which again decreases vascular resistance [46]. Since there were no measurable effects on the resistance index with CH, it might be speculated that Lautsaenger leads to a deeper relaxation. This could also be supported by the fact that CH did not affect peripheral blood pressure, while a slight but significant reduction in systolic blood pressure was observed with Lautsaenger. No changes were observed in terms of aortic blood pressure. An increase in Aix, which is also a marker for arterial stiffness and a determinant of central hemodynamics, was found in both treatment arms. This is physiological because the Aix is directly dependent on heart rate and a reduction in heart rate leads to an increase in Aix [47]. Presumably, the increase in Aix is only a brief maladaptive response, outweighed by beneficial effects on heart rate and vascular stiffness. Although we were able to demonstrate positive effects after a single intervention, regardless of the headphone system, we cannot answer whether they are long-lasting. This problem needs to be addressed in further clinical investigations.

The modified sound generation by centripetal forces is a novel technology [18]. The intention of the Lautsaenger is not a further improvement of previous loudspeaker technology, but the creation of a living sound, equivalent to a musical instrument or live performances. No differences were found in our cohort with regard to subjective sound perception or the rating of the two headphone systems. For example, just as many subjects would recommend the Lautsaenger as the CH to others. Man has a penchant for habits. This is also expressed in the evaluation of music. In a case study in which Schumann's *Träumerei* was interpreted by 13 different pianists, the most "average" durational expressions were evaluated best [48]. This can be observed especially for well-known pieces of music. Thus, nominally more patients with CH than with Lautsanger indicated that they would use music for coping stress, presumably due to the more familiar sound experience with CH.

Limitations

Participants in this study received only a single brief intervention. Thus, the duration and frequency of the intervention might have been too short to demonstrate effects on physiological parameters such as HRV. Data were skewed in terms of the rate of participants with burnout risk favoring the group using conventional headphones. This imbalance could have been avoided by using an individual cross-over study design. Likewise, a cross-over design would have allowed a thorough individual evaluation of both headphone systems. However, as this study was not planned for formal comparison purposes, this was beyond the scope of our study.

CONCLUSION

In this double-blind randomized trial of healthy volunteers reporting subjective symptoms of stress, a relatively high proportion of burnout symptoms was observed. A single short-term sound intervention using two different headphone systems was able to improve cardiovascular parameters, that have prognostic relevance as risk markers for cardiovascular diseases. In addition, a reduction in stress with an increase in emotional well-being could be achieved within both arms. Our results indicate additional benefit in terms of “vascular age” and resistance index, which could only be observed with the “Lautsaenger” system, possibly due to a deeper relaxation.

REFERENCES

1. Kivimäki, M. & Steptoe, A. Effects of stress on the development and progression of cardiovascular disease. *Nat Rev Cardiol* **15**, 215–229 (2018).
2. Patriquin, M. A. & Mathew, S. J. The Neurobiological Mechanisms of Generalized Anxiety Disorder and Chronic Stress. *Chronic Stress* **1**, 247054701770399 (2017).
3. Hammen, C. Stress and Depression. *Annu. Rev. Clin. Psychol.* **1**, 293–319 (2005).
4. Lin, S.-H. & Huang, Y.-C. Life stress and academic burnout. *Active Learning in Higher Education* **15**, 77–90 (2014).
5. Wang, M. & Saudino, K. J. Emotion Regulation and Stress. *J Adult Dev* **18**, 95–103 (2011).
6. Kim, H.-G., Cheon, E.-J., Bai, D.-S., Lee, Y. H. & Koo, B.-H. Stress and Heart Rate Variability: A Meta-Analysis and Review of the Literature. *Psychiatry Investig* **15**, 235–245 (2018).
7. Kong, J. O. *et al.* Relationship between Job Stress and Pulse Wave Velocity as a Cardiovascular Risk Factor. *Korean J Occup Environ Med* **16**, 450 (2004).
8. de Witte, M. *et al.* Music therapy for stress reduction: a systematic review and meta-analysis. *Health Psychology Review* **0**, 1–26 (2020).
9. Hanser, S. B. Music Therapy and Stress Reduction Research. *Journal of Music Therapy* **22**, 193–206 (1985).
10. Juslin, P. N. & Västfjäll, D. Emotional responses to music: The need to consider underlying mechanisms. *Behavioral and Brain Sciences* **31**, 559–575 (2008).
11. Kemper, K. J. & Danhauer, S. C. Music as Therapy. *Southern Medical Journal* **98**, 282–288 (2005).
12. Koelsch, S. Music-evoked emotions: principles, brain correlates, and implications for therapy: Functional neuroanatomy of music-evoked emotions. *Ann. N.Y. Acad. Sci.* **1337**, 193–201 (2015).
13. de Witte, M., Spruit, A., van Hooren, S., Moonen, X. & Stams, G.-J. Effects of music interventions on stress-related outcomes: a systematic review and two meta-analyses. *Health Psychology Review* **14**, 294–324 (2020).
14. Robb, S. L., Carpenter, J. S. & Burns, D. S. Reporting Guidelines for Music-based Interventions. *J Health Psychol* **16**, 342–352 (2011).
15. Bradt, J. Randomized Controlled Trials in Music Therapy: Guidelines for Design and Implementation. *Journal of Music Therapy* **49**, 120–149 (2012).
16. Maslach, C. & Jackson, S. E. The measurement of experienced burnout. *Journal of Organizational Behavior* **2**, 99–113 (1981).
17. Jin Oh, Y. Experimental Study of Cymatics. *IJET* **4**, 434–436 (2012).
18. Lautsänger | Kymatik | Hirschhorn. *lautsaenger.com* https://www.lautsaenger.com.
19. Schumacher, G., Kaden, J. J. & Trinkmann, F. Multiple coupled resonances in the human vascular tree: refining the Westerhof model of the arterial system. *Journal of Applied Physiology* **124**, 131–139 (2018).
20. Weber, T. Grundlagen: Zentraler Blutdruck, Pulswellenreflexion, Pulswellengeschwindigkeit. *Journal für Hypertonie - Austrian Journal of Hypertension* **14**, 9–13 (2010).
21. Massmann, A. *et al.* Automated oscillometric blood pressure and pulse-wave acquisition for evaluation of vascular stiffness in atherosclerosis. *Clin Res Cardiol* **106**, 514–524 (2017).
22. Trinkmann, F. *et al.* Automated Noninvasive Central Blood Pressure Measurements

by Oscillometric Radial Pulse Wave Analysis: Results of the MEASURE-cBP Validation Studies. *American Journal of Hypertension* **34**, 383–393 (2021).
23. Li, Z. *et al.* A longitudinal study in youth of heart rate variability at rest and in response to stress. *International Journal of Psychophysiology* **73**, 212–217 (2009).
24. Linnemann, A., Ditzen, B., Strahler, J., Doerr, J. M. & Nater, U. M. Music listening as a means of stress reduction in daily life. *Psychoneuroendocrinology* **60**, 82–90 (2015).
25. Plieger, T., Melchers, M., Montag, C., Meermann, R. & Reuter, M. Life stress as potential risk factor for depression and burnout. *Burnout Research* **2**, 19–24 (2015).
26. Shadid, A. *et al.* Stress, Burnout, and Associated Risk Factors in Medical Students. *Cureus* **12**, e6633.
27. Maske, U. E., Riedel-Heller, S. G., Seiffert, I., Jacobi, F. & Hapke, U. [Prevalence and Comorbidity of Self-Reported Diagnosis of Burnout Syndrome in the General Population]. *Psychiatr Prax* **43**, 18–24 (2016).
28. Williams, J. E. *et al.* Vital Exhaustion as a Risk Factor for Adverse Cardiac Events (from the Atherosclerosis Risk In Communities [ARIC] Study). *The American Journal of Cardiology* **105**, 1661–1665 (2010).
29. Melamed, S., Shirom, A., Toker, S., Berliner, S. & Shapira, I. Burnout and risk of cardiovascular disease: Evidence, possible causal paths, and promising research directions. *Psychological Bulletin* **132**, 327–353 (2006).
30. Schwartz, A. R. *et al.* Toward a Causal Model of Cardiovascular Responses to Stress and the Development of Cardiovascular Disease: *Psychosomatic Medicine* **65**, 22–35 (2003).
31. Teckenberg-Jansson, P. *et al.* Effects of live music therapy on heart rate variability and self-reported stress and anxiety among hospitalized pregnant women: A randomized controlled trial. *Nordic Journal of Music Therapy* **28**, 7–26 (2019).
32. Latha, R., Srikanth, S., Sairaman, H. & Dity, N. E. Effect of music on heart rate variability and stress in medical students. *International Journal of Clinical and Experimental Physiology* **1**, 131–131 (2014).
33. Chennafi, M., Khan, M. A., Li, G., Lian, Y. & Wang, G. Study of Music Effect on Mental Stress Relief Based on Heart Rate Variability. in *2018 IEEE Asia Pacific Conference on Circuits and Systems (APCCAS)* 131–134 (2018). doi:10.1109/APCCAS.2018.8605674.
34. Hohneck, A. *et al.* Differential Effects of Sound Intervention and Rest on Cardiovascular Parameters in Cancer Patients: A Randomized Cross-over Trial. *Integr Cancer Ther* **20**, 153473542199523 (2021).
35. Chuang, C.-Y., Han, W.-R., Li, P.-C. & Young, S.-T. Effects of music therapy on subjective sensations and heart rate variability in treated cancer survivors: A pilot study. *Complementary Therapies in Medicine* **18**, 224–226 (2010).
36. Lee, E.-J. & Bhattacharya, J. Heart Rate Variability During Monochord- Induced Relaxation in Female Patients With Cancer Undergoing Chemotherapy. *Music and Medicine* **5**, 177–186 (2013).
37. Holmes, C., Knights, A., Dean, C., Hodkinson, S. & Hopkins, V. Keep music live: music and the alleviation of apathy in dementia subjects. *International Psychogeriatrics* **18**, 623–630 (2006).
38. Horne, -Thompson Anne & Bolger, K. An Investigation Comparing the Effectiveness of a Live Music Therapy Session and Recorded Music in Reducing Anxiety for Patients with Amyotrophic Lateral Sclerosis / Motor Neurone Disease. *Australian Journal of Music Therapy* **21**, 23–38.
39. Swarbrick, D. *et al.* How Live Music Moves Us: Head Movement Differences in Audiences to Live Versus Recorded Music. *Frontiers in Psychology* **9**, (2019).

40. Shoda, H., Adachi, M. & Umeda, T. How Live Performance Moves the Human Heart. *PLOS ONE* **11**, e0154322 (2016).
41. Frühholz, S., Trost, W. & Grandjean, D. The role of the medial temporal limbic system in processing emotions in voice and music. *Progress in Neurobiology* **123**, 1–17 (2014).
42. Bradt, J., Dileo, C., Magill, L. & Teague, A. Music interventions for improving psychological and physical outcomes in cancer patients. *Cochrane Database of Systematic Reviews* (2016) doi:10.1002/14651858.CD006911.pub3.
43. Li, Y. *et al.* The effectiveness of music therapy for patients with cancer: A systematic review and meta-analysis. *Journal of Advanced Nursing* **76**, 1111–1123 (2020).
44. Vlachopoulos, C. *et al.* Music decreases aortic stiffness and wave reflections. *Atherosclerosis* **240**, 184–189 (2015).
45. Safar, M. E., Henry, O. & Meaume, S. Aortic Pulse Wave Velocity: An Independent Marker of Cardiovascular Risk. *The American Journal of Geriatric Cardiology* **11**, 295–304 (2002).
46. Delong, C. & Sharma, S. Physiology, Peripheral Vascular Resistance. in *StatPearls* (StatPearls Publishing, 2022).
47. Williams, B., Lacy, P. S. & null, null. Impact of Heart Rate on Central Aortic Pressures and Hemodynamics. *Journal of the American College of Cardiology* **54**, 705–713 (2009).
48. Shoda, H. & Adachi, M. Why live recording sounds better: a case study of Schumann's Träumerei. *Frontiers in Psychology* **5**, (2015).

TABLES

Table 1. Baseline characteristics

	All patients n=100	CH n=50	Lautsaenger n=50	p-value CH vs Lautsaenger
Sex, female (%)	83 (83.0)	39 (78.0)	44 (88.0)	0.18
Age, years	32.5 (21.0; 71.0)	32.0 (21.0; 71.0)	33.0 (21.0; 63.0)	0.21
BMI (kg/m^2)	22.9 (18.5; 49.6)	24.4 (18.5; 49.6)	22.4 (18.5; 38.8)	0.09
Profession				
Student	42 (42.0)	24 (48.0)	18 (36.0)	0.23
Physician	7 (7.0)	2 (4.0)	5 (10.0)	0.24
Nursing staff	15 (15.0)	4 (8.0)	11 (22.0)	0.051
Administration	18 (18.0)	9 (18.0)	9 (18.0)	1.00
Others	18 (18.0)	11 (22.0)	7 (14.0)	0.30
Married, yes	28 (28.0)	14 (28.0)	14 (28.0)	0.83
Children, yes	34 (34.0)	19 (38.0)	15 (30.0)	0.40
Hearing difficulties *	1 (1.0)	1 (2.0)	-	0.32
Sleeping problems	29 (29.0)	15 (30.0)	14 (28.0)	0.83
Medication	39 (39.0)	19 (38.0)	20 (40.0)	0.84
Regular physical activity	72 (72.0)	38 (76.0)	34 (68.0)	0.38
Preferred music genre (multiple responses possible)				
Pop	66 (66.0)	33 (66.0)	33 (66.0)	1.00
Rock	37 (37.0)	19 (38.0)	18 (36.0)	0.84
Jazz	14 (14.0)	8 (16.0)	6 (12.0)	0.57
Classical music	34 (34.0)	18 (36.0)	16 (32.0)	0.68
Hits	6 (6.0)	2 (4.0)	4 (8.0)	0.40
Hip Hop	19 (19.0)	10 (20.0)	9 (18.0)	0.80
Others	20 (20.0)	7 (14.0)	13 (26.0)	0.14
Burnout risk (according to the MBI)	8 (8.0)	1 (2.0)	7 (14.0)	**0.03**
Reduced performance	31 (31.0)	12 (24.0)	19 (38.0)	0.13
Emotional exhaustion	22 (22.0)	12 (24.0)	10 (20.0)	0.63
Depersonalization	5 (5.0)	3 (6.0)	2 (4.0)	0.65
male / female	4/1	3/0	1/1	0.31

Data are present as median (range) or numbers (frequencies). BMI, body mass index; CH, conventional headphones; MBI, Maslach Burnout Inventory. Bold values mark statistical significance.
* not defined as serious hearing impairment

Table 2. Cardiovascular parameters

	CH (n=50)	Lautsaenger (n=50)	p-value (Mann-Whitney-U test)
Heart rate (bpm)			
pre	67.5 (36.0 – 94.0)	66.8 (37.5 – 89.5)	0.39
post	61.0 (35.0 – 92.5)	65.5 (39.0 – 86.0)	0.12
Difference post - pre	-3.3 (-15.5 – 4.0)	-2.0 (-15.0 – 5.0)	0.41
p-value	**< 0.001**	**0.0001**	
Brachial systolic BP (mmHg)			
pre	119.5 (101.0 – 140.0)	117.0 (95.0 – 159.5)	0.58
post	119.3 (95.0 – 133.0)	116.5 (93.5 – 164.5)	0.61
Difference post - pre	-2.0 (-15.0 – 10.0)	-1.5 (-12.5 – 7.5)	0.99
p-value	0.08	**0.01**	
Brachial diastolic BP (mmHg)			
pre	68.3 (46.5 – 85.0)	68.0 (47.0 – 95.5)	0.97
post	69.5 (48.0 – 89.0)	69.0 (48.0 – 94.5)	0.87
Difference post - pre	1.5 (-11.0 – 11.5)	0.5 (-11.0 – 8.5)	0.85
p-value	0.31	0.27	
RMSSD (ms)			
pre	50.5 (13.0 – 144.0)	44.0 (10.0 – 94.0)	0.29
post	43.5 (16.0 – 163.0)	44.5 (11.0 – 100.9)	0.37
Difference post - pre	-0.5 (-31.0 – 66.0)	-0.5 (-23.0 – 42.0)	0.67
p-value	0.56	0.79	
Compliance index			
pre	0.6 (0.4 – 0.7)	0.6 (0.4 – 0.7)	0.12
post	0.6 (0.4 – 0.7)	0.6 (0.4 – 0.7)	0.46
Difference post – pre	0.0 (-0.2 – 0.1)	0.0 (-0.2 – 0.2)	0.72
p-value	0.83	0.45	
Resistance index			
pre	20.2 (8.8 – 45.3)	22.1 (6.6 – 74.0)	0.15
post	18.4 (4.5 – 45.6)	19.0 (8.0 – 63.9)	0.57
Difference post - pre	-0.9 (-18.7 – 14.1)	-1.7 (-21.8 – 5.4)	0.14
p-value	0.25	**0.0008**	
Aortic systolic BP (mmHg)			
pre	99.8 (80.6 – 123.2)	99.9 (77.9 – 149.7)	0.76
post	100.7 (76.2 – 128.3)	99.2 (74.4 – 157.3)	0.43
Difference post - pre	-0.4 (-9.3 – 12.6)	-0.4 (-13.1 – 8.2)	0.61
p-value	0.80	0.55	
Aortic diastolic BP (mmHg)			
pre	69.5 (47.8 – 86.5)	69.3 (48.0 – 97.6)	0.99
post	71.1 (49.1 – 90.7)	70.8 (48.5 – 96.2)	0.91
Difference post - pre	1.3 (-10.2 – 11.2)	0.1 (-11.3 – 8.7)	0.90
p-value	0.47	0.38	

Aix (%)			
pre	2.4 (-14.4 – 41.3)	6.2 (-23.9 – 47.4)	0.90
post	4.6 (-12.1 – 45.0)	5.1 (-21.5 – 52.8)	0.52
Difference post - pre	3.5 (-6.0 – 27.0)	1.7 (-13.3 – 8.0)	0.051
p-value	**< 0.001**	**0.02**	
Aortic PWV (m/s)			
pre	6.8 (5.4 – 37.0)	6.8 (3.4 – 11.8)	0.84
post	6.6 (5.3 – 10.5)	6.6 (5.0 – 11.5)	0.83
Difference post - pre	-0.2 (-29.2 – 0.6)	-0.2 (-2.0 – 2.8)	0.58
p-value	**< 0.001**	**0.0003**	
Vascular age			
pre	36.1 (18.1 – 61.5)	36.9 (18.0 – 75.0)	0.38
post	34.9 (18.3 – 62.9)	33.9 (17.7 – 71.1)	0.92
Difference post - pre	-0.5 (-14.4 – 18.3)	-2.3 (-17.3 – 20.3)	0.37
p-value	0.31	**0.02**	

Data are presented as median (range). Bold values mark statistical significance.
Aix@75, augmentation index standardized to a heart rate of 75 bpm (beats per minute); BP, blood pressure; CH, conventional headphones; LVET, left ventricular ejection time; LVPT, left ventricular plateau time; PRT, pulse raise time; PWV, pulse wave velocity; RMSSD, root mean square of successive difference.
Note: the two groups are compared using the Mann-Whitney-U test while the change between the measurement time points is compared using the Wilcoxon signed rank sum test

Table 3. Emotions and stress

	CH (n=50)	Lautsaenger (n=50)	p-value (Mann-Whitney-U test)
Emotional well-being			
pre	69.0 (26.0 – 99.0)	63.5 (27.0 – 98.0)	0.24
post	78.0 (37.0 – 100.0)	75.0 (30.0 – 100.0)	0.11
Difference post - pre	9.0 (-5.0 – 35.0)	6.5 (-16.0 – 29.0)	0.76
p-value	**< 0.001**	**< 0.001**	
Pain			
pre	5.0 (0.0 – 94.0)	6.5 (0.0 – 59.0)	0.72
post	4.5 (0.0 – 98.0)	6.0 (0.0 – 60.0)	0.81
Difference post - pre	0.0 (-39.0 – 25.0)	0.0 (-22.0 – 31.0)	0.89
p-value	0.10	0.22	
Anger			
pre	5.0 (0.0 – 75.0)	7.5 (0.0 – 59.0)	0.60
post	2.5 (0.0 – 44.0)	4.0 (0.0 – 60.0)	0.14
Difference post - pre	-1.0 (-62.0 – 2.0)	-1.0 (-24.0 – 3.0)	0.64
p-value	**< 0.001**	**0.0001**	
Anxiety			
pre	6.5 (0.0 – 67.0)	8.0 (0.0 – 64.0)	0.79
post	3.0 (0.0 – 64.0)	4.0 (0.0 – 61.0)	0.33
Difference post - pre	-1.0 (-44.0 – 2.0)	-2.0 (-20.0 – 5.0)	0.74
p-value	**< 0.001**	**< 0.001**	
Sadness			
pre	4.0 (0.0 – 78.0)	7.5 (0.0 – 63.0)	0.52
post	3.0 (0.0 – 52.0)	5.0 (0.0 – 69.0)	0.36
Difference post - pre	-1.0 (-55.0 – 12.0)	-2.0 (-26.0 – 44.0)	0.59
p-value	**0.0003**	**0.0007**	
Stress			
pre	57.5 (4.0 – 87.0)	57.5 (3.0 – 84.0)	0.50
post	26.0 (0.0 – 73.0)	33.5 (0.0 – 77.0)	0.21
Difference post - pre	-21.5 (-80.0 – 14.0)	-14.3 (-51.0 – 3.0)	0.08
p-value	**< 0.001**	**< 0.001**	
Music for coping stress			
pre	60.0 (30.0 – 83.0)	59.5 (29.0 – 97.0)	0.73
post	72.0 (35.0 – 100.0)	64.5 (22.0 – 100.0)	0.29
Difference post - pre	8.0 (-17.0 – 37.0)	2.0 (-50.0 – 31.0)	**0.03**
p-value	**< 0.001**	**< 0.001**	

Data are presented as median (range). Bold values mark statistical significance.
Aix@75, augmentation index standardized to a heart rate of 75 bpm (beats per minute); BP, blood pressure; CH, conventional headphones; LVET, left ventricular ejection time; LVPT, left ventricular plateau time; PRT, pulse raise time; PWV, pulse wave velocity; RMSSD, root mean square of successive difference.
Note: the two groups are compared using the Mann-Whitney-U test while the change between the measurement time points is compared using the Wilcoxon signed rank sum test

Supplemental Table ST1. Subjective sound perception and rating of the headphones

	All patients (n=100)	CH (n=50)	Lautsaenger (n=50)	p-value
Imagination	65.0 (2 – 100)	66.5 (15 – 100)	63.0 (2 – 100)	0.42
Size of the room	63.0 (9 – 100)	65.5 (14 – 100)	62.0 (9 – 90)	0.32
Natural sound	93 (93.0)	48 (96.0)	45 (90.0)	0.20
Pleasant sound	97 (97.0)	48 (96.0)	49 (98.0)	1.00
Feeling of pressure	4 (4.0)	2 (4.0)	2 (4.0)	1.00
Recommendation	86 (86.0)	41 (82.0)	45 (90.0)	1.00
Music track recognized	37 (37.0)	20 (40.0)	17 (34.0)	0.53

Data are present as median (range) or numbers (frequencies). CH, conventional headphones.

FIGURES

Figure 1. Study design

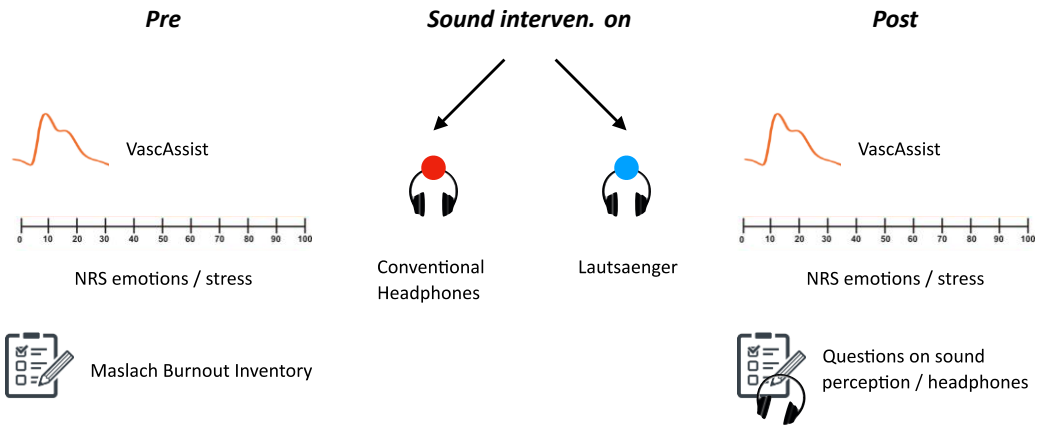
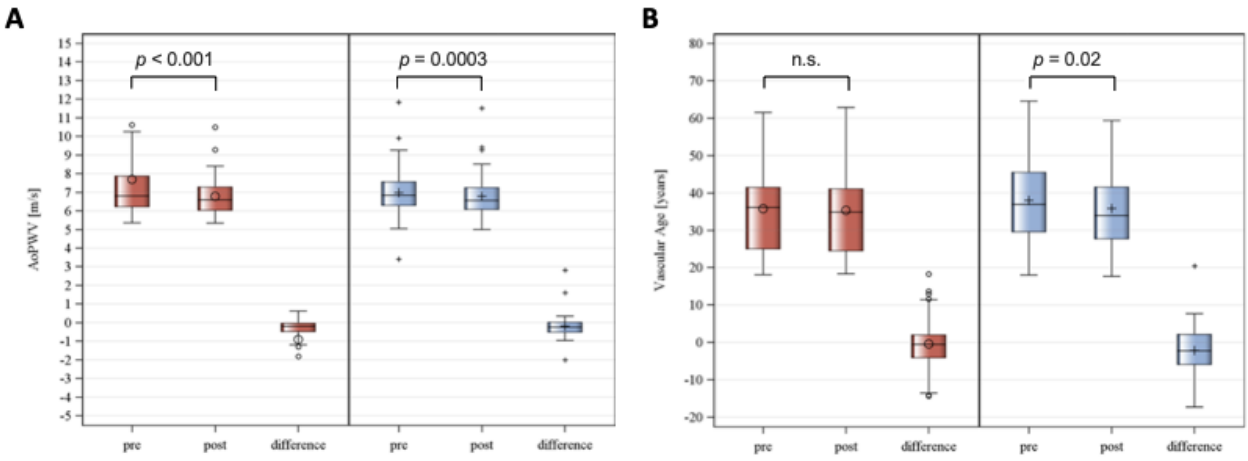
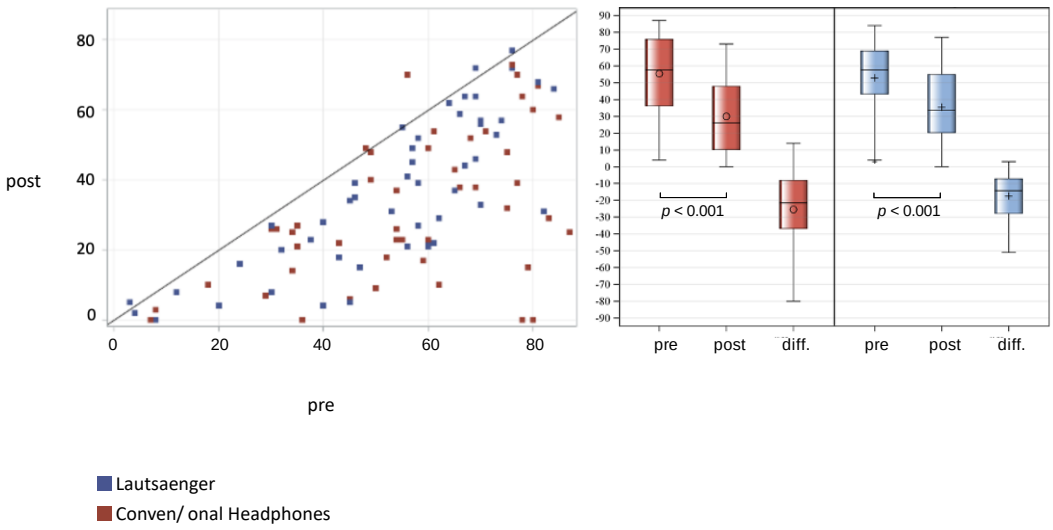


Figure 2. Cardiovascular parameters



Comparison of A) aortic pulse wave velocities (AoPWV) and B) vascular age for sound intervention with conventional headphones (red) and Lautsaenger (blue). While both treatment arms led to a significant reduction in AoPWV, vascular age was only influenced by Lautsaenger.

Figure 3. Stress reduction after a sound intervention



Scatter plot and boxplots displaying the effects of a sound intervention with conventional headphones (red) and Lautsaenger (blue) on stress. Both treatment arms led to a significant stress reduction ($p < 0.001$).