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**UNIVERSITY OF SPLIT
SCHOOL OF MEDICINE**

Johannes Pampel

**EXPLORATIVE STUDY ABOUT THE EFFECT OF CLASSICAL MUSIC ON
PROCEDURE RELATED ANXIETY IN PATIENTS WITH PERIPHERAL ARTERY
DISEASE**

Diploma thesis

**Academic year:
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**Mentor:
Prof. Johannes Brachmann, MD, PhD**

Split, July 2022

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List of Abbreviations

ABI - ankle brachial index

APAIS - Amsterdam Preoperative Anxiety and Information Scale

ASS - acetylsalicylic acid, Aspirin

AV - Fistula - arterio-venous Fistula

BWV - Bach Werke Verzeichnis - Bach works catalogue

CAD - coronary artery disease

CCDS - color coded duplex sonography

CRP - C reactive protein

CTA - computerized tomographic angiography

CV - cardiovascular

CVD - cardiovascular disease

DAMP - damage-associated molecular patterns

DSA - digital subtraction angiography

ESC - European Society of Cardiology

ESVM - European Society for Vascular Medicine

HDL - high density lipoprotein

IC - intermittent claudication

ICD - implantable cardiac device

ICU - intensive care unit

LEAD - lower extremity artery disease

LDL - low density lipoprotein

MACE - major adverse cardiac events

M-CSF - monocyte colony stimulating factor

MI - myocardial infarct

MMCS - Mönckeberg medial calcific sclerosis

MRA - magnetic resonance angiography

mNRS - for anxiety modified NRS

NRS - numerical rating scale 0 – 10

PAD - peripheral artery disease

PCI - percutaneous coronary intervention

PTA - percutaneous transluminal angioplasty

REACH registry - The REduction of Atherothrombosis for Continued Health

STAI - Spielberger's State-Trait Anxiety Inventory

VCAM 1 - vascular cell adhesion molecule 1

1. INTRODUCTION

1.1. Atherosclerosis

1.1.1. Terminology

Atherosclerosis and arteriosclerosis are often used interchangeably and incorrectly. Arteriosclerosis is the more generic term which stems from Greek language and literally translates to “artery hardening”. It subsumes atherosclerosis, Mönckeberg medial calcific sclerosis (MMCS) and arteriolosclerosis. These pathologies share characteristics such as arterial stiffening and arterial wall thickening but should be differentiated otherwise. Atherosclerosis is a chronic systemic inflammatory disease with formation of subendothelial atheroma and described in detail in the following sections. MMCS is a process involving calcifications of the tunica media of large and medium sized arteries. In contrast, arteriolosclerosis describes the thickening of small arterioles by hyalin deposits or hyperplasia (1-3).

1.1.2. Definition of atherosclerosis

Atherosclerosis is a chronic inflammatory disease in large and medium sized arteries, where oxidized lipoproteins accumulate subendothelial along with immune cells and extracellular matrix. Endothelial dysfunction is precipitated by risk factors and underlies the disease enabling the deposition of fat molecules in the tunica intima of arteries. Elevated plasma cholesterol levels above 150 mg/dl are probably the most important risk factor next to others including arterial hypertension, smoking, diabetes mellitus, male sex as well as inflammatory markers such as C reactive protein (CRP) and cytokines. On the other hand, protective factors against the development of atherosclerotic disease are alcohol, exercise, and high-density lipoprotein (HDL) containing apoA-I. The latter prevents atherogenic changes of low-density lipoprotein (LDL) and facilitates “reverse cholesterol transport” (4, 5).

1.1.3. Pathogenesis of atherosclerosis

The starting point of atherosclerosis is the subendothelial deposition of cholesterol loaded LDL due to endothelial dysfunction. Oxidized LDL has similarities with damage-associated molecular patterns (DAMP), triggering endothelial cells and starting an

inflammatory immune response. Activated endothelium expresses leucocyte adhesion molecules like vascular cell adhesion molecule 1 (VCAM 1), thereby facilitating monocyte adhesion. In response to monocyte colony stimulating factor (M-CSF), monocytes differentiate into macrophages. A positive feedback loop enhances migration into the evolving lesion and further inflammation. This chronic inflammation starts proliferation of vascular smooth muscle cells, thus reducing vascular lumen. Due to their scavenger function, macrophages incorporate LDL and become lipid rich foam cells. Over the course of the disease, foam cells accumulate, die by apoptosis and form, with other necrotic debris, the core of atherosclerotic plaque covered by a thin fibrous cap. B lymphocytes can produce inflammatory cytokines and IgG antibodies, while T lymphocytes, especially Th1 cells producing IFN- γ , also play an important role in the development of atherosclerotic disease (4, 5). The progression of atherosclerotic disease is depicted in Figure 1.

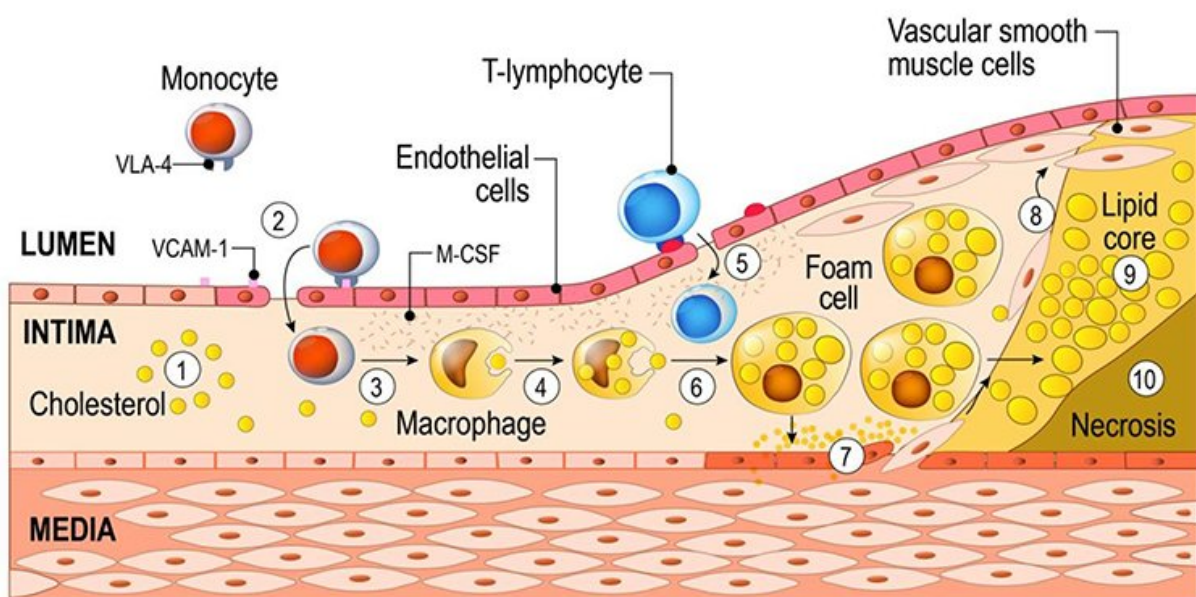


Figure 1: Progression of atherosclerosis. Source: Minelli S, Minelli P, Montinari MR. Reflections on Atherosclerosis: Lesson from the Past and Future Research Directions. J Multidiscip Healthc. 2020;13:621-33

Notes: The oxidized-LDL induce the activation of endothelial cells and the expression of various leukocyte adhesion molecules (such as VCAM1) and consequent monocyte adhesion to the endothelium (1,2); subsequent transmigration of monocytes into the intima, where they differentiate into macrophages (3,4); T lymphocytes join macrophages in the intima during plaque evolution (5); macrophages, incorporating modified lipoproteins, become lipid-rich

foam cells (6); the inflammatory response stimulates migration and replication of vascular smooth muscle cells, which accumulate in the plaque to form a fibroproliferative lesion (7,8); macrophages in the plaque show abnormal lipid metabolism with a reduction of the cholesterol efflux, (9) which leads to accumulation of apoptotic bodies and necrotic debris, forming a necrotic core (10).

1.1.4. Epidemiology of atherosclerosis

Today, the various clinical manifestations of atherosclerosis represent the most frequent cause of death in the US and one of the most frequent causes of morbidity, disability, and hospitalization (6). Since atherosclerosis is a systemic disease progressing and causing symptoms in different vascular beds, resulting pathologies are often termed according to vascular bed involved, e.g. peripheral artery disease (PAD), coronary artery disease (CAD), carotid artery disease and cerebral vascular disease (7). Therefore, all cardiovascular patients generally which are affected at one site are at risk for fatal and non-fatal cardiovascular (CV) event already. But as stated above, atherosclerosis is often generalized too (8). REACH registry connected common cardiovascular risk factors like hypertension, hypercholesterolemia, diabetes, and obesity to patients with aforementioned diseases (9, 10).

Atherosclerosis itself is very rarely fatal, but superimposed atherothrombosis on ruptured or exposed atherosclerotic plaque is. Depending on vascular bed and site, it manifests as acute myocardial infarction (MI), ischemic stroke or arterial occlusion for instance of lower limb artery (4).

Lifestyle interventions e.g., Mediterranean diet, exercising, smoking cessation and weight control offer nonpharmacological protection against atherosclerotic diseases. Anti-inflammatory therapy e.g., statins, antithrombotic (ASS) and antihypertensive medication is also widely used. Both can help to halt progression of atherosclerotic disease (5).

1.2. Peripheral artery disease - PAD

1.2.1. Terminology

According to 2017 European society of cardiology (ESC) guidelines on the management of peripheral arterial disease, the acronym PAD stands for peripheral arterial disease, including

all vessels except coronary arteries and aorta (8). Distinct from that, 2019 European society for vascular medicine (ESVM) guidelines refer to PAD as atherosclerotic peripheral artery disease of the lower limb, which is defined by ESC as lower extremity artery disease (LEAD) (11). This thesis refers to PAD as defined by ESVM.

1.2.2. Definition

Atherosclerosis is the underlying pathology for PAD in about 95% of cases, but other reasons include genetic, traumatic, or inflammatory causes. PAD occurs when there is a blood circulation disorder in the supplying arteries of the affected limb. Blood circulation disorders are differentiated into partial or complete, due to stenosis or occlusion respectively. Insufficient blood supply to an organ or limb will produce ischemic pain e.g., coronary artery disease leads to angina. In PAD, the ischemic pain of the lower limb is known as intermittent claudication (IC), which is associated with walking and relieved by resting. In later stages of the disease, ischemic pain is present while resting as well, progressing ultimately to ischemic necrosis (11, 12). To classify PAD clinically and symptomatically, Fontaine stage is used in Europe and Rutherford category in the US, as seen in Figure 2.

Fontaine Stage	Clinical symptoms	Rutherford		Clinical symptoms
		Grade	Category	
I	Asymptomatic	0	0	Asymptomatic
II a	Walking distance > 200 m	I	1	Mild claudication
II b	Walking distance < 200 m	I	2	Moderate claudication
		I	3	Severe claudication
III	Rest pain	II	4	Rest pain
IV	Ischemic ulcers or gangrene	III	5	Limited Ischemic ulceration not exceeding ulcer of the digits of the foot
		III	6	Severe ischemic ulcers or frank gangrene

Figure 2: Fontaine and Rutherford scale for PAD. Source: Frank U, Nikol S, Belch J, Boc V, Brodmann M, Carpentier PH, et al. ESVM Guideline on peripheral arterial disease. Vasa. 2019;48(Supplement 102):1-79

1.2.3. Diagnosis

1.2.3.1. Ankle brachial index

Many people with PAD do not report any symptoms like IC or report atypical symptoms (12). Therefore, IC alone is not suitable for diagnosis and another objective diagnostic criterion for PAD is needed. To screen a population's potential patients and recognize asymptomatic patients with PAD, a noninvasive method is warranted. Most commonly the ankle brachial index (ABI) is used. Measurement is performed with Doppler ultrasonographic device to detect pulses and blood pressure cuff with sphygmomanometer. To calculate ABI, systolic blood pressure of posterior tibial artery or anterior tibial artery is divided by brachial artery systolic blood pressure. The diagnostic cut off value used for PAD is less than 0.9. Verified by gold standard angiography, the sensitivity of ABI less than 0.9 for presence of minimum 50% stenosis is reported to be 95%, with specificity of almost 100% (13). Other non-invasive diagnostic methods are color coded duplex sonography (CCDS), computerized tomographic angiography (CTA) and magnetic resonance angiography (MRA) (8, 11).

1.2.3.2. Diagnostic gold standard: Intra-arterial digital subtraction angiography (DSA)

Intra-arterial digital subtraction angiography (DSA) is considered to be the gold standard for accurate and clear vascular imaging. Contrast agent is injected localized intraarterial through a catheter to visualizes blood vessels, in contrast to CTA. With the help of digital fluoroscopy radio-opaque structures like bones are subtracted by using of a pre-contrast image. It has many advantages, primarily the opportunity to combine diagnosis and treatment in one procedure as well as good documentation. DSA can be applied to many blood vessels and locations in the body and is therefore used as technical basis for many endovascular interventions, for example in cardiology for percutaneous coronary intervention (PCI), in angiology for peripheral transluminal angioplasty (PTA) as well as in interventional radiology. The invasiveness however also carries risks like hematoma, bleeding, aneurisma spurium, arterio-venous (AV) fistula and contrast agent related problems. Therefore, in angiology DSA is nowadays less used purely for diagnosis and more in a combined diagnostic and therapeutic approach, since methods like color coded duplex sonography (CCDS) offer very good results noninvasively as well (11, 14, 15).

1.2.4. Therapy of PAD

1.2.4.1. Conservative treatment - Risk factor management

According to ESVM Guidelines, cardiovascular risk factor management is the main objective of conservative treatment of PAD. The objective is firstly to reduce the risk of future cardiovascular events, and secondly, to improve all aspects of the disease from walking distance, pain and quality of life to limb preservation. Modifiable risk factors should be reduced with lifestyle intervention such as exercise, smoking cessation, and weight control. Antiplatelet medication, control of arterial hypertension, diabetes mellitus and dyslipidemia are the basis of PAD therapy (11).

The presence of concomitant reactive depression is however of increasingly high importance. Reduced walking distance can be causative for depression, but depression in turn further diminishes the quality of life and walking distance as well (16).

1.2.4.2. Minimally invasive: Percutaneous transluminal angioplasty (PTA)

Stenosis or occlusion of an artery is treated endovascular with minimally invasive angioplasty or balloon angioplasty, also called percutaneous transluminal angioplasty (PTA). First, after local anesthetic administration, a small incision at the inner thigh near the groin is made, to access the femoral artery via punctation in Seldinger technique in order to insert a guide wire. Other access sites are possible, depending on location of stenosis. The guide wire is advanced to the site of stenosis or blockade, while the course of the wire is tracked with DSA. With injection of contrast agent, the lumen of the artery is made visible. Along the guide wire a catheter is inserted and advanced through the stenosis or occlusion, where an inflatable balloon or stent can be deployed, to widen and reopen the artery. The atherosclerotic plaque is pushed in the wall of the artery; therefore, blood flow is restored to the distal part of the affected limb. This is procedure performed with conscious patients and without sedation (17, 18). Being subjected to PTA may cause procedure related anxiety in patients and is discussed further in the following.

1.2.5. Prevalence and risks of PAD

From a systematic review it was estimated in 2010, that the global prevalence of PAD is approximately 202 million. Within the EU, incidence rate increased between 2000 and 2010 28.7% in low-income countries (19). After accounting for conventional risk factors, patients with PAD show increased mortality, cardiovascular mortality and morbidity such as stroke and MI (12).

Even the diagnostic tool ankle brachial index (ABI) of less than 0.9 is connected with more than doubling of 10 y coronary event, cardiovascular mortality and total mortality (20).

20% of patients with intermittent claudication (IC) present after 5 years with MI or stroke and mortality is 10-15% (21). Importantly, REACH registry found in a one year follow up, that symptomatic PAD patients showed a significantly higher mortality rate than CAD patients with 2.4% and 1.8% respectively. The annual amputation rate was 1.3% (9, 10). Epidemiological data shows the high prevalence and increasing incidence of PAD with resulting mortality and morbidity in patients, showing the importance of more research needed in the population suffering from PAD.

1.3. Anxiety in medicine and cardiovascular patients

Anxiety is generally caused by transient fears, uncertainty, and apprehensiveness about the future. Anxiety is a normal feeling but can become a pathology itself, if felt frequently, with great intensity and not suitably to the situation (22). Patients awaiting a medical procedure such as surgery or vascular intervention often experience anxiety because they assume situations with uncertainty, discomfort and potential health risk. Anxiety also causes a sympathetic stress response including elevated heart rate, blood pressure and blood cortisol level, impeding healing (23). Anxiety disorders are greatly more prevalent in patients with cardiovascular diseases, than in the normal population. They are associated with 26% increased risk for heart diseases and 48 % increase for cardiac mortality in initially healthy patients (24). Anxiety is an independent predictor of major adverse cardiac events (MACE), since persons with high levels of anxiety are at greater risk of CAD, congestive heart failure, stroke, fatal arrhythmias and sudden cardiac death (25).

As stated above, fears and anxiety are common in general as well as in medicine and not always pathologic; here it can be characterized differently according to health care setting or situation. Examples include preoperative anxiety and procedure related anxiety.

In a study on preoperative anxiety, 40.5% of subjects stated high anxiety, which can be subdivided into anesthesia related fears and surgery related fears, assessed with the Amsterdam Preoperative Anxiety and Information Scale (APAIS) and for anxiety modified numerical rating scale (mNRS) (26).

1.3.1. Anxiety scales

Anxiety and fear can be assessed with many different questionnaires and scales. State and trait anxiety is often assessed with Spielberger's State-Trait Anxiety Inventory (STAI). It includes 20 items for assessing trait and state anxiety each (27). Others are the Amsterdam Preoperative Anxiety and Information Scale (APAIS) or modified numerical rating scale (mNRS) for anxiety (26, 28). To allow quick assessment in order not to increase procedure related anxiety, mNRS was chosen in this thesis.

1.3.2. Procedure related anxiety

Being subjected to a medical procedure can cause anxiety. The patient has a passive part and is not in control. Uncertainty about the disease, the procedure itself and severity of diagnosis all participate in the process of fear and anxiety occurrence, for example in patients undergoing coronary angiography (29).

Feelings of anxiety are common in patients planned for PCI and mostly concern apprehension about the outcome of the intervention; when the patient is discharged procedure related anxiety is significantly reduced post procedure, since uncertainty is resolved (30).

In a 10 year follow up with patients after PCI, anxiety related to an increased risk of all-cause mortality and was prevalent in 27.7% of patients (31). Patients suffering from CAD and PAD may be comparable, since the underlying pathology is identical and the interventional endovascular therapeutic technique is similar, just differing in targeted blood vessel and site. However, levels of procedure related anxiety may differ between PCI and PTA patients, since

intervention at heart or leg may be perceived differently. This is the first pilot study conducted on procedure related anxiety in patients suffering from PAD.

1.4. Music in medicine

Many studies have already been conducted on the use of music in various healthcare setting. Examples for positive effect of music include anxiety reduction, pain reduction, physiologic parameter reduction in many applications. A systematic review found that anxiety in patients during normal hospital care is reduced with music, but no effect on vital parameters was seen (32). In arousal conditions due to stress, music has a strong effect on increasing relaxation (33).

A large Cochrane review on music intervention for preoperative anxiety with 2051 included subjects found a significant decrease in preoperative anxiety in patients listening to prerecorded music as well as a small decreasing effect in heart rate and diastolic blood pressure reduction (23). Patients awaiting surgery often experience fears and anxiety. Therefore, premedication with midazolam is usually prescribed, but anxiolytic drugs can have side effects as well. Relaxing music decreases anxiety more than midazolam without hazardous side effects (34). This effect is proven in various medical fields. Preoperative music intervention in cataract surgery significantly reduces anxiety before the start of surgery and lowers mean pain during the surgery and at time of discharge (35). When patients undergoing hernia surgery listened to calming music postoperatively they reportedly needed less morphine, pain and anxiety were lower and cortisol levels decreased significantly more than in the control group (36).

In a randomized clinical trial in an intensive care unit (ICU), patients receiving mechanical ventilatory support showed that patient directed music therapy reduces anxiety levels and amount of sedative drugs significantly when compared to the control group (37).

Another study demonstrated that relaxing music is able to significantly reduce pain, heart rate and respiratory rate in patients needing a c clamp application after undergoing PCI, when tested against 45 minutes of resting (38).

When comparing the effect of classical music with silence, noises and heavy metal music, only classical music showed a decreasing effect on diastolic blood pressure and heart rate in healthy volunteers (39). Therefore, classical music should be applied in patients with PAD as well, to decrease their procedure related anxiety.

2. OBJECTIVES

2.1. Aims of the study

The aim of this study was to evaluate a newly assembled classical music playlist with a qualitative survey and its effect on procedure related anxiety measured with mNRS and physiologic parameters in patients with PAD. Therefore, patients receiving percutaneous transluminal angioplasty (PTA) were randomly assigned to a music and control group. In addition, anamnestic and demographic data was analyzed.

2.2. Hypotheses

1. A playlist with classical music is perceived positively as reflected in the qualitative survey.
2. Classical music helps to reduce procedure related anxiety, reflected in NRS reduction in music group.
3. Reduction of heart rate, blood pressure and respiratory rate is recorded in the music group.

3. MATERIALS AND METHODS

3.1. Study design

This explorative pilot study was performed between January and February 2021 at REGIOMED Vascular-Centre Sonneberg, Germany. Patients scheduled for PTA were screened in the waiting area of the angiology laboratory for this study. Patients were considered for this study if they met the inclusion criteria of age above 18 years, presented with a Rutherford category between 2 and 6 and provided written informed consent. Exclusion criteria consisted of severe presbycusis or deafness, medical history of anxiety disorders, intervention is a medical emergency procedure, or the responsible physician stating reasons deeming the patient not suitable. After informing the patient about the purpose of this study, written informed consent was obtained. Enrolled patients were then randomized with the excel function 'RANDBETWEEN': even numbers resulted in the patient being allocated to the study group (music intervention), odd numbers lead to allocation to the control group. The medical intervention (PTA) of all participants was conducted according to the standard-of-care of the European Society for Vascular Medicine (ESVM) guidelines (11). Participants in the music group received headphones (Tune 500 BT, JBL) with a newly assembled playlist with classical music playing continuously for the duration of the medical treatment. The music had a regular rhythm, slow tempo with 60 to 80 beats per minute (bpm), low pitch, and was instrumental only. Music included Mozart symphony number 40 and 41, J. S. Bach suite number 3 (BWV 1068) and cantata number 9 (BWV 169) as well as J. Strauss II operettas number 114, 117, 257, 279, 314, 354, 418 (39-41). This study can be classified as music medicine, or music intervention applied by medical professionals, but not as music therapy, since playlist is listened to passively and no music therapist was present (23). Subjects in the control group underwent PTA with normal ambient noise in the angiology laboratory. After 25 patients, this explorative pilot study was ended to analyze results and conclude about potential changes or improvements for future studies with increased sample size.

3.2. Data collection

During the medical intervention, data of physiological parameters and mNRS for procedure related anxiety were recorded at **three** defined time points: before, during and after intervention. Time point "during" is reached when the catheter wire is switched from a diagnostic to a therapeutic one. At baseline, anamnestic and demographic data, such as age,

sex, Rutherford category, previous implanted cardiac device (ICD), arterial hypertension, atrial fibrillation, and prescription of β -blockers were obtained. For both study groups, procedure related anxiety was assessed with a mNRS ranging from 0 (no anxiety or discomfort was felt) to 10 (worst imaginable anxiety or discomfort was felt). The physiological parameters (blood pressure (mmHg), heart rate (bpm), and respiratory rate (RR/min)) were noted as objective stress markers. Additionally, at the third time point for data collection, the patients were asked to assess their impressions of the ambient noise or the played music.

Answers were noted in a qualitative survey. The music group was asked the following questions: How did you like the music played during the intervention? If noticed, how did you like the ambient sound in the catheterization laboratory? Did the music reduce anxiety during the medical treatment? Would you like to listen to music again if another medical intervention is required in future? On the other hand, the control group was asked: How did you like the ambient noise in the catheterization laboratory? Did the ambient noise cause or aggravate discomfort? Would you like to listen to music in the future if another medical intervention is required? Open questions were rated on a 5-point Likert scale from 1 (not at all comforting) to 5 (to very comforting), with 5 representing the best answer. Closed questions on the other hand were answered with yes or no.

3.3. Ethical approval

This study was approved by the institution review board (IRB) of the REGIOMED Medical School/University of Split School of Medicine. The study also complies with the Declaration of Helsinki ethical guidelines. All included subjects were informed about this study and provided written informed consent. All data was anonymized and allows no referencing to individual patient or personal data.

3.4. Statistical analysis

The statistical analysis was performed using JASP (JASP 0.16.1, Amsterdam, Netherlands). The normal distribution of metric data was analyzed using Shapiro Wilk test. Normal distributed metric variables are reported as mean \pm standard deviation and statistically analyzed with Student t-test, whereas skewed data is reported with median and interquartile range and analyzed with Mann-Whitney-U test. Ordinal data was tested with Mann-Whitney U

test as well. Nominal data was analyzed with Chi-square test. Frequencies of anamnestic and demographic data as well as qualitative survey results are reported with relative (%) and absolute numbers (n). A significance level of $P < 0.05$ is used.

4. RESULTS

In January and February 2021, 25 patients were recruited for this pilot study and randomly allocated into music or control group. Two datasets (8%) had to be excluded, since only diagnostic angiography was performed, and no intervention was needed. Two participants out of the music group (8%) withdrew consent, because they objected and did not like the played music. Overall, 21 subjects were thus statistically analyzed, 10 in the music group (48%) and 11 in the control group (52%). The cohort had a mean age of 68 years with a standard deviation of 11.1, ranging from 48 to 89 years old. 16 participants (76%) had male sex and 5 (24%) had female sex. Patients presented most often with Rutherford category 5 (15/71.5%) and arterial hypertension (18/85.7%). No statistically significant differences between music and control group were discovered in anamnestic and demographic data. A complete overview of anamnestic and demographic data can be seen in Table 1.

A comparison of given answers in the qualitative survey yielded the following results: All subjects (100%) in the music group stated that they would like to listen to music again if in the future the same procedure needed to be performed again. 70% of subjects stated further, that music helped to reduce their procedure related anxiety. 90% of patients ranked their perception of the playlist from ok to very comforting, from which 50% alone found playlist very comforting. Ambient noise was not reported to be of any concern since all patients (100%) ranked perception from ok to very comforting.

50% of participants of the control group on the other hand stated that they would wish to listen to music in the future. Despite that, 100% found ambient noise not to increase their procedure related anxiety and rated their perception of ambient sounds in 90% from ok to comforting. In contrast, 10% reported the ambient noise as not comforting. Graphical presentation of the qualitative survey is depicted in Figures 3 and 4.

Both groups showed a reduction in procedure related anxiety quantified with NRS score during the progression of the medical intervention. In the music group, the median NRS score at timepoint “before” was 5, which reduced to a value of 4 in the middle of the intervention and concluded with a median NRS score of 1 after the intervention. The control group started with a lower median NRS value of 2, showed no change at timepoint “during” and finished with NRS value of 0. Thus, the music group decreased in procedure related anxiety from timepoint to timepoint and with a greater difference than the control group. However, no statistically significant differences between groups were discovered.

Mean systolic blood pressure was higher in the music group than control group at all three timepoints but decreased over the course of the intervention from 161 mmHg to 157

mmHg. Contrary to that, in the control group mean systolic blood pressure increased from 148 mmHg to 153 mmHg.

Mean diastolic blood pressure at all three timepoints was higher in the music group than in the control group but decreased more from timepoint “before” to “during”. In both groups, mean diastolic blood pressure was lowest at the timepoint “during”. Significant differences between groups in mean diastolic blood pressure were seen at timepoint “before” and “during”, with $P = 0.026$ and $P = 0.014$, respectively.

The mean heart frequency was highest with 83 bpm at timepoint “during” but lowest at endpoint with 78 bpm in the music group, whereas the heart frequency in the control group increased over the duration of the medical intervention from 72 bpm to 79 bpm.

Respiratory frequency showed no change in the examined time period. Mean values were 21 breaths per minute in the music group and 20 breaths per minute in the control group. No further significant differences between groups in physiologic parameters were found. A complete overview of physiologic parameters and NRS can be seen in Table 2 and Figure 5.

Parameter		Music Group (n = 10)	Control Group (n = 11)	Total (n =21)	<i>P</i>
Age		69.5±11.8	66.8±10.9	68.1±11,1	0.594*
Sex	male	8(80%)	8(72.7%)	16(76%)	0.696†
	female	2(20%)	3(27.3%)	5(24%)	
Rutherford	3	2(20%)	2(18.2%)	4(19%)	0.399‡
	4	2(20%)	0	2(9.5%)	
	5	6(60%)	9(81.8%)	15(71.5%)	
Hypertension		9(90%)	9(81.8%)	18(85.7%)	0.593†
B Block		4(40%)	5(45.5%)	9(42%)	0.801†
Atr. Fibrillation		0	1(9.1%)	1(4.8%)	0.329†
ICD		1(10%)	1(9.1%)	2(9.5%)	0.943†

Table 1. Anamnestic and demographic data. Data is reported with relative (%) and absolute (n) frequencies or as mean ± standard deviation. (*) Student t test; (†) Chi square test; (‡) Mann-Whitney U test

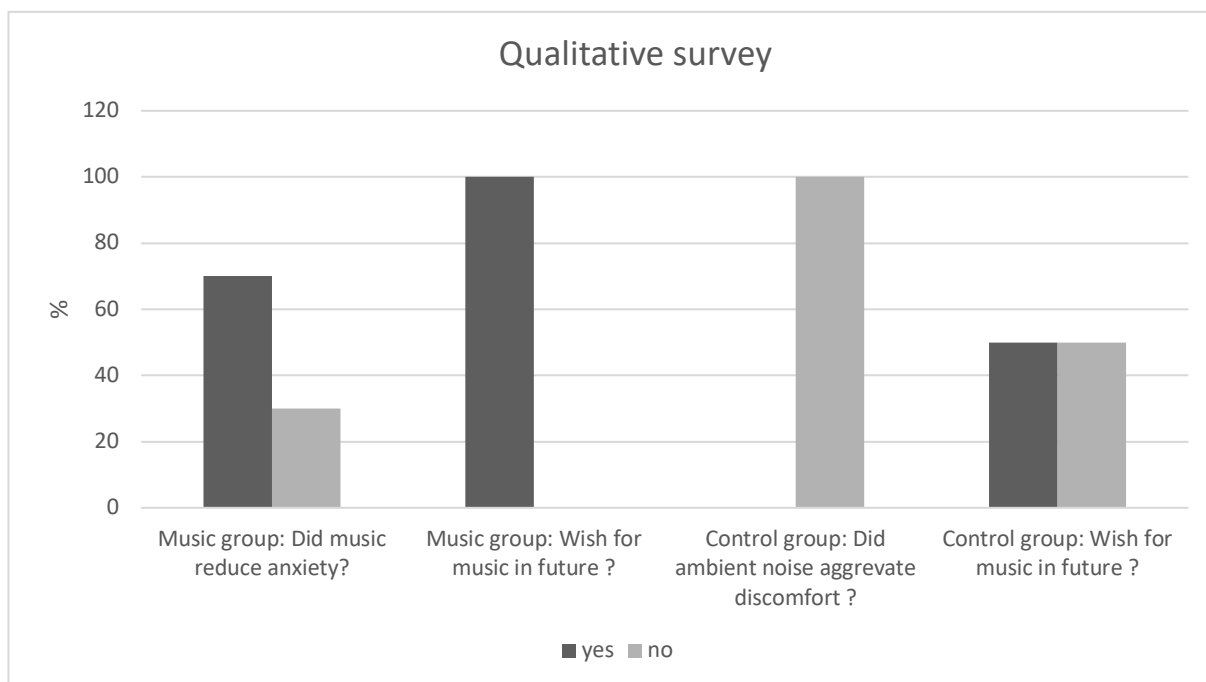


Figure 3. Qualitative survey. Depicted are results of qualitative survey to evaluate music playlist and impression of ambient noise with yes/ no question.

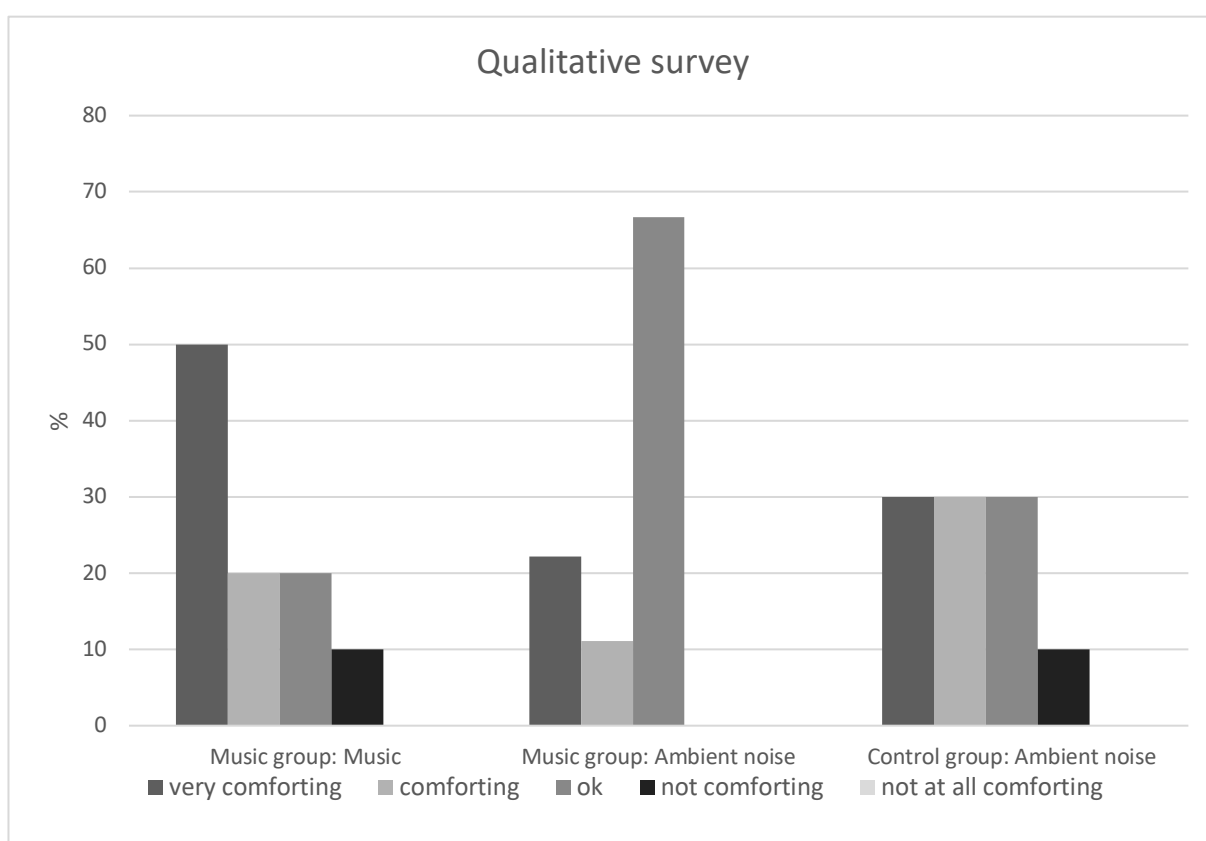
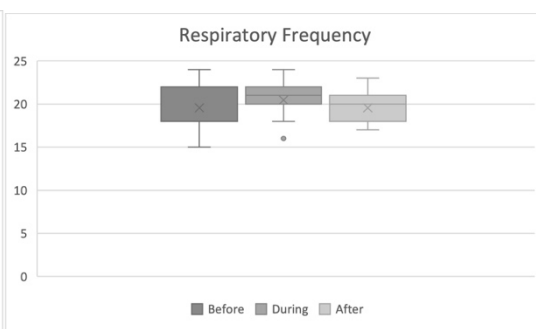
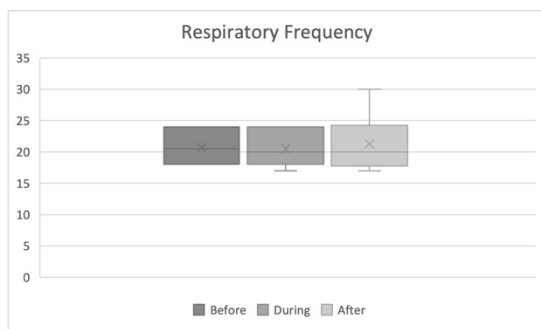
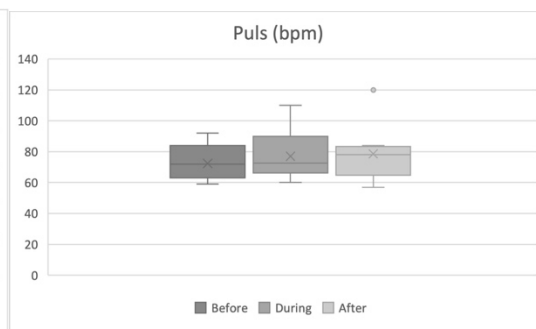
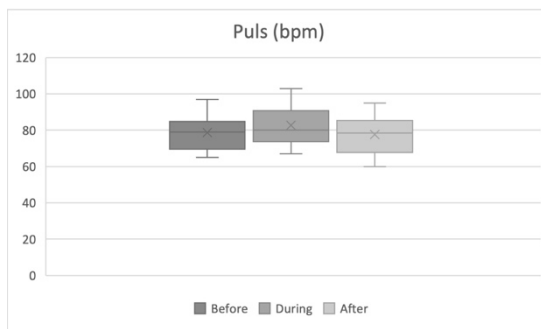
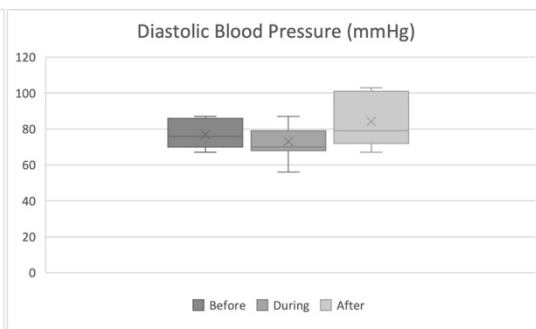
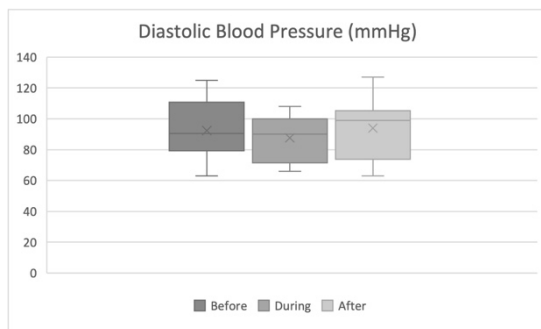
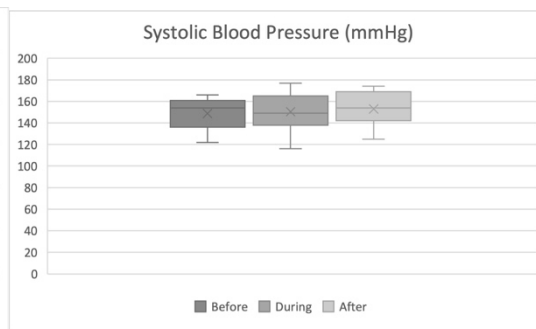
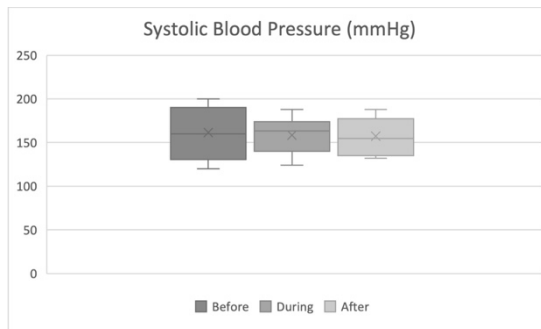


Figure 4. Qualitative survey. Results of perception of Music/ ambient noise, graded in 5 step Likert scale from very comforting to not at all comforting.

Parameter		Music Group (n = 10)	Control Group (n = 11)	P
Systolic Blood Pressure (mmHg)	Before	161±29	148±15	0.223*
	During	158±21	150±18	0.351
	After	157±20	153±17	0.603
Diastolic Blood Pressure (mmHg)	Before	92±19	77±7	0.026
	During	88±15	73±9	0.014
	After	94±19	84±15	0.201
Pulse (bpm)	Before	79±10	72±12	0.202
	During	83±11	77±15	0.353
	After	78±11	79±17	0.878
Respiratory Frequency (per minute)	Before	20.5 (5.5)	20±3	0.376*
	During	21±3	20±2	0.966
	After	21±4	20±2	0.249
NRS	Before	5 (1.75)	2 (3)	0.056*
	During	4 (5.25)	2 (4.5)	0.642*
	After	1 (4)	0 (3)	0.849*

Table 2. Physiological Parameters and NRS. Normally distributed data is reported as mean ± standard deviation and Student t test; skewed data and ordinal data is reported with median (IQR) and Mann-Whitney U test (*)



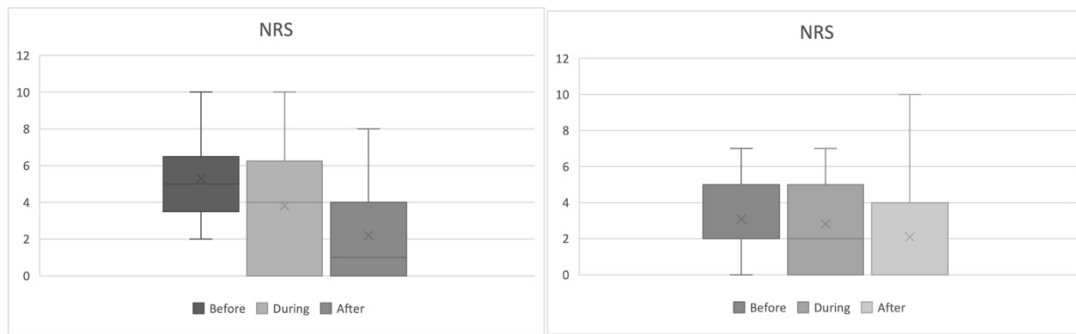


Figure 5. Box plot. Physiological data and NRS at 3 timepoints. Left column: music group; Right column: control group.

5. DISCUSSION

As indicated in the results section above, the qualitative survey about the classical music playlist yielded very positive results in included subjects. 100% of included subjects would like to listen to music in the future again, 70% found music helpful in reducing procedure related anxiety and 90% found the playlist at least “ok”.

Ambient noise at large does not seem to be of great concern since 100% in the music and 90% in the control group found ambient sound at least “ok”. One person (10%) in the control group however found ambient noise “not comforting”.

However, two patients withdrew consent after listening to the playlist, because they did not like the music offered. Previous studies suggest from high numbers of conducted trials and significant results that classical music is most appropriate. Perception of different music genres is however highly individual and personal, and probably influenced by region and age as well. For future studies, a more generally acceptable classical music playlist or another genre may reduce withdrawals. Alternatively with new streaming platforms like Spotify, a more individualized music choice would be possible. Generally, it is assumed that music works in refocusing attention away from medical procedures, and that anxiolysis is mediated by relaxing effect on sympathetic nervous system (23).

Since this explorative pilot study had a small sample size of 25, differences between groups were probably too small to be significantly detectable. Groups were also insufficiently balanced, which is visible at median NRS score and mean diastolic blood pressure being highest in the music group. However, this sample size was specifically chosen to evaluate the playlist and change it if needed, before enrolling a larger cohort.

Having defined exclusion criteria including previously diagnosed anxiety disorders to enable a homogeneous sample, the median NRS score was nevertheless higher at starting point in the music group as the sample was inadequately balanced. Procedure related anxiety is characterized by natural reduction after cessation of the causative procedure (30). Therefore, a reduction in the median NRS score was expectable in both groups. Still, the music group presented with a greater difference in reduction overall and reduced anxiety at every timepoint in contrast to the control group. In previous studies, anxiety reduction with music is widely reported, such as preoperatively, postoperatively, in ventilated patients and in general hospital care. It reportedly even has a stronger anxiolytic effect than midazolam (23, 32, 36, 37).

Demographic data and anamnestic data visualize the elderly patient with PAD, suffering from arterial hypertension in 85.7% and presenting with Rutherford 5 (small ischemic ulcer) in 71.5%. Therefore, their cardiovascular system is diseased in general, and cardiovascular

reactability is influenced and dampened by comorbidities and prescribed medication. In patients with PAD, cardiovascular data is therefore less likely to show significant changes after music intervention, because normal cardiovascular control mechanisms are probably not functioning anymore. In contrast, Trappe *et al.* could demonstrate the effect of classical music on the reduction of heart rate and diastolic blood pressure in healthy individuals with good cardiovascular reactability. Selected music from this trial was included in the playlist of this pilot study as well (39).

Systolic blood pressure was higher at all timepoints in the music group but decreased steadily over the progression of the medical intervention, whereas systolic blood pressure of control patients increased. Studies likewise found significant evidence about the reduction in systolic blood pressure in a meta-analysis (23).

Diastolic blood pressure also showed a significant difference when groups were compared at the two timepoints “before” and “during”. Mean diastolic blood pressure was however higher in the music group and highest at the end of intervention whereas studies suggest a reduction of diastolic blood pressure (23, 39).

The mean heart rate was highest in the music group at the timepoint “during” but decreased at the end of the intervention, whereas in the control group heart rate increased continuously. Contrarily, literature suggest a decrease in heart rate in healthy subjects, in preoperative subjects and in subject needing c clamp after percutaneous coronary intervention (PCI) (23, 38, 39).

The breathing rate did not show any change at all and was identical at the three timepoints in each group. Ultimately it has to be suspected that music does not affect breathing rate in patients with PAD, whereas in patients undergoing c clamp procedures after percutaneous coronary intervention (PCI) music did show a reductive effect on the breathing rate (38).

Patients were recruited at a single site and conclusively represent the population with PAD in upper Franconia and southern Thuringia, limiting the generalizability of results. The sample therefore classifies as a cluster sample. Measurement bias is limited with the use of standardized equipment for physiological data. Unfortunately, blinding of subject was however not possible in a study with music intervention, so detection bias cannot be excluded. The sample size was small with 25 patients and therefore not optimally balanced. Thus, further research on procedure related anxiety in patients with PAD should be conducted in the future.

6. CONCLUSION

1. Classical playlist yielded very good results in qualitative survey.
2. Procedure related anxiety was reduced in music group.
3. Physiologic parameters did not show significant changes in reaction to classical music.

7. REFERENCES

1. Dos Santos VP, Pozzan G, Castelli V, Caffaro RA. Arteriosclerosis, atherosclerosis, arteriolosclerosis, and Monckeberg medial calcific sclerosis: what is the difference? *J Vasc Bras.* 2021;20:e20200211.
2. Fishbein GA, Fishbein MC. Arteriosclerosis: rethinking the current classification. *Arch Pathol Lab Med.* 2009;133(8):1309-16.
3. Mitchell GF, Powell JT. Arteriosclerosis: A Primer for "In Focus" Reviews on Arterial Stiffness. *Arterioscler Thromb Vasc Biol.* 2020;40(5):1025-7.
4. Falk E. Pathogenesis of atherosclerosis. *J Am Coll Cardiol.* 2006;47(8 Suppl):C7-12.
5. Minelli S, Minelli P, Montinari MR. Reflections on Atherosclerosis: Lesson from the Past and Future Research Directions. *J Multidiscip Healthc.* 2020;13:621-33.
6. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. *Circulation.* 2019;139(10):e56-e528.
7. Duvall WL, Vorchheimer DA. Multi-bed vascular disease and atherothrombosis: scope of the problem. *J Thromb Thrombolysis.* 2004;17(1):51-61.
8. Aboyans V, Ricco JB, Bartelink MEL, Björck M, Brodmann M, Cohnert T, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries. Endorsed by: the European Stroke Organization (ESO), The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). *Eur Heart J.* 2018;39(9):763-816.
9. Zeymer U, Senges J, Parhofer KG, Röther J. Risk Factors and Event Rates in Patients With Atherothrombotic Disease in Germany: Results of the REACH Registry. *Dtsch Arztebl Int.* 2008;105(45):769-75.
10. Ohman EM, Bhatt DL, Steg PG, Goto S, Hirsch AT, Liao CS, et al. The REduction of Atherothrombosis for Continued Health (REACH) Registry: an international, prospective, observational investigation in subjects at risk for atherothrombotic events-study design. *Am Heart J.* 2006;151(4):786.e1-10.
11. Frank U, Nikol S, Belch J, Boc V, Brodmann M, Carpentier PH, et al. ESVM Guideline on peripheral arterial disease. *Vasa.* 2019;48(Supplement 102):1-79.

12. Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. *Circ Res*. 2015;116(9):1509-26.
13. Xu D, Zou L, Xing Y, Hou L, Wei Y, Zhang J, et al. Diagnostic value of ankle-brachial index in peripheral arterial disease: a meta-analysis. *Can J Cardiol*. 2013;29(4):492-8.
14. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *European Heart Journal*. 2018;39(2):119-77.
15. Glick Y, El-Feky, M. Digital subtraction angiography. Reference article, Radiopaedia.org. 2018 [updated 01.07.2022. Available from: <https://radiopaedia.org/articles/digital-subtraction-angiography>.
16. Wattanakit K, Williams JE, Schreiner PJ, Hirsch AT, Folsom AR. Association of anger proneness, depression and low social support with peripheral arterial disease: the Atherosclerosis Risk in Communities Study. *Vasc Med*. 2005;10(3):199-206.
17. Care SH. Percutaneous Transluminal Angioplasty (PTA) 2022 [updated 01.07.2022. Available from: <https://stanfordhealthcare.org/medical-treatments/p/percutaneous-transluminal-angioplasty-femoral-artery.html>.
18. The Johns Hopkins University TJHH, and Johns Hopkins Health System. Percutaneous Transluminal Angioplasty 2022 [updated 01.07.2022. Available from: <https://www.hopkinsmedicine.org/health/treatment-tests-and-therapies/percutaneous-transluminal-angioplasty>.
19. Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, et al. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet*. 2013;382(9901):1329-40.
20. Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, Chambless LE, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *Jama*. 2008;300(2):197-208.
21. Weitz JI, Byrne J, Clagett GP, Farkouh ME, Porter JM, Sackett DL, et al. Diagnosis and treatment of chronic arterial insufficiency of the lower extremities: a critical review. *Circulation*. 1996;94(11):3026-49.
22. Cohen BE, Edmondson D, Kronish IM. State of the Art Review: Depression, Stress, Anxiety, and Cardiovascular Disease. *Am J Hypertens*. 2015;28(11):1295-302.

23. Bradt J, Dileo C, Shim M. Music interventions for preoperative anxiety. *Cochrane Database of Systematic Reviews*. 2013(6).
24. Tully PJ, Harrison NJ, Cheung P, Cosh S. Anxiety and Cardiovascular Disease Risk: a Review. *Curr Cardiol Rep*. 2016;18(12):120.
25. Olafiranye O, Jean-Louis G, Zizi F, Nunes J, Vincent M. Anxiety and cardiovascular risk: Review of Epidemiological and Clinical Evidence. *Mind Brain*. 2011;2(1):32-7.
26. Eberhart L, Aust H, Schuster M, Sturm T, Gehling M, Euteneuer F, et al. Preoperative anxiety in adults - a cross-sectional study on specific fears and risk factors. *BMC Psychiatry*. 2020;20(1):140.
27. Spielberger CD, Gorsuch, R. L., Lushene, R., Vagg, P. R., & Jacobs, G. A. . Manual for the State-Trait Anxiety Inventory. Palo Alto, CA: Consulting Psychologists Press.; 1983.
28. Moerman N, van Dam FS, Muller MJ, Oosting H. The Amsterdam Preoperative Anxiety and Information Scale (APAIS). *Anesth Analg*. 1996;82(3):445-51.
29. Heikkilä J, Paunonen M, Laippala P, Virtanen V. Patients' fears in coronary arteriography. *Scandinavian Journal of Caring Sciences*. 1999;13(1):3-10.
30. Trotter R, Gallagher R, Donoghue J. Anxiety in patients undergoing percutaneous coronary interventions. *Heart Lung*. 2011;40(3):185-92.
31. van Dijk MR, Utens EM, Dulfer K, Al-Qezweny MN, van Geuns RJ, Daemen J, et al. Depression and anxiety symptoms as predictors of mortality in PCI patients at 10 years of follow-up. *Eur J Prev Cardiol*. 2016;23(5):552-8.
32. Evans D. The effectiveness of music as an intervention for hospital patients: a systematic review. *J Adv Nurs*. 2002;37(1):8-18.
33. Pelletier CL. The effect of music on decreasing arousal due to stress: a meta-analysis. *J Music Ther*. 2004;41(3):192-214.
34. Bringman H, Giesecke K, Thörne A, Bringman S. Relaxing music as pre-medication before surgery: a randomised controlled trial. *Acta Anaesthesiol Scand*. 2009;53(6):759-64.
35. Guerrier G, Bernabei F, Lehmann M, Pellegrini M, Giannaccare G, Rothschild PR. Efficacy of Preoperative Music Intervention on Pain and Anxiety in Patients Undergoing Cataract Surgery. *Front Pharmacol*. 2021;12:748296.
36. Nilsson U, Unosson M, Rawal N. Stress reduction and analgesia in patients exposed to calming music postoperatively: a randomized controlled trial. *Eur J Anaesthesiol*. 2005;22(2):96-102.

37. Chlan LL, Weinert CR, Heiderscheit A, Tracy MF, Skaar DJ, Guttormson JL, et al. Effects of patient-directed music intervention on anxiety and sedative exposure in critically ill patients receiving mechanical ventilatory support: a randomized clinical trial. *JAMA*. 2013;309(22):2335-44.
38. Chan MF. Effects of music on patients undergoing a C-clamp procedure after percutaneous coronary interventions: a randomized controlled trial. *Heart Lung*. 2007;36(6):431-9.
39. Trappe H-J, Brecker I. Effects of Different Styles of Music on Human Cardiovascular Response: A Prospective Controlled Trial. *Music and Medicine*. 2016;8:8.
40. Trappe H-J, Voit G. The Cardiovascular Effect of Musical Genres. *Deutsches Aerzteblatt Online*. 2016.
41. Bernardi L, Porta C, Casucci G, Balsamo R, Bernardi NF, Fogari R, et al. Dynamic interactions between musical, cardiovascular, and cerebral rhythms in humans. *Circulation*. 2009;119(25):3171-80.

8. SUMMARY

Objectives: The aim of this study was to evaluate a newly assembled classical music playlist with a qualitative survey as well as its effect on procedure related anxiety measured with mNRS and physiologic parameters in patients with peripheral artery disease (PAD). Therefore, patients receiving percutaneous transluminal angioplasty (PTA) were randomly assigned to a music and control group. In addition, anamnestic and demographic data was analyzed.

Subjects and methods: 25 patients were enrolled in this study, whereof 21 were statistically analyzed. Randomization resulted in 10 patients in the music group and 11 patients in the control group. All patients underwent PTA according to the standard of care, while the music group was listening to classical music with headphones and the control group was exposed to normal ambient noise of the catheterization laboratory. Groups were compared using a mNRS for procedure related anxiety and physiologic parameters at three timepoints. Finally, subjects were asked to answer a qualitative survey assessing their perception of music or ambient noise respectively.

Results: The qualitative survey assessing the music playlist yielded very positive results; 100% of subjects would like to listen to music again, 70% of subjects stated that music helped to reduce their procedure related anxiety, and 90% of patients ranked their perception of the playlist from ok to very comforting. Ambient noise was reportedly not increasing procedure related anxiety. The mNRS showed a higher reduction in the music group, but results were not statistically significant. Physiologic parameters showed significant differences between groups in mean diastolic blood pressure at timepoint “before” and “during”, with $P = 0.026$ and $P = 0.014$ respectively. Heart rate, systolic blood pressure and respiratory rate on the other hand did not yield significant differences.

Conclusion: The newly assembled classical music playlist yielded very positive results in a qualitative survey in included subjects. However, mNRS and physiological parameters used to assess procedure related anxiety did not show reliable statistically significant data when music and control group were compared.

9. CROATIAN SUMMARY

Naslov: Eksplorativna studija o učinku klasične glazbe na anksioznost povezanu s postupkom u bolesnika s perifernom arterijskom bolešću

Cilj: Cilj ove studije bio je kvalitativnom anketom ocijeniti novosastavljenu listu za reprodukciju klasične glazbe i njezin učinak na anksioznost povezanu s postupkom mjerenu mNRS-om i fiziološkim parametrima u bolesnika s perifernom arterijskom bolešću (PAB). Stoga su pacijenti koji primaju perkutanu transluminalnu angioplastiku (PTA) nasumično raspoređeni u glazbenu i kontrolnu skupinu. Dodatno su analizirani anamnestički i demografski podaci.

Materijali i metode: U ovu studiju bilo je uključeno 25 pacijenata, od kojih je 21 bio statistički obrađen. Randomizacija je rezultirala s 10 pacijenata u glazbenoj skupini i 11 pacijenata u kontrolnoj skupini. Svi pacijenti su podvrgnuti PTA prema standardu skrbi, dok je glazbena grupa slušala klasičnu glazbu sa slušalicama, a kontrolna grupa bila je izložena normalnoj ambijentalnoj buci kateterizacijskog laboratorija. Grupe su uspoređene pomoću mNRS-a za anksioznost povezanu s postupkom i fiziološke parametre u tri vremenske točke. Na kraju, ispitanici su zamoljeni da odgovore na kvalitativnu anketu kojom se procjenjuje njihova percepcija glazbe odnosno okolne buke.

Rezultati: Kvalitativno istraživanje koje je procjenjivalo glazbenu listu za reprodukciju dalo je vrlo pozitivne rezultate; 100% ispitanika željelo bi ponovno slušati glazbu, 70% ispitanika izjavilo je da im je glazba pomogla u smanjenju tjeskobe povezane s postupkom, a 90% pacijenata rangiralo je svoju percepciju popisa za reprodukciju od ok do vrlo utješno. Ambijentalna buka nije povećavala tjeskobu povezanu s postupkom. mNRS je pokazao veće smanjenje u glazbenoj grupi, ali rezultati nisu bili statistički značajni. Fiziološki parametri pokazali su značajne razlike između skupina u srednjem dijastoličkom krvnom tlaku u vremenskoj točki "prije" i "tijekom", s $P=0,026$ odnosno $P=0,014$. S druge strane, otkucaji srca, sistolički krvni tlak i brzina disanja nisu dali značajne razlike.

Zaključci: Novosastavljena lista za reprodukciju klasične glazbe dala je vrlo pozitivne rezultate u kvalitativnom istraživanju uključenih predmeta. Međutim, mNRS i fiziološki parametri korišteni za procjenu anksioznosti povezane s postupkom nisu pokazali pouzdane statistički značajne podatke u usporedbi glazbene i kontrolne skupine.

10. CURRICULUM VITAE

