A retroperspective pre-post analysis of changes in the heart rate variability parameters in chronic pain patients performing a 4-week multimodal pain therapy

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List of Abbreviations

ACh	-	Acetylcholine
ACTH	-	Adrenal corticotropin hormone
ANS	-	Autonomic nervous system
AP	-	Action potential
ASICs	-	Acid sensing ion channels
AV	-	Atrioventricular
CGRP	-	Calcitonin gene related peptide
CB	-	Cannabinoid receptor
CNS	-	Central nervous system
COMT	-	Catechol- O- methyltransferase
e.g.	-	*exempli gratia*
ESC	-	European society of cardiology
ECG	-	Electrocardiography
FNE	-	Free nerve endings
GABA	-	Gamma aminobutyric acid
HRV	-	Heart rate variability
HF	-	High frequency
HPA	-	Hypothalamic- pituitary- adrenal axis
IASP	-	International association for the study of pain
i.e.	-	*id est*, that is
IQR	-	Interquartile range
LF	-	Low frequency
LC	-	Locus coeruleus
M1	-	First measurement at beginning of multimodal pain therapy
M2	-	Second measurement at the end of the multimodal pain therapy
MAO	-	Monoamine oxidase
MI	-	Myocardial infarction
MS	-	Milliseconds
NASPE	-	North American society of pacing and electrophysiology
NMDA	-	N-Methyl-D-Aspartate
NRM	-	Nucleus raphe magnus
NRS	-	Numerical rating scale

NSAIDs	-	Non steroidal anti-inflammatory drugs
PAG	-	Periaqueductal grey
pNN50	-	Percentage of adjacent RRi that differ by more than 50 ms
PNS	-	Parasympathetic nervous system
PSC	-	Primary somatosensory cortex
RRi	-	R to R wave interval
RSA	-	Respiratory sinus arrhythmia
SA	-	Sinoatrial
SD	-	Standard deviation
SE	-	Standard error
SI	-	Stress index
SNS	-	Sympathetic nervous system
TCAs	-	Tricyclic antidepressants
TRP	-	Transient receptor potentials
TRPV	-	Transient receptor potentials of vanilloid type
ULF	-	Ultra low frequency
VLF	-	Very low frequency
WHO	-	World health organization

1 INTRODUCTION

1.1 Heart rate variability

First documentations of the Heart rate variability (HRV) are found in the fragmentary writings of the Greek scientist and physician Herophilos of Chalcedon. During his lifetime, ca. 335- ca. 280 BC, he made remarkable anatomical observations of the human anatomy and for this he´s acknowledged as the father of anatomy. He contributed to the distinction between arteries and veins based on the thickness of their walls and the fact that arteries pulsate rhythmically. Herophilos of Chalcedon then went on to investigate and study the arterial pulse, demonstrating the rhythmic pulsatile nature of arteries (1). Some 450 years later, his great admirer, Galen of Pergamon (ca. 129- ca. 199 AD) had a lasting influence on the use of the pulse in medical practice for the next sixteen centuries. He composed 8 treatises and more than 18 books about the application of the pulse for diagnosis and prognosis of diseases (2). It was not possible to record the periodic variation of the arterial pulse until more accurate timepieces were invented. In 1733 Stephan Hales (1677- 1761) was the first to report the changes of the beat-to-beat interval and blood pressure during the respiratory cycle. His German colleague Carl Ludwig (1816- 1895) refined this method by his invention of a Kymograph (an analogue device that detects and monitors changes in motion or pressure). He documented regular fluctuations in the timing and amplitude of blood pressure during breathing. He was the first to record an increase in heart rate during inspiration and a decrease in heart rate during expiration, a concept that is now known as respiratory sinus arrhythmia (RSA). With the subsequent introduction of the electrocardiogram (ECG) in ambulatory use, it became possible to assess the beat-to-beat change in even more detail. In 1965 Hon and Lee recognized that in the newborn, a change in HRV precedes fetal distress during labor, before a change in fetal pulse is observed (3). In the consecutive years, researchers among others Wolf et al. and Akselrod et al. demonstrated the clinical impact of HRV. Wolf et al. showed an association between low HRV and an increased risk of mortality after myocardial infarction (MI). The ability to perform power spectral analysis of heart rate fluctuation allowed Akselord et. al. to reveal the influence of the sympathetic and parasympathetic nervous systems on the HRV (4).

Today, the clinical use of HRV is finding its way in all areas of clinical practice and sports physiology. A reduction in the HRV in intensive care unit patients is linked to an increase in mortality. Furthermore it is an useful predictor of worsening in critically ill patients due to sepsis and imminent multi organ dysfunction risk (5). In chronic pain patients, autonomic disbalance can be assessed by HRV. A systemic meta-analysis showed a decrease in parasympathetic activation in chronic pain patients (6) as further discussed in chapter 1.1.4.

Sport scientists use the HRV to monitor systemic fatigue and recovery status. Modern fitness trackers and wearables usually have the ability to measure HRV, providing amateur athletes with important information about their fitness progress, as well as their state of stress or recovery (7, 8).

1.1.1 Definition of HRV

The heart rate variability is the physiological variation in time between each consecutive regular heartbeat (9). It underlies the influence of the autonomic nervous system (ANS) and its modulating effect on the sinus node (5). In a healthy individual the heart reacts highly sensitive to internal and external signals and adjusts to these stimuli with small variations in the heart rate. The ability of the heart to adapt to these rapidly switching changes in stress and challenge to the cardiovascular system is called HRV (10). The ANS is divided into the sympathetic (SNS) and parasympathetic (PNS) nervous systems (11). In a healthy person, there's a balance between the SNS and PNS controlling the blood pressure, heart rate and other factors that need to respond quickly to intrinsic and extrinsic stimuli. For example, acute ischemia, pain, and changes in mental or physical activity strongly influences the ANS. During rest, the PNS dominates and down-regulates the heart rate by releasing Acetylcholine (ACh) from the vagus nerve (5). The action of ACh on the M2 receptors of the Sinoatrial node, the Atrioventricular node and in the atrial myocardium slows down the heart rate and decreases the myocardial contractility (12). The short latency and rapid metabolism by acetylcholinesterase in the synaptic cleft leads to a rapid response of the SA- node, resulting in high frequency parasympathetic beat-to-beat modulation (13). This leads to an immediate lengthening of the RR interval, resulting in an increase in the HRV (14). The SNS competes with this regulation every time the body is exposed to a stressful situation, regardless of whether it’s some environmental danger, psychological or internal stress, the so called “fight or flight” response is triggered (15). Efferent postganglionic nerves of the SNS release catecholamines, which increase the heart rate, contractility, and conduction velocity by stimulating beta-adrenergic receptors in the heart. SNS hyperarousal leads to an increase in heart rate, a stronger contraction of the myocardium and a faster conduction in the conducting system (16, 17). In contrast to acetylcholine, up to 90% of the released catecholamines are reabsorbed by the nerve terminal and metabolized there by monoamine oxidase (MAO) and catechol-O- methyltransferase (COMT). The reuptake of noradrenaline is slower compared to the direct metabolism of ACh in the synaptic cleft, herefore the adaptation of the heart to changes in the SNS has a longer

delay and a potentially longer lasting effect. The difference of these two systems operating on the heart can be identified and quantified (18). As mentioned above, reduced HRV is a predictor of mortality in critically ill patients demonstrating the crucial role of the ANS in preserving health (18). In the next section the physiological and technical aspect are explained along with the measured values.

1.1.2 Measurable values and metrics

The heart is a fascinating highly precise, continuous pumping organ, suppling the body with oxygen and removes metabolites by beating approximately 100 000 times a day and more than 2.7 billion times over a lifetime. Although highly adaptable to external and internal stimuli, there are small beat-to-beat variations that can be monitored non-invasively with an ECG. The interval between consecutive R-waves (RRi) of the ECG is used, demonstrating a linear connection to both parasympathetic and sympathetic activation, providing a reliable reflection of modulating physiological influences on the heart rhythm by the ANS (19, 20). Due to the continuous increasing and decreasing activity of the SNS and PNS, the HRV fluctuates. Although the vagal and sympathetic nerves exert opposing effects on heart rate, these effects are not symmetrical. As explained earlier, the vagal effect has a shorter latency and duration than the sympathetic effect. These habitual latency and duration characteristics of the two arms of the ANS allows for a frequency domain measurement, with high frequencies corresponding to PNS activity and low frequencies corresponding to SNS activity. This frequency domain measurement calculates the distribution of variance into four frequency bands, the ultra-low-frequency (ULF), very-low- frequency (VLF), low- frequency (LF), and high- frequency (HF) bands. This division was established by the Task Force of the European Society of cardiology (ESC) and the North American Society of Pacing and Electrophysiology (NASPE) (1996). Only the HF and LF are relevant for the present research and will be discussed further, the ULF and VLF are not meaningful in short term measurements (<5 minutes) and should therefore be avoided according to the ESC and NASPE (21). The cyclical change in RRi that occurs in relation to in and exhaling, with shortening and prolongation of RRi respectively, is known as respiratory sinus arrhythmia. RSA is an index of cardiac vagal innervation of the heart (20). Because these oscillations are measured as high frequency bands (typically 0,15- 0,4 Hz) and can be abolished by vagal blockade researchers have linked this frequency band to the activity of the PNS (18, 22, 23). The underlying physiological mechanism is as follows. During inspiration the diaphragm is pulled downwards, causing a greater negative pressure in the chest,

which leads to a drop in blood pressure activating the baroreceptor reflex leading to an inhibition of vagal outflow from the cardiovascular center thus the heart rate increases and the RRi shortens (16). Defective vagal inhibition is linked to an increased morbidity (24).

On the other hand, the low frequency band (0,04-0,15 Hz) is more controversial and discordant (23). Some researchers link it directly to the SNS activity while others suggest that it is under the influence of both the SNS and PNS (18, 20). M. Pagani showed a close correlation between the low frequency band and sympathetic activity innervating the muscles, whereas a sympathetic inhibition leads to a predominance of the high frequency band (25). Low frequency oscillations are provoked by an increase in sympathetic activity, which synchronizes with the Meyer waves (26). Meyer waves are cyclic rises and falls in arterial pressure that occur at lower frequencies than the respiratory oscillations (27). The amplitude of the Meyer waves is thought to represent the sympathetic vasomotor activity (5, 28). In contrast, Keselbrener and Akselrod show that vagal blockade not only ceases the HF band but also modulates the LF band, suggesting that there is an additional parasympathetic contribution to this cyclic activity (29). At present it is believed that the low frequency is influenced by the baroreflex with a combination of sympathetic and parasympathetic efferent nerves innervating the SA- node (30). Regardless of this calculating the LF/HF ratio was introduced as a measurement of the sympathovagal balance, revealing the relative dominance of either the SNS or PNS (5).

Other parameters used in this research are the NN50 and the pNN50. This so called time-domain parameters of the HRV represents the general autonomic modulation with mainly parasympathetic contribution (31). These parameters are obtained by measuring the time interval between consecutive normal R-waves during the recording period. NN50 represents the absolute number of consecutive RR that differ from each other more than 50 milliseconds (ms), and pNN50 represents the percentage of differences greater than 50 ms (30). It mainly indicates the parasympathetic modulation of the heart. No single value among the time domain parameters reflects solely the sympathetic regulation of the heart (31). The following Table 1 illustrates the different parameters used in this study.

Table 1 Measurement parameters used in this study.

Parameter	Unit	Description
Frequency- Domain		
LF power	ms²	Absolute power of the low-frequency band (0.04–0.15 Hz)
HF power	ms²	Absolute power of the high-frequency band (0.15–0.4 Hz)
LF / HF	%	Ratio of LF-to-HF power
Time- Domain		
NN50		number of RRi exceeding 50 ms from the preceding interval
pNN50	%	Percentage of consecutive RRi that deviate by more than 50 ms

Compiled from source (23)

1.1.3 Measurement

In the next section the measurement of heart rate variability and its clinical implications are discussed. HRV, a non-invasive practice, defined as the change in consecutive RRi, displays the heart's adaption of the heart to numerous environmental and psychological stimuli such as mental stress, breathing, exercise, and change in homeostasis (32). Thanks to advances in technology and computer science, HRV data can be easily collected and analyzed by researchers. In addition, HRV is a painless, inexpensive, and straightforward measurement making it applicable for many researchers. It is assessed by electrocardiogram recordings of various length. An ECG records the electrical currents generated by the cardiac impulses as they pass through the conduction system and are registered by electrodes placed on the skin. In a healthy person the ECG is composed of a P wave, a QRS complex and a T wave, each wave representing a specific phase of the cardiac cycle (33). The P wave represents the atrial depolarization, that initiates a heartbeat. The electrical impulse passes through the atrioventricular node, where a short delay of 0.1 seconds occurs, before the signal spreads via the Purkinje fibers into the ventricles initiating ventricular depolarization represented by the QRS complex. The ventricles then recover from the depolarization and repolarize, represented by the T wave. Most studies of HRV use the R wave as it has the highest amplitude and is therefore the easiest to detect on the ECG. Analyzing the beat-to-beat variation in RRis

contributes to the HRV indices. To remove artefacts such as muscle twitches, and extrasystoles or premature ectopic beats, initial filtering methods are used before evaluating the HRV (22). Distinct analytical approaches are used to evaluate the HRV. The most common are power spectral density analysis and time domain analysis. Both methods ascertain the RRi time and filter out ectopic beats and artefacts (11). Fast fourier transformation and autoregressive models are used to convert the original RRi cyclic fluctuation into frequency domains previously discussed. Time domain measures are simpler to calculate and the RRi variance is quantified by statistical methods. Because time domain indices are always calculated in a similar way, data from different studies can be compared if the recording length is the same. The most commonly used are the SDNN (the standard deviation between RRis), RMSSD (root mean square of successive differences between normal heartbeats), pNN50 (percentage of adjacent RRis that differ by more than 50 ms). Only the latter will be used in this research.

In order to obtain measurements that are as comparable as possible, standardization of methodological processes is required to eliminate as many interfering factors as possible and to ensure comparability between different laboratories. This can be divided into three groups, the subject variables, participant preparation and data collection site standards. HRV is influenced by many individual factors such as age, gender, heart rate, health, smoking, weight, and medication (34, 35). Women have higher mean heart rates, therefore smaller Riis, and lower SDNN, lower LF but higher HF (36). With and increasing heart rate the HRV decreases because the time between the beats is reduced and the chances of RRis varying decreases. At slower heart rates the reverse is true, the time between RRis lengthen and the opportunity to vary increases. This is known as the cycle length dependence (37). Regardless of this resting heart rates above 90 bpm are associated with higher mortality (38). Various drugs have an effect on HRV, including illicit drugs and cardioactive drugs of which beta blockers are of particular interested. They significantly increase the HRV (39). Enquire about these confounding factors prior to the HRV measurement enables the researcher to exclude participants. Therefore, researchers should review the individual's demographic and clinical data to identify known diagnoses, recent illnesses, surgeries, medications and lifestyle habits (40). Participants need to be prepared and given some guidelines on factors that influence HRV to obtain results that are as comparable as possible. The day before the measurement, they should abstain from alcohol, caffeine, nicotine, energy drinks and if possible from medication (41). Intense physical exercise should be avoided before the measurement. Immediately before the HRV measurement, the patient should rest and be asked about sticking to the instruction and his general health.

The site used to collect the data should meet certain consistent standards. The measurement should occur in a quiet environment with no people interrupting. The room temperature and humidity should be controlled and set at 20 to 24 degrees, and 40 to 60% humidity (41, 42). To minimize the influence of the circadian rhythm on HRV, the measurements should always be taken at the same time of day (43). Within the same research project, the same equipment should be used to measure HRV, and the same recording duration should be used. There's a wide range of devices available, from short-term heart rate monitors to long-term devices such as the 24-hour Holter system. The length of recording, short or long-term, depends on the conducted study, and needs to be standardized. Long-term measurements usually last 18- 24 hours while short-term measurements last 5 minutes or 300 heartbeats (40).

In summary it is important to check the health status and taken medications, prepare the patient accordingly and standardize the measurement environment and adhere to an HRV measurement system as well as a defined recoding length.

1.1.4 Clinical impact

Since Hon and Lee showed in 1965 that alterations in HRV precede fetal distress prior to any other heart rate alterations, the clinical importance and use of HRV has increased constantly (44). Lower HRV in diabetic patients predicts autonomic neuropathy before the onset of symptoms and corelates with disease progression and an unfavorable prognosis (45, 46). HRV is used for cardiac risk stratification in post-myocardial infarction patients and for risk assessment of arrhythmic events. Changes in HRV are linked to a fivefold increase in mortality in post-MI patients (47). In intensive care units, HRV parameters are an independent predictor of 30-day mortality and provide an additional parameter to the APACHE II scores in critical ill patients (48). Low HRV provides an independent predictor of future health problems and correlates with the all-cause mortality risk (49, 50). Changes in autonomic function along with a decreased HRV have been demonstrated in various non-cardiological diseases. Among others this include stroke, multiple sclerosis, muscular dystrophy, Parkinson’s disease, end-stage renal disease, cardiomyopathy, congestive heart failure, and patients awaiting heart transplant (30, 31). Indirect evidence suggests that decreased HRV may be associated with illness and mortality because it implies reduced regulatory capacity, which is the capability to adapt to physical and emotional challenges such as stress and exercise. For example, patients suffering from depression or anxiety disorder have lower HRV. The lower HRV has been linked

to a variety of unfavorable long-term health effects, such as cardiovascular disease, mood disorders and elevated morbidity (6). It is also an indicator of behavioral flexibility and resilience, revealing a person's ability to respond successfully to altering social or environmental stressors (11). Interestingly not only does lower HRV provides valuable information, recent studies suggest a relationship between higher resting HRV and better performance on cognitive performance task (51).

1.1.5 HRV in chronic pain

Research has shown that people with chronic pain often present with lower HRVs than healthy controls. This is thought to be due to the fact that chronic pain is associated with an overactive sympathetic nervous system, which can lead to a decrease in HRV. In addition, chronic pain is also associated with decreased parasympathetic activity, which further contributes to a decrease in HRV (52). A systemic review conducted in 2013 showed a connection between HRV measurement and experimentally induced pain. 20 different publications are reviewed in which pain was induced mainly by either pain inducing substances (hypertonic acid) or physical agents (temperature, pressure) to determine the pain threshold (stimulus at which the subject first perceives pain) and tolerance (upper limit of stimulus intensity that can be tolerate). The authors concluded that HRV is a promising indicator of the autonomic response to a nociceptive stimulus. An increased LF domain and concomitant decreased HF domain in response to pain were reported (28). Slow deep breathing or meditation can increase the vagal mediated parasympathetic component of HRV and practicing yoga for 6 years can modulate the autonomic response to pain, meaning that a thermal painful stimulus is not recognized as such and elicits the same response as a warm stimulus (53-55). In chronic pain patients, HRV is reduced, especially the high frequency band, representing impaired function in both the SNS and PNS. Chronic pain may directly cause ANS dysregulation, further reducing one's ability to respond adequately to stressors (*e.g.* pain). Low parasympathetic tone, on the other hand, may increase the likelihood of chronic pain due to a reduced ability to respond to sensory and emotional stimuli. Regardless of the mechanism, both carry an increased likelihood of mortality (6).

1.2 Pain

1.2.1 Definition of pain

The International Association for the Study of Pain (IASP) evaluated and rewrote its definition of pain in 2020. They replaced the terminology of the 1979 definition, which relied on a person's ability to describe the experience to qualify as pain, thus excluding infants, the elderly and animals who are not capable to verbally express their pain experience. The new revised definition reads as follows:" An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage". The IASP has further specified that pain is influenced by different factors such as psychological, biological, and social factors. Pain must be learned and experienced consistently and is therefore always a subjective perception. Pain perception and nociception are two distinct phenomena. Pain does not result solely from the activity of sensory neurons, whereas nociception is the reaction of the nervous system to noxious stimuli (thermal, mechanical, chemical) (56). In order to experience pain, a harmful event does not necessarily have to be present and vice versa. This will be discussed in more detail later in chapter 1.2.2 (57). Any sign of pain should be taken seriously because, although pain usually subsides, it can have a negative long-term impact on quality of life, performance and psychological wellbeing (58). Pain is a subjective experience that is essential to our survival, a warning signal that something is misaligned in the body and needs attention. Pain can be classified based on various factors such as duration, location, and cause. Understanding the different classifications of pain is crucial for effective pain management. In this section, we will explore the different types of pain and their characteristics (59).

Acute pain is sudden, severe and of short duration. It is usually caused by tissue damage, inflammation, or injury and is relieved when the cause is treated (57). The purpose of acute pain is to eliminate the cause of the pain, for example, pulling your hand back when you touch the hot stove. We learn that pain is localized to where the pain receptors respond. Pain intensity is modulated by other sensory influences, emotional state, or time of the day. Examples of acute pain include a broken bone, a cut or a burn (60).

Chronic pain is persistent pain that lasts for more than three months despite treatment or medication and is connected to significant psychological distress and functional impairment (61, 62). Chronic pain can be debilitating and have an enormous impact on a person's quality of life, affecting around 17% in Germany and one in five people worldwide (63, 64). According to the German Society for Psychological Pain Therapy and Research, the gender prevalence in

Germany is at the expense of women with about 60% versus 40% of men (65). In contrast to acute pain, chronic pain is a completely different situation, for which there is no biological purpose. In the case of continuous or constantly recurring pain, the warning character is lost and the processing of information leads merely to harmful consequences (66). A so-called "pain memory" develops, the learning ability of individual sensory nerve cells is relevant for this chronification process. Every impulse changes the nerval activity and with sufficient repetition, a slight stimulus is enough to be registered as a painful impulse and is perceived as unpleasant, even though the actual trigger can be absent. The Immune unit genes, of which more than 100 are known, play a key role in this change. This can be detected both biochemically and morphologically. Centrally sensitization occurs through synaptic long-term potentiation and alteration in the ratio of inhibitory to excitatory transmitters in the dorsal horn of the spinal cord. These processes are presumably reversible, and the best therapeutic approach is to prevent the occurrence of sensitization. It is worth noting that pain memory is independent of consciousness, which means that it can also be formed during anesthesia (56, 60).

Nociceptive pain is caused by the activation of nociceptors as a result of actual or threatened injury to non-neural tissue. Nociceptors are free nerve endings (FNE), that are activated by different noxious chemical, mechanical or thermal stimuli and send high threshold noxious impulses to the central nervous system (CNS) (67, 68). Nociceptive pain can be further subdivided into somatic or visceral, depending on the tissue of origin. Somatic pain is superficial or deep pain that originates in the muscles, bones, skin, or joints. Visceral pain is pain that is felt in the organs or abdomen, such as the stomach or the liver (69). An important characteristic of nociceptive pain is sensitization. This is an increase in the responsiveness of nociceptive neurons to their normal input, lowering the nociceptor threshold and increasing their firing rate (56, 69). Peripheral sensitization occurs after repeated exposure to sufficient stimuli triggering an action potential (AP). Due to the pseudo-unipolar nature of the primary afferent neurons and non-neuronal cells, inflammatory mediators (bradykinin, ATP, hydrogen, prostaglandins) are released around the nociceptor, stimulating and sensitizing it (67, 70). This process is closely related to hyperalgesia, in which a normal pain stimulus provokes a tremendous pain sensation (71). A similar process, central sensitization, can also occur. Hyperexcitability is established at the level of the spinal cord, resulting in enhanced perception of nociceptive stimuli. Several mechanisms are known to be involved in central sensitization of which 3 are briefly addressed below. Excited A and C-fibers release glutamate and other neurotransmitters onto second order neurons in the lamina of the dorsal horn. This activates

normally silent N-Methyl-D-Aspartate (NMDA) glutamate receptors on the postsynaptic membrane, initiating signaling pathways that will facilitate the signal transmission of painful stimuli.

In disinhibition, inhibitory interneurons release GABA in the lamina of the dorsal horn, modulating pain transmission. If damaged, this inhibition can be reduced or even vanish, resulting in hyperalgesia. This can allow non-nociceptive type Aβ fibers to send signals that trigger a painful stimulus.

Microglia cells release growth factor and other cytokines that facilitate excitability and reinforce pain in respond to both painful and innocuous stimuli (67).

Neuropathic pain results from direct damage to the nerves that transmit pain signals or from diseases such as shingles, diabetic neuropathy or post-herpetic neuralgia (72). Neuropathic pain is a considerable burden for individuals, communities, and healthcare systems, because it is associated with more intense pain, more sick days at work, and higher healthcare costs (73).

Nociplastic pain arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain (62, 69).

1.2.2 Physiology and neuroanatomy of pain

Pain is an unpleasant sensation that is vital for survival. It serves as a warning signal for the body to respond and protect itself from potential harm. Pain is a complex phenomenon involving both sensory and emotional components. Understanding the anatomy and physiology of pain is essential for developing effective pain management strategies. In this section, we look at the genesis of pain, different types of receptors and pathways and how pain is processed in the brain. The genesis of pain involves the activation of specialized free nerve endings called nociceptors, nociceptive fibers and neurotransmitter substances (68). The free nerve endings are part of the nociceptive fibers, more precisely the peripheral axon of a first order pseudo-unipolar neuron that projects into the tissue, with its cell body located in the dorsal root ganglia. Pseudo- unipolar means that the nociceptors can send and receive information from either end. This is important for the plasticity, modulating and enhancing nature of pain processing (67). The FNE respond to noxious stimuli and can signal to the central nervous system that tissue damage has occurred. There are two different types of fibers, A and C-fibers

(59). The A-fibers are further divided into 3 subgroups, of which only the Aδ is of interest for the development of pain, as the other two, Aα and Aβ, are responsible for proprioception, touch, and pressure. The main differences between A and C-fibers (presented in Table 2) are the myelinated characteristic that is common for all type A-fibers and their dimeters. Thus, the conduction velocity of A-fibers is much faster than that of C-fibers, 6- 30 m/ sec compared to 0.5- 2 m/sec respectively (74). In terms of the characteristics of pain, A-fibers are responsible for the initial fast onset of sharp localized pain whereas C-fibers produce a sensation of a delayed, diffuse aching and burning pain (75). A-fibers are also responsible for reflex withdrawal of the hand away from a hot object (76).

Table 2 Features of pain fibers.

Feature	Aδ-fibers	C-fibers
Function	Nociception of fast and sharp pain	Nociception of slower diffuse pain
Myelin sheath	Myelinated	Non- myelinated
Diameter	1- 5 μm	0.2- 1.5 μm
Conduction velocity	6- 30 m/sec	0.5- 2 m/sec

Comparison of Aδ-fibers and C-fibers.
Compiled from sources: (33, 59, 75, 76)

Electrophysiological research on cultured neurons gives an idea of how noxious stimuli (heat, mechanical, chemical) are converted into a perceptible signal that elicits an action potential. This process of converting stimuli into ionic currents is called sensory transduction. Conduction of the information along the nerve fibers in the form of an action potential occurs after transduction and results in the release of neurotransmitters in the dorsal horn (77). Different types of channels allow the detection of various stimuli sources and intensity of pain. The transient receptor potential (TRP) channel family consists of 28 cation permeable channels, of which the vanilloid type (TRPV) is expressed in sensory neurons and is associated with nociception (78). Originally known for their activation by capsaicin, the spicy substance found in chili peppers, they react to temperature above 40°C in heat-sensitive C-fibers and above 52°C in A-fibers. Activated by capsaicin or heat the TRPV opens for calcium ions causing an influx of calcium and consecutive a localized depolarization (receptor potential) occurs, which in turn opens voltage-gated sodium channels, generating an action potential that propagates along the

pain fiber into the lamina of the dorsal horn (59, 79-81). This initial local depolarization induces a state of neuroinflammation through the mediated release of several pro- inflammatory cytokines (substance P, neurokinin A, calcitonin- gene- related- peptide (CGRP)), which active surrounding sensory and immune cells. In the skin this process produces the typical visible redness and swelling (59). The same mechanism underlies the painful reaction to cold, but with a different type of receptor, called TRPM8 (67). TRPV receptors can also be activated by chemical molecules, namely bradykinin (pro-inflammatory), prostaglandins (pro-inflammatory), acidic pH (hydrogen protons). Another type of TRP channel, the TRPA type, has merged as a particularly interesting member of this group in relation to the environmental and endogenous irritants which are mentioned above (77). Acid-sensing ion channels (ASICs) are another type of non-voltage gated cation channels that can sense noxious change in tissue pH. Extracellular acidosis, caused for example by inflammation, hypoxia, fractures, or cell death, activates the ASCIs. Upon proton binding to the ASCI, it undergoes a conformational change and sodium influx follows. This results in membrane depolarization and generation of an action potential (82-84). In response to physiological stress, tissue injury, or inflammation the endogenously produced chemicals are liberated and sensitize nociceptors either alone or in combination with thermal or tractile stimuli, thereby lowering the pain threshold. By enhancing protective reflexes in the aftermath of injury, the chemo-nociception serves as a crucial mediator between acute and persistent pain (67). FNE can detect a wide range of mechanical stimuli, from the finest brush stroke to the distention of the bladder wall, to painful stress placed directly on bones or nerves. Different types of mechanosensitive subtypes are specialized to sense this wide range of mechanical stimuli. The Aα and Aβ play a role in the physiological range for the perception of mechanical, pressure and positional changes in the skin, joints, and organs, but play a minor role in the case of pain. Therefore, we will only briefly look at the mechanical nociceptors relevant to pain. Electrophysiological and live imaging methods studies have shown that applied pressure causes mechanosensitive cation channel to open, generating a sudden depolarization (61, 71). However, no specific receptor or group has yet been identified. There are some interesting candidates, but these are still the subject of ongoing research. The most promising receptors are the already described TRP channels, (TRPV and TRPA) and the ASIC (67, 83).

Now that we have understand how a noxious stimulus is sensed and transduced into an action potential, we will have a look at the transduction from the periphery to the CNS and brain and its modulation there.

There are two main pathways by which nociceptive signals can travel to reach the brain. One pathway is the spinothalamic pathway (Figure 1), responsible for the transmission of fast pain sensations carried by the Aδ fibers. The other much older Paleospinothalamic tract, mainly corresponds to the slow chronic pain pathway. The spinothalamic pathway consists of three neurons, the cell bodies of the first-order neurons are located in the dorsal root ganglion, their peripheral axons extend into the innervated tissue, and their central axons project to the dorsal horn of the spinal cord. In the rexed laminae of the dorsal horn they synapse onto second-order neurons of the spinothalamic tract. These send out long fibers which immediately cross to the contralateral side in the anterior white commissure and ascend in the anterolateral columns of the spinal cord to the ventrobasal complex and the posterior nucleus of the thalamus. The third neurons are located in the thalamus, and project to the primary somatosensory cortex (PSC) and other basal structures, such as the insula and the anterior cingulate nucleus both of which are part of the limbic system and the hypothalamus. The PSC encodes the intensity and location of the pain stimulus, whereas the limbic structures and the hypothalamus provide the emotional integration of pain and the psychological arousal associated with pain (70, 80, 85). In the nuclei of the thalamus the medial lemniscal tract influences the nociceptive information by carrying information about proprioception, fine touch, and 2-point discrimination, allowing the pain to be precisely localized. The main neurotransmitter that is released at the end of Aδ nerve fiber is glutamate, and in the slower C-fiber substance P and CGRP are released for synaptic transmission (59, 79, 80, 86, 87). Responsible for the slower C- fibers mediated pain, the paleospinothalamic tracts first order neurons follow a similar pathway as the spinothalamic tract. Their first order neurons synapse mainly in the rexed laminae 2 and 3. The majority of the impulses subsequently travel through dorsal horn short fiber neurons before arriving mostly in rexed lamina 5. From there second order neuron follow the spinothalamic tract, crossing the midline in the anterior white commissure and ascend towards the brain in the anterolateral pathway, where its third order neuron project towards the PSC and thalamus (80). The different incoming pain stimuli are filtered and modulated at various levels before they reach the brain. The gate control theory, and the descending tract, regulate the incoming nociceptive input. Ronald Melzack published his gate control theory in 1965, over the years his concept has been revised and there is now a consensus that incoming pain impulses are first locally manipulated at synaptic level in the dorsal horn before being transmitted to second order neurons (88-90). At the site of injury, not only are C and Aδ-fibers exited, but non-nociceptive mechanoreceptors of the Aβ type are also stimulated, sending their axons trough the dorsal horn and giving of collateral branches to inhibitory interneurons. These inhibitory interneurons laying in the

substantia gelatinosa of the dorsal horn are called gates. Gamma- aminobutyric acid (GABA), the main inhibitory neurotransmitter in the CNS, is released by the activated interneurons and inhibits the Aδ and C-fibers in the synaptic terminal from releasing glutamate or substance P, thereby reducing AP transmission and propagation of the signal onto second-order neuron. This reduces the severity of pain perception. The common rubbing response after a blow to the elbow, or the use of cold pack after an injury to lessens the pain is based on this pain- relieving effect (89, 91, 92). At the same level of the spinal cord, but originating from Supraspinally, the descending analgesic system coordinates the endogenous opiate system in the dorsal horn. Originating from the periaqueductal grey (PAG), the serotonin rich nucleus raphe magnus (NRM), the nucleus reticularis and the locus coeruleus (LC) are part of the inhibitory descending pain pathway. The PAG is the switchboard, connected to the hypothalamus, the prefrontal cortex, the amygdala, and the anterior cingulate cortex, and communicates directly with the ascending tract. The PAG processes the incoming nociceptive information and acts on the above-mentioned nuclei of the midbrain, which in turn send their signals downwards to the substantia gelatinosa (68, 91, 93, 94). Here serotonergic neurons from the NRM release serotonin onto another group of interneurons. The release of endogenous opioids (enkephalins, endorphins, dynorphins) from the interneuron inhibit nociceptive signaling, leading to a reduction in nociceptive transmission from the periphery to the brain by reducing neurotransmitter release and hyperpolarizing cells, thereby reducing their excitability. Opioids are ligands for the opioid receptors (μ, δ and κ), at the level of the spinal cord, binding to these receptors causes potassium channels to open and calcium channels to close. The positive charged potassium effluxes and hyperpolarizes the cell (95, 96). Subsequently, the action of substance P and glutamate is brought to a halt, dampening the upward propagation of incoming nociceptive signals. The same mechanism applies to the noradrenergic neurons from the LC, except that they secret norepinephrine (97). These mechanisms filter and repress the incoming pain signals and thus can lead to an altered perception of pain.

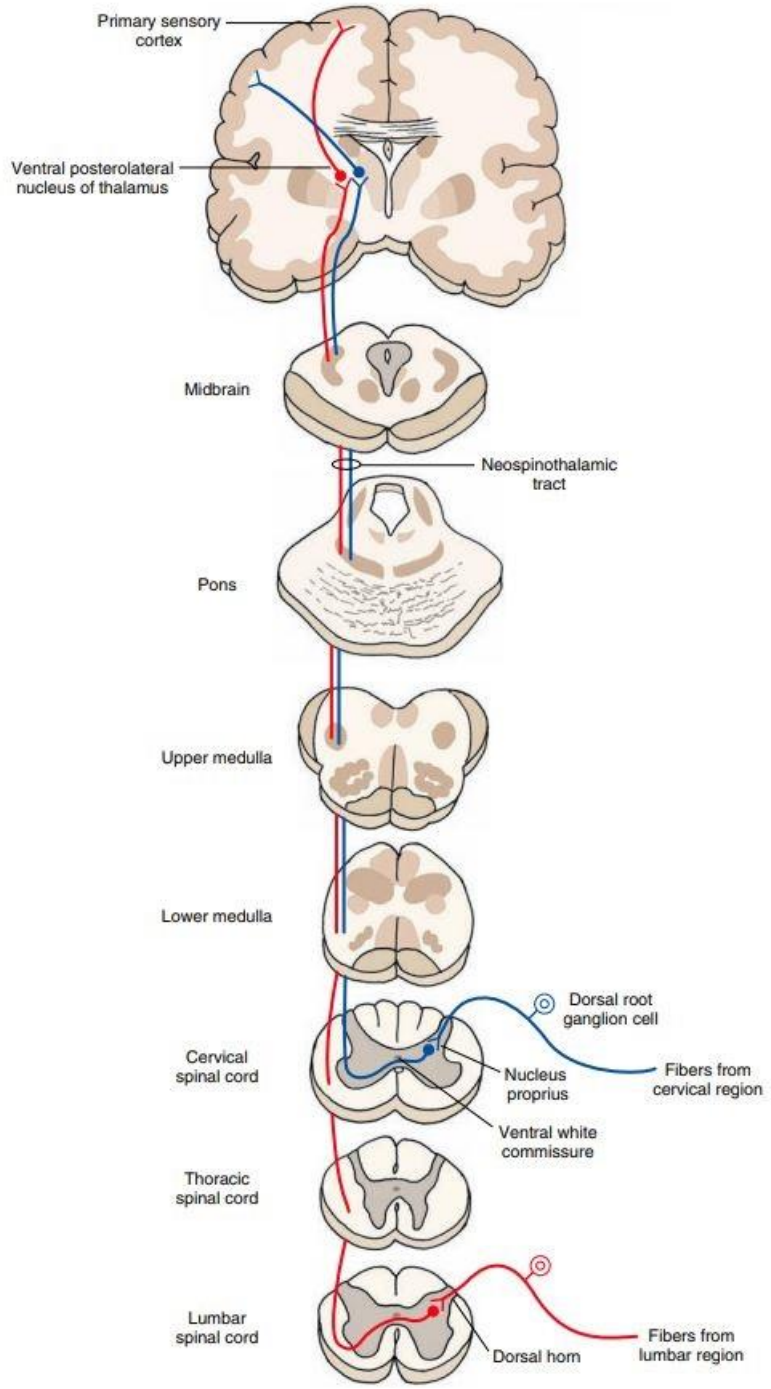

Figure 1 Spinothalamic tract and its projections: First order neurons of the spinothalamic tract entering the spinal cord, synapsing in the dorsal horn onto second order neurons, which in turn cross the midline and ascend in the anterolateral columns towards the brain, where third order neurons project to the PSC and the thalamus.
Special thanks to the copyright holder Wolters Kluwer Health, Inc. for permission of use. (98).

1.2.3 Chronic and neuropathic pain

Chronic pain has been characterized as pain that persists beyond the typical healing period and therefore lacks the acute warning function of acute pain. It may coexist with an ongoing peripheral pathology, such as arthritis, and can be constant or intermittent. It can interfere with people's ability to work, eat healthily, participate in physical activity and, most importantly, enjoy life. Chronic pain is a serious medical problem that can and should be treated (61, 66, 99). Pain is usually considered chronic when it persist for more than 3-6 months despite medication or treatment, and the patient is affected physically (loss of mobility and functional impairment), psycho-cognitively (state of mind, mood and thinking) and socially impaired (61, 100, 101). Approximately 20% of people worldwide suffer from this disease (63). In Germany alone 12-15 million people are affected, generating an annual cost of around 38 billion euros, most of which is due to sick pay, absenteeism from work and early retirement, and only 25% of which is due to the actual costs of treatment (102).

The development of chronic pain is not uniform, and different diseases and circumstances contribute to it. Complex changes occur in afferent neurons following exposure to inflammatory mediators, chemical molecules, or nerve injury. By causing an increase in excitability, a decrease in inhibition, and a structural remodeling of synaptic connections in the dorsal horn, this results in an abnormal reactivity of the somatosensory system, which manifests as hypersensitivity to otherwise innocuous stimuli. An important role is assigned to peripheral and central sensitization described in chapter 1.2. The release of cytokines, prostaglandins and neuropeptides modify the nociceptors and change the chemical milieu, lowering the threshold and facilitating excitability, which in turn increases the number of neuronal discharges to the point of developing spontaneous activity, as occurring in chronic inflammation. The sensation of pain is exaggerated and innocuous stimuli, which are usually non painful, are sufficient to trigger pain. In contrast, central sensitization of posterior horn neurons is caused by increased release of neuropeptides, increased activation and recruitment of NMDA receptors and loss of inhibitory control (67, 70, 103, 104) Calcium influx activates protein kinase C, leading to phosphorylation of the NMDA receptor, displacing the blocking magnesium from the receptor, resulting in increased glutamate sensitivity. The deficit in descending inhibition alters the receptive field of dorsal horn neurons from solely high threshold cells towards low and high threshold sensitive cells (104). Another gene expression pathway (C-fos), so far only demonstrated in animal experiments, can even lead to cell death of inhibitory neurons (105). There is an increasing evidence that dysregulation and disruption of the descending pain

modulatory system contributes to the development and maintenance of chronic pain. According to recent research it is one of the key factors in determining whether pain becomes chronic. This thesis is supported by the success of adjuvant pain medications such as serotonin/ norepinephrine reuptake inhibitors, which increase the noradrenergic activity in the spinal cord (106). Modification, a permanent structural change in the receptors and ion channels, the expression of transmitters, and cytoarchitectural changes in the neurons, alters the response to stimuli. This link between modification and the progression from acute to chronic pain is plausible (107). It is important to note that although there are several chemical mediators that interact with nociceptive neurons, each sensitizing signaling molecule may act on a different receptor, but collectively they produce the same effects by initiating the same intracellular signal pathways that activate protein kinase A (PKA) or protein kinase C (PKC). It is therefore unlikely that inhibition of a single chemical molecule will effectively prevent peripheral sensitization. This justifies the need for multimodal analgesic strategies. This is presumably analogous to the central sensitization process (108, 109).

Also of interest, but not yet fully understood, is the influence of genetics on pain perception and its contribution to the development of chronic pain. Different pain-related genes have been discovered including polymorphisms in the μ-opioid receptor gene or the COMT, as well as polymorphisms that alter pharmacokinetics, *i.e.* the rate at which a particular substance (*e.g.* morphine) is metabolized (85, 105, 110). The development of chronic pain is also significantly influenced by unique individual patient factors. Female gender, obesity, and smoking increase the risk of developing chronic pain (111). Psychosocial factors also influence the etiology of chronic pain. Individual personal experiences, emotions and resilience have an impact on how each person perceives pain. More anxious and catastrophizing individuals are in a hypervigilant state and are more likely to develop chronic pain. In addition, maladaptive behavior and response to pain correlates with increased perception of the pain stimulus and the ability to appropriately adapt and modify one's behavior in order to respond appropriately to pain (85). The same is true for patients suffering from depression, post-traumatic stress disorder and neuroticism (110). However, it is generally difficult to determine whether these factors cause chronic pain or vice versa (107).

1.2.4 Pain's effect on serum cortisol levels

Severe and chronic pain has a significant effect on the hormone levels of the endocrine system, leading to serum hormone abnormalities that can serve as biomarkers for severe pain of which cortisol is of special interest. Severe pain activates the hypothalamic- pituitary-adrenal axis (HPA). Various forms of stress including peripheral pain signals stimulate the hypothalamus (see chapter 1.2.2) to increase the release of corticotropin-releasing hormone, which in turn causes an increase in the release of adrenal corticotropin hormone (ACTH) from the pituitary gland. ACTH stimulates the adrenal gland to release cortisol and, to a certain extent, adrenaline as well. If this axis becomes permanently activated, as it is in the case of chronic pain, Cushing- like symptoms such as hypertension, hyperlipidemia, osteoporosis, mental deterioration, and joint degeneration can occur. If the pain goes on for too long, cortisol production can no longer keep up with the demand, and serum cortisol levels fall below normal. Hypocortisolism, which in the worst case can lead to sudden death if left untreated, should be suspected in chronic pain patients with muscle wasting, weight loss, low blood pressure and brown skin pigmentation. Therefore, serum testing is essential to assess hormone levels in pain patients. Depending on the progress of pain's effect on the HPA, cortisol levels can be too high or too low. Replacement therapy may be necessary to achieve hormone homeostasis and thereby yield an improvement in pain control. Serum hormone levels serve as an adjuvant evaluation tool for pain severity and should be considered in clinical pain treatment. Before starting treatment with long-acting opioids and other pain management methods that have potential risks, it is advisable to conduct a simple hormonal assessment. This assessment aims to determine whether patients with chronic pain have normal serum cortisol levels. Initial clinical observations suggest that optimizing hormonal balance prior to the introduction of opioids, and potentially other medications, may lead to reduced need for these agents. However, it is important to emphasize that the patient's self-report of pain and their requirement for analgesic medication should always be the primary consideration, and serum hormone levels should never be the sole determinant for appropriate pain relief (112, 113).

1.3 Pain Management

1.3.1 Medical pain therapy

Successful pain management may sound simpler than it is, because, as we have seen, not all pain is the same and therefore everyone reacts differently to pain and its treatment. The first step in proper pain management is to make an accurate diagnosis so that the treatment can be tailored to the individual patient as much as possible. The goal of a pain management may not be the complete pain relief, but a significant reduction in pain is already considered a success. However, the priority is to interrupt the pain stimulus at an early stage and treat until the patient is as pain-free as possible. In 1986, the World Health Organization (WHO) published a strategy for adequate pain management for cancer and palliative care patients, the WHO analgesic ladder. Over the time, the analgesic ladder has been improved and further developed by various expert committees and is now the standard of care for managing acute, chronic and cancer pain in both clinical and private practice. The ladder prescribes a defined treatment algorithm, using non-steroidal anti-inflammatory drugs (NSAIDs) for mild pain or combing them with opioids for more severe pain (114-116). A standardized pain analysis such as the numerical rating scale (NRS) or visual analogue scale is used to subjectively assess pain severity and monitor improvement during treatment (117). If medication consisting of basic therapy and on-demand medication is no longer sufficient at a given step, meaning that the average pain persists despite adequate medication intake, a step-up within the scheme must be taken and escalated to the next step. Co-analgesics can be administered at all three levels. It is important to know that some patients with a score of 6 on the NRS are satisfactorily pain free and prefer to keep a clear head, while others with a score of 2 may want an intensification of their pain medication, so it is important to choose an appropriate combination in close cooperation with the patient (118). The first step is to use NSAIDs plus and an optional adjuvant for mild pain. A weak opioid is added if the pain persists or is completely exhausted, or immediately for mild to moderate pain. For moderate to severe or inadequate step 2, a strong opioid is added. Table 3 gives a list of examples for each step (116, 119-125).

Table 3 WHO analgesic ladder

Step 1	**Step 2**		**Step 3**	
NSAIDs	Weak opioid		Strong opioid	
± Adjuvant	+ NSAIDs		+ NSAIDs	
	± Adjuvant		± Adjuvant	
Ibuprofen	Tramadol	(0,1*; 6-9†; <60‡)	Morphine	(1*; 3-4†; 30-90‡)
Diclofenac	Tilidin	(0,16*; 4-6†; 10-15‡)	Oxycodone	(2*; 11-14†; 60‡)
Celecoxib	Dihydrocodeine	(0,16*; 3-4†; 30-60‡)	Fentanyl	(100*; 1†;)
Acetaminophen			Pethidine	(0,2*; 3-5†; 60-120‡)
Metamizol			Buprenorphine	(30*; 6-8†; 90‡)
			Piritramide i.m.	(0,7*; 4-6†; 10-15‡)

If Pain persists or increases, escalate to the next step.

In brackets (*therapeutic potency, morphine sets the baseline with 1; †duration of action in hours; ‡onset of action in minutes)

Note: transdermal fentanyl has a duration of action of 70-100h.

Compiled from sources: 116, 119-125.

A more detailed description of the mechanism of action and use now follows. The most widely used drugs belong to the group of the over the counter NSAID. They mainly function by inhibiting the two isoforms of the enzyme cyclooxygenase enzyme (COX-1 & COX-2), thus preventing the synthesis of thromboxanes, prostacyclin and prostaglandins in the periphery and centrally, thus disrupting the inflammatory and algetic process (126-128). Prostaglandins lower the excitation threshold of pain fibers, making the nociceptors more sensitive to pain stimuli. When prostaglandin synthesis in the dorsal horn of the spinal cord is inhibited, as in the case of NSAIDs, nociceptors become less sensitive to pain mediators (85, 129, 130).There is disagreement about the primary site of action of acetaminophen (Paracetamol), whether it's the inhibition of prostaglandin synthesis or the activation of cannabinoid receptors through an active metabolite. Due to its lack of peripheral anti-inflammatory activity, it doesn't belong to the group of NSAIDs (115, 131). Nevertheless its central analgesic effect is mediated by stimulating descending serotonergic pathways (132). The main indications for NSAIDs are acute and chronic inflammatory triggered pain conditions. Monotherapy is often sufficient for tumor and non-tumor related pain conditions characterized by involvement of muscles, joints,

or bone structures. Other important indications are rheumatic diseases, nociceptive tumor pain, the treatment and partly the prophylaxis of migraine (129).

When pain is no longer adequately controlled with step 1 medications, escalation to opioids of either step 2 or 3 is indicated. The analgesic effect of the juice of the poppy plant *papaver somniferum* was known and used already by the Mesopotamians, Egyptians and Persians as early as 3400 BC (133). Opium and its derivates exert their effect at almost all sites of pain generation, transmission and processing. They act on opioid receptors, see chapter 1.2.2, pre- and postsynaptically, at the spinal level and in the periphery. In the substantia gelatinosa of the dorsal horn, opioids block the presynaptic voltage- gated calcium channels, thereby reducing calcium influx and inhibiting the subsequent release of neuropeptides (such as substance P) and glutamate from the primary afferent terminal. Postsynaptically, opioids open potassium channels that hyperpolarize the postsynaptic membrane of ascending fibers (134-136). Supraspinally, opioid receptors are distributed in the periaqueductal grey, the locus coeruleus and the rostral ventral medulla controlling the pain processing in the brain. Opioid receptors on primary afferent neurons and the dorsal root ganglia contribute to the peripheral analgesic effect of opioid ligands. The inflammatory mediators in the tissue induce the expression of peripheral opioid receptors. Blocking these receptors causes a local analgesic effect by suppressing calcium currents (136, 137). In its 2022 report, the Centers for Disease Control and Prevention states that opioids should be used with caution and that non-opioid therapies are preferred for acute, subacute and chronic pain. If the benefits for pain and function are expected to outweigh the risks to the patient, opioid therapy can be considered, for severe pain conditions (134, 138).

Adjuvant analgesics are drugs whose main use is the management of another medical condition with additional analgesic benefits (139). Commonly used adjuvants include corticosteroids, antidepressants, anticonvulsants, bisphosphonates, and neuroleptics.

Anticonvulsants such as carbamazepine, can lessen pain by acting on central sites while also regulating aberrant sodium channel activity in peripheral neurons. Both epilepsy and chronic pain have increased neuronal activity in common, and the use of such drugs in chronic pain conditions relies specifically on reducing neuronal hyperexcitability through regulation of voltage-gated channel (95).

Another group of adjuvants are antidepressants, tricyclic antidepressant (TCAs), including amitriptyline and imipramine, whose analgesic properties

were discovered as early as the 1960s, belong to this group (140). The following neurobiologically supported analgesic mechanisms of action of antidepressants have been described in the literature. TCAs enhance the effect of the inhibitory descending pathway by inhibiting serotonin and noradrenaline reuptake in the locus coeruleus and nucleus raphe. They also antagonize newly expressed nociceptive NMDA receptors, thereby reducing neuronal sensitization. Like anticonvulsants, antidepressants also have a membrane stabilizing effect by blockading sodium channels. Finally, they can increase the affective pain tolerance in the anterior cingulate gyrus and thus contribute to a better pain acceptance (140-143).

Neuroleptics play a minor role in pain management and should only be used as a last resort due to their adverse effects such as early dyskinesia and possible antidopaminergic side effects such as akinesia, tremor, rigor or akathisia. Nevertheless, they are used in treatment of pain-related sleep disorders, anxiolysis and acute treatment of agitation and confusion (129).

Glucocorticoids, like NSAIDs, inhibit the synthesis of prostaglandins, but at an earlier stage by inhibiting phospholipase A, which catalyzes the cleavage of phospholipids and the cell membrane. They also inhibit the synthesis of numerous cytokines, oedema formation and leukocyte migration, as well as the local accumulation of granulocytes and macrophages at the site of inflammation (144). Glucocorticoids are used in particular for systemic inflammatory diseases such as rheumatic diseases and as short-term, high-dose treatment for acute inflammatory conditions (145). In neoplastic soft tissue infiltrations, for example, the decongestant effect can reduce tissue pressure on healthy tissue, thereby influencing pain and function (146). Due to the side-effect profile, long-term use should be avoided and, if necessary, only used with caution (115). Additionally, attention should be drawn to the control of serum cortisol levels described in chapter 1.2.4. For optimal pain therapy, serum cortisol levels should be within the normal limits, because cortisol is needed for opioid receptor binding. Therefore, in patients with hypocortisolism, hydrocortisone should be given to supplement their lack of cortisol (112, 113).

Recently, cannabinoids have received increased attention. They are ligands for the cannabinoid receptor (CB), CB-1 and CB-2, of the endocannabinoid system, which is involved in a variety of neuronal processes, including the inhibition of TRPV1 receptors on GABAergic and glutamatergic interneurons, which play a central role in the facilitation of neuropathic pain. CB1 receptor density is high in many structures involved in the generation and control of pain, particularly in the basal ganglia, periaqueductal grey and amygdala, but also in the

hippocampus. However, experimental studies in humans have shown that tetrahydrocannabinol (THC) influences the affective perception of pain rather than its intensity. Therefore, cannabinoids have no place in acute pain therapy. CB2 receptors are found in many immune-active cells. They specifically increase the release of neurotransmitters that are important for neuroplasticity. The common indications are neuropathic and tumor pain as well as central pain in multiple sclerosis, but occasionally indications such as fibromyalgia or rheumatoid arthritis have also been investigated. Many of the studies using cannabinoids in the above-mentioned indications have serious methodological flaws and inconsistent results with rather weak effects have been found. Despite the limitations, cannabinoids are a valuable option in selected individual cases (129).

1.3.2 Multimodal pain management

For the purposes of this thesis, multimodal pain management will be briefly discussed below. For the sake of brevity, individual aspects will not be described in detail.

Multimodal pain management is a highly specialized, interdisciplinary, and integrative form of treatment for patients with advanced, severe chronic pain. Pain in the sense of an autonomic disorder has been gaining in importance in Germany for many years. It can be carried out on an inpatient basis, day-care or outpatient basis and differs from therapies that offer the individual components, but in which the components involved act largely independently of each other. Multimodal pain management is based on close interdisciplinary cooperation in a team consisting of doctors, psychologists and psychotherapists, physiotherapists, and occupational therapists. All participants are equal partners, and a central point of the approach are regular team meetings and the resulting unified treatment recommendations and goals for the individual patient. The therapy is composed of different building blocks from different disciplines. The length of therapy varies from a minimum of 7 to well over 21 days and from a minimum of 20 to more than 84 therapy units. The therapeutic interventions include specialist treatment approaches (*e.g.* optimization of analgesic therapy, recognition of maladaptive cognition, development and implementation of a physical exercise program), but are also partly interdisciplinary. The tasks of all disciplines involved include educational aspects in the sense of conveying an overarching biopsychosocial model of the disease. In addition to the main objectives of reducing pain and providing a comprehensive understanding of pain, other goals are also being pursued. For example, the prevention of

excessive immobilization can only be successful if the patient is instructed to move and, after initial problems, experiences that he or she is able to do so and that it even feels good. Motivation for self-responsible disease management as well as reducing dysfunctional patterns of pain management and recognizing and reflecting on factors that increase or decrease pain under the influence of interpersonal experience and behavior. It also promotes a positive perception of the body and a better balance between tension and relaxation, stress, and relief, and helps to avoid overexertion and improves physical performance through better recognition of performance limits (129).

2 OBJECTIVES

2.1 Aim of the study

The aim of this study is to investigate the effects of multimodal pain therapy on patients' heart rate variability (HRV) and whether the HRV has improved within 4 weeks.

2.2 Hypothesis

A 4-week Multimodal pain therapy can improve the Heart rate variability of chronic pain patients.

3 SUBJECTS AND METHODS

3.1 Ethical Approval

On February 27, 2023, the Institutional Review Board of the Medical School Regiomed Coburg approved this research project based on §2 of its statutes. Further study registration was not required due to the retrospective nature of this project.

3.2 Study design

The study design is a retrospective case series. All data were collected at the Pain Centre of the Regiomed Hospital Coburg, Bavaria, Germany and from the hospital's own information system Orbis. The resulting data were anonymized, and no personal patient-related information is traceable by third party.

3.3 Data collection

The required data were extracted from the HRV measurement program NilasMV.Ink version 2.0.4. All patients who actively participated in the multimodal pain therapy at the Pain Centre of the Regiomed Hospital Coburg during the period from Mai 2022 till January 2023, were included in the study. Heart rate variability recordings were performed by trained personnel during the first week of the therapy (M1) and at the end of therapy (M2). Serum cortisol levels were obtained from the patients' laboratory data, which were also taken at the start and end of treatment. Termination of the therapy, incomplete measurement data, or taking betablockers led to exclusion from the data collection.

3.4 Variables

From the above-mentioned data multiple parameters are of interest. As standard characteristics such as gender, age, BMI are used. From the heart rate variability parameters, explained under 1.1.2, the heart rate, high frequency, low frequency, HF/LF ratio, NN50, pNN50, and additionally blood cortisol levels (chapter 1.2.4) are used to evaluate the change in the HRV parameters. To get an overview of the patients' general stress profile, cortisol levels and stress index were also considered.

3.5 Statistical analysis

For the statistical analysis JASP (Version 0.17.2.0) [Computer software], Amsterdam, Netherlands, was used. Categorical data is presented as numbers (N) and percentages (%), and continuous data is reported as mean ±standard deviation (±SD) or median with the Interquartile range. For the descriptive statistics of continuous variables, to determine whether a given dataset follows a normal distribution the Shapiro- Wilk test was performed. The test evaluates the null hypothesis that the data is normally distributed against the alternative hypothesis that the data does not follow a normal distribution. The significance level of $P<0.05$ is used and represents the threshold below which the null hypothesis is rejected. Normally distributed data was then compared with a paired samples Student T Test. The findings are illustrated using the mean, standard deviation, standard error and Cohen's d for the effective size. Whereby Cohen's d values around 0.2 indicate a small effect, values around 0.5 indicate a medium effect and values around 0.8 indicate a large effect. Non-normally distributed data was compared with the Mann-Whitney-U test (Wilcoxon signed- rank). The data was presented using median and interquartile range. The significance cut-off was set to a P value of $P<0.05$. The outcomes are illustrated with the rank biserial correlation, this measures the strength and direction of the relationship between the ranks of the paired observations and the group to which they belong. Ranging from -1 to 1, where values closer to -1 or 1 indicate a stronger relationship, while values closer to 0 indicate a weak or no relationship.

4 RESULTS

A total of 49 patients provided informed consent for their data being used in future studies. 30 of these 49 patients who participated in a 4-week multimodal pain therapy at the Pain Centre of the Regiomed Hospital Coburg met the inclusion criteria to participate in the retrospective study. 19 were excluded due to the usage of ß-blockers or incomplete data. The mean age of the whole study group was 51,2 (±10.17) (N=30) years, with a minimum of 27 and a maximum of 63 years, and a gender distribution of 24 women and 6 men (80% vs 20%, respectively). Specifically, the median age in women was 52.0 (IQR=15.5) (N=24) years, while men have a median age of 60.0 (IQR=11.00) (N=6) years. The mean BMI was 26,34 (±5,5) (N=30), and the median was 24.2 (IQR=6.35) (N=24) and 27.05 (IQR=7.33) (N=6), in women and men, respectively

The Shapiro Wilk test for normal distribution gave the results presented in Table 4. Only the heart rate and the cortisol levels at the second measurement are normally distributed, all other parameters follow a non-normally distribution. Therefore, a T-test was performed for the heart rate and a Wilcoxon test for the remaining parameters.

Table 4 Shapiro Wilk test for normal distribution

N=30

	HR*-M1†,	**HR-M2‡**	**SI§-M1**	**SI-M2**	**HF‖-M1**	**HF-M2**	**LF¶-M1**	**LF-M2**
Shapiro-Wilk	0.988	0.968	0.898	0.636	0.629	0.778	0.560	0.412
P-value of Shapiro-Wilk	**0.978**	**0.479**	0.008	< .001	< .001	< .001	< .001	< .001

	HF/LF Ra-tio M1**	**HF/LF Ratio M2**	**NN50††-M1**	**NN50-M2**	**pNN50 (%)‡‡-M1**	**pNN50 (%)-M2**	**Cor-tisol M1**	**Cor-tisol M2**
Shapiro-Wilk	0.543	0.640	0.537	0.569	0.541	0.567	0.920	0.967
P-value of Shapiro-Wilk	< .001	< .001	< .001	< .001	< .001	< .001	0.014	**0.367**

Note: Significant results suggest a deviation from normality. *P*= 0.05.
Bold marks the normal distributed data.
* Heart rate
† First measurement at beginning of multimodal pain therapy
‡ Second measurement at the end of the multimodal pain therapy
§ Stress index
‖ High frequency
¶ Low frequency
** High frequency to Low frequency ratio
†† number of RRi exceeding 50 ms from the preceding interval
‡‡ Percentage of adjacent RRi that differ by more than 50 ms

The result of the paired sample Student T test for the normally distributed heart rates showed a non-significant difference. Since the p-value, 0.124, is greater than the given significance level of *P*= 0.05, it is concluded that there is not enough evidence to support a significant difference in heart rate measurements. Additionally, this is reflected in the low effect size of Cohen's d= 0.289 (Table 5). The Mean of heart rate M1 which is 78.93 with a SD of 12.01 and the mean of M2 which is 76.63 with a SD of 10.45. The Figure 2 shows the Mean of the two measurements with its standard error (SE) of 2.193 for M1 and a SE of 1.908 for M2. The second measurement turns out to be lower than the first one, presented by a mean difference of 2.3 between the two measurement points.

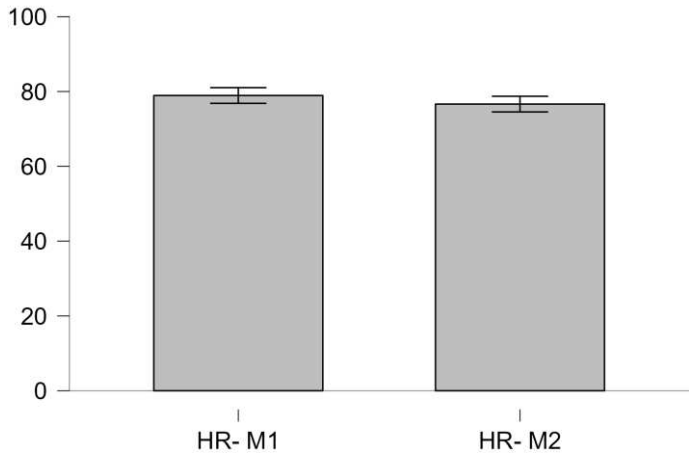

Figure 2 Mean of heart rate with SE.

Table 5 Descriptive data for Heart rate measurement.

N=30

Measure 1	Measure 2	p	Mean Difference	Cohen's d
HR- M1	HR- M2	0.124	2.300	0.289

In addition, a Wilcoxon signed-rank test was performed to check whether the non-normally distributed data have changed significantly between the beginning and the end of the therapy. This data contains the results from the measurement of stress index, high frequency, low frequency, ratio of high and low frequency, NN50 and pNN50. Furthermore, considering that the M1 data did not follow a normal distribution, a Wilcoxon signed-rank test was performed for the cortisol values. The two mean values from measurements M1 and M2 were compared with each other. The test results are shown in Table 6 and are briefly described.

Table 6 Wilcoxon signed-rank test

N=30

Measure 1	**Measure 2**	**Mean of M1**	**Mean of M2**	**p**	**Rank-Biserial Correlation**
SI- M1	SI- M2	600.897	456.63	0.080	0.368
HF- M1	HF- M2	275	235.5	0.116	-0.331
LF- M1	LF- M2	333.367	393.133	0.136	-0.320
HF/LF Ratio M1	HF/LF ratio M2	2.434	2.875	0.715	-0.080
NN50- M1	NN50- M2	19.333	14.433	0.596	-0.127
pNN50 (%)- M1	pNN50 (%)- M2	6.533	4.867	0.811	-0.072
Cortisol- M1	Cortisol- M2	14.475	12.797	0.093	0.327

Results for the non-normally distributed data presented as Mean, *P*-value and Rank-Biserial correlation.

The mean stress index of the patients, presented in Figure 3 and Table 6, shows a lower mean of 456.63 at the second measurement compared to 600.897 at the first one. This trend is visualized in Figure 3. Whereas the Wilcoxon signed- rank test yielded a *P*-value of 0.08, meaning that the decrease is not significant. The Rank-Biserial Correlation of 0.368 expresses a weak relationship between M1 and M2.

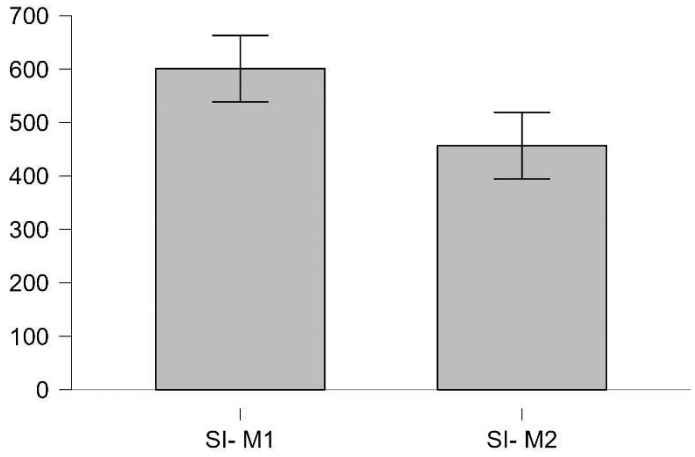

Figure 3 Mean of Stress index with SE

For the changes in the high frequency bands, representing the parasympathetic influence as explained in chapter1.1.2, there is only limited evidence to suggest a significant difference between HF-M1 and HF-M2 (p= 0.116). The Rank-Biserial Correlation is -0.331, indicating a weak negative relationship between the ranks and the measures. The mean HF values for M1 and M2, 274.767 and 235.5 respectively, are shown in Figure 4.

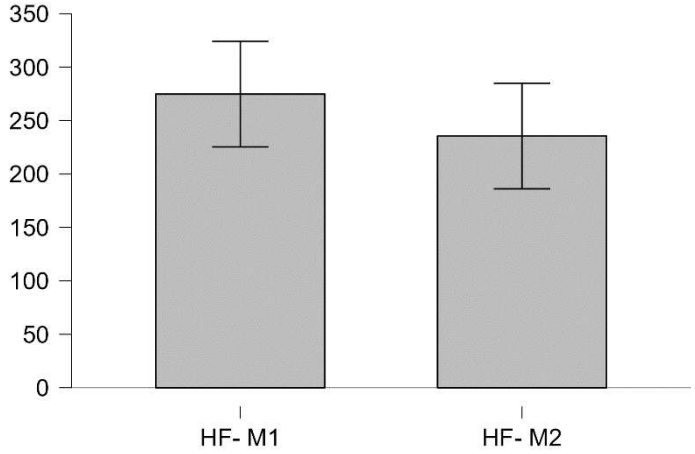

Figure 4 Mean of high frequency bands with SE

The difference in the low frequency measurements, M1 with a mean of 333.367 and M2 mean of 393.133, seen in Figure 5, is considered non-significant with a *P*-value of 0.136. A weak negative relationship between the ranks and the measures is indicated by Rank-Biserial Correlation of -0.320.

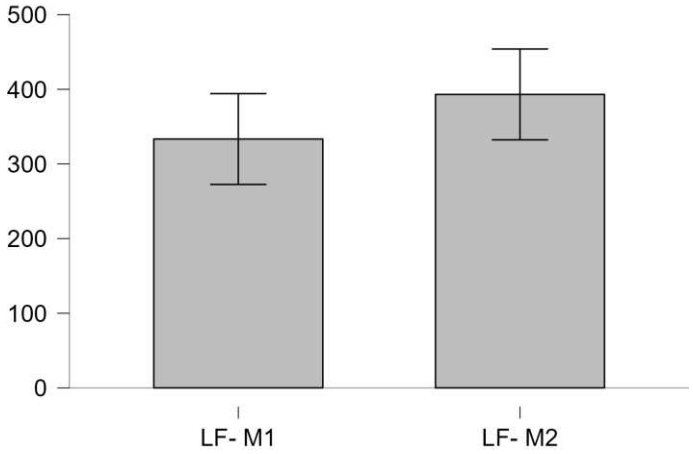

Figure 5 Mean of low frequency bands with SE

The same is the case for the HF/LF ratio, The *P*-value of 0.715 implies that there is no significant evidence to support a statistical difference between the two measurements. With a mean of 2.434 and 2.875 for M1 and M2 respectively. The Rank Biserial Correlation of -0.08 suggests a very weak negative correlation.

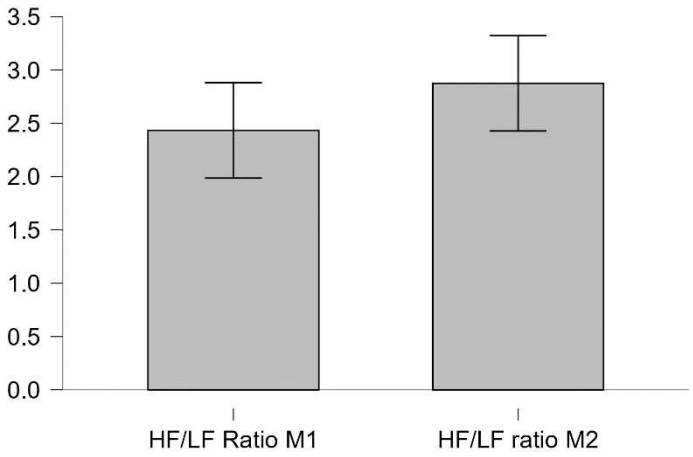

Figure 6 Mean of HF/LF ratio with SE

Both the NN50 and pNN50 variables exhibited non-significant changes between the two measurement points, as indicated by their respective P values of 0.596 and 0.811. Appropriately to this, the Rank Biserial Correlation of -0.127 and -0.072 respectively, point to a weak and very weak negative correlation. The mean value of NN50 at the first measurement was 19.333 and decreased to 14.433 at the second measurement. Similarly, the mean value of pNN50 at the first measurement was 6.533 and decreased to 4.867 at the second measurement. This is displayed in Figure 7 for NN50 and Figure 8 for pNN50.

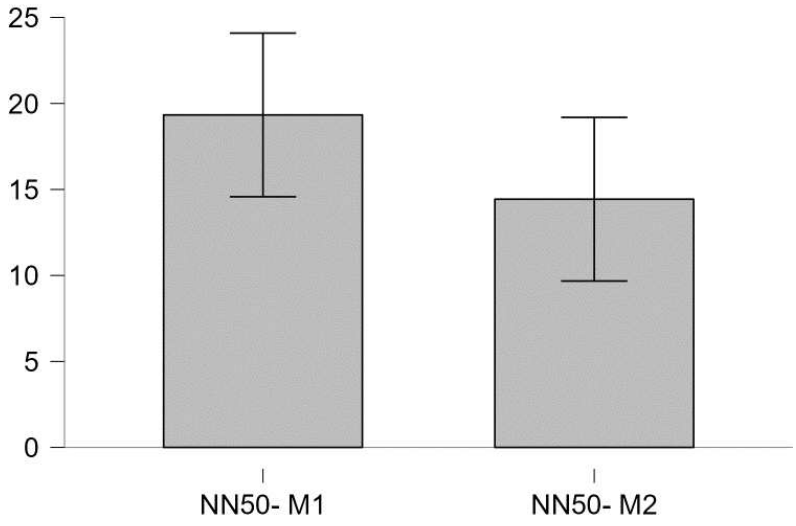

Figure 7 Mean of NN50 with SE

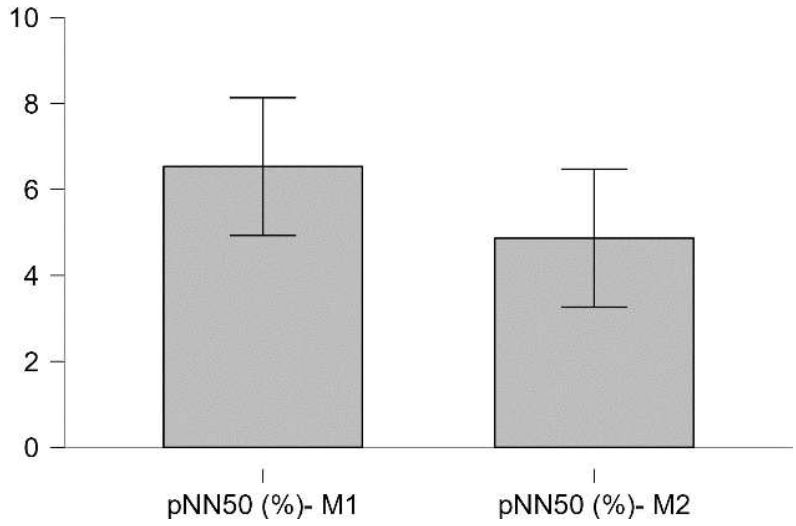

Figure 8 Mean of pNN50 with SE

The serum cortisol level mean at the start of therapy were higher, with a mean of 14.475, comparted to a mean of 12.797 after 4 weeks, illustrated in Figure 11. The result of the Wilcoxon signed-rank test yields a non-significant improvement displayed by a P value of 0.093.

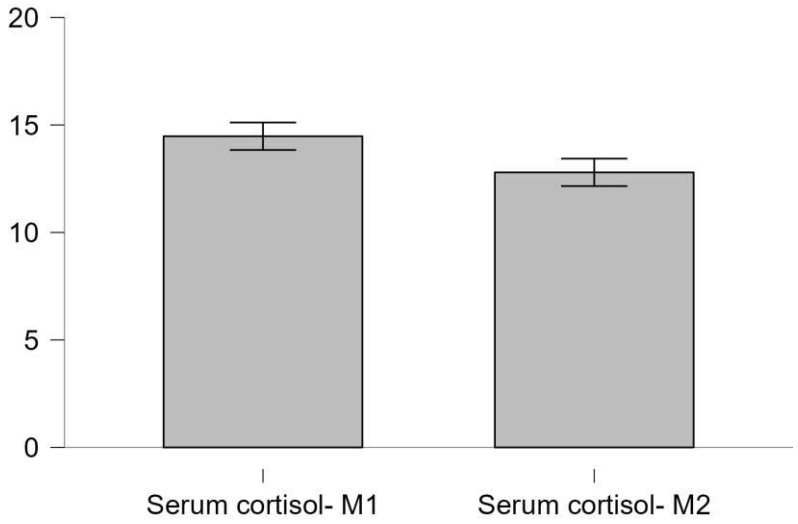

Figure 9 Mean of cortisol serum level with SE

In general, the results of this retrospective study about the HRV parameters in chronic pain patients demonstrated no significant change in the parameters, as determined by the appropriate statistical tests. However, it can be noted that for the values including SI (P=0.08) and serum cortisol (P=0.093), the p-values are close to the 0.05 significance level indicating a positive trend.

5 DISCUSSION

5.1 Interpretation of results

The study findings indicate that HRV does not exhibit statistically significant changes following a four-week multimodal pain therapy. Nevertheless, it is important to acknowledge that for the serum cortisol levels, and the stress index, which is the best summarizing integration of the individual HRV parameters, show a noticeable, but non-significant, improvement over the 4 weeks of therapy. This improvement may be attributed to habitational effect, wherein the patients already know what to expect during the measurement procedure and are consequently more comfortable during the second measurement. On the other hand, an alternative explanation would be that the adoption of an improved pain management strategy and the resulting reduction in pain levels may contribute to lower stress levels, leading to a subsequent reduction in heart rate, stress index and cortisol.

5.2 Discussion

The present study aimed to investigate the potential effects of a four-week multimodal pain therapy on heart rate variability in a retrospective study involving 30 participants. The initial hypothesis stated that a 4-week multimodal pain therapy can improve the HRV of the patients, with the idea of potentially using HRV as a monitor parameter for the effectiveness of multimodal pain therapy. However, the statistical analysis revealed a non-significant change in HRV over the 4 weeks of therapy, leading to the rejection of the hypothesis. The results suggest that the multimodal pain therapy applied in this study did not significantly influence the HRV. These findings indicate that the intervention did not result in the expected improvements in autonomic nervous system regulation, as reflected by HRV measures. The lack of a significant change in HRV may be attributed to various factors. For instance, the study has some statistical limitations, and the study design should be revised for future studies on this topic.

One possible explanation is the small group size of 30 participants. A small sample size reduces the statistical power of an analysis, making it less likely to detect true effects or relationships between variables. With a small sample size, the study may lack the necessary representation and variability to draw accurate conclusions about the target population. This increases the risk of Type II errors, where true effects may not have been detected due to limited sample representation. The generalizability of the findings may also be compromised due to the small and potentially unrepresentative sample. A larger sample size would have provided more robust statistical estimates and potentially increased the likelihood of observing significant

effects if they were present. Additionally, the gender distribution in the study also differs from that of chronic pain patients in Germany's general population. There were considerably more women than men participating in the study, 80% compared to 20% respectively (65).

Another limitation is the absence of a control group. This limits the ability to rule out other causes or to determine whether a deterioration would be expected without intervention. The problem is that it is ethically difficult to withhold therapy from a control group, especially if there is an established standard of care. The well-being and safety of study participants lies in the responsibility of the researcher. Denying treatment to the control group may be seen as withholding potential benefits or exposing them to unnecessary harm. Furthermore, participants have certain expectations when enrolling in a medical study, including the expectation of receiving a treatment that may alleviate their condition. Failing to meet this expectation by allocating them to a control group without treatment could negatively impact their trust in the research project and may cause them to drop out of the study and look for alternative treatment options.

As described in the introduction under point 1.2.2, pain is a highly subjective perception that can vary greatly among individuals (56, 59). This subjectivity introduces a significant challenge when attempting to operationalize a subjective sensation into an objectively measurable parameter, as one's own perception is usually of greater importance than the results of a measurement. It is plausible that the lack of a significant change in HRV-parameters could be attributed to the individual differences in pain perception within the study sample as well as the individual opinion if the 4-week multimodal pain therapy had any positive influence at all on their disease course. With the results of a standardized pain questionnaire and using the NRS to determine the individual pain severity and wellbeing, it would be possible to include patient self-assessment in the analysis. In particular, the emotional state during the measurements should be enquired, as HRV can be influenced by emotional imbalances (32)

Moreover, the relatively short duration of only four weeks between measurements limits our understanding of any potential long-term effects of the intervention. A longer follow-up period would be valuable to determine whether the observed changes in HRV or other outcomes may only appear at a later stage, or if they diminish over time. Longitudinal studies with extended follow-up periods can provide more comprehensive insights into the effects of interventions. Furthermore, other confounding factors might have influenced the results. The retrospective nature of the study makes it difficult to control for potential confounders that could

impact HRV, such as medication use, comorbidities, or individual differences in pain perception (39). These uncontrolled variables may have obscured any potential effects of the multimodal pain therapy on HRV, leading to non-significant results.

Serum cortisol levels are vulnerable to various factors. The cortisol secretion follows a circadian rhythm, highest in the morning, therefore different sampling times can distort the results and therefore need always to be at the same time, best in the morning. Besides chronic stress, exercise, medications, and medical conditions can also impact cortisol levels. Complicating matters is the fact that cortisol levels can be elevated by inflammation and infection. Most of the measurements were taken during the autumn and winter months, when the overall incidence of infections is higher than at other times of the year. This influence can be minimized by sampling blood always at the same time and by collecting data throughout the year.

Despite the non-significant findings, this study provides valuable insights into the relationship between multimodal pain therapy and HRV. The results highlight the need for further research with larger sample sizes, follow up and more robust study designs to comprehensively evaluate the effects of such interventions on HRV. Future studies should consider incorporating additional subjective measures and using prospective designs to minimize confounding factors and enhance the reliability of the findings.

6 CONCLUSION

In conclusion, the retrospective study examining the effects of a four-week multimodal pain therapy on heart rate variability did not yield significant changes in HRV, leading to the rejection of the hypothesis that a four-week multimodal pain therapy has a positive effect on HRV. The non-significant results highlight the need for cautious interpretation, considering the limitations associated with the study design. The small sample size, short duration between measurements, and subjective nature of pain perception, are important factors to consider when interpreting the findings. Future research should employ larger sample sizes, longer intervention periods, and objective pain assessment measures to further investigate the effects of multimodal pain therapy on HRV. Additionally, efforts should be made to ensure representative demographic characteristics in study populations to enhance the generalizability of the findings. Overall, these findings emphasize the need for robust, well-controlled studies to provide more comprehensive insights into the relationship between pain therapy, HRV, and its clinical implications.

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8 SUMMARY

Objectives: Previous studies have shown that heart rate variability is reduced in chronic pain patients. The aim of this was to investigate the effects of a 4-week multimodal pain therapy on the heart rate variability parameters in chronic pain patients and whether they will improve.

Materials and methods: A retrospective pre post analysis was performed analyzing the HRV records of 30 patients who participated at a 4-week multimodal pain therapy at the Pain Centre of the Regiomed Hospital Coburg, Bavaria, Germany in the period of 9 months, from Mai 2022 till January 2023. The HRV parameters collected at the beginning and end of the therapy considered in this study are as follows: heart rate, stress index, high frequency, low frequency, HF/LF ratio, NN50, pNN50. In addition, the cortisol levels were also taken into account for a general stress profile. The collected data was analyzed with JASP (Version 0.17.2.0), and normally distributed data were compared with a paired samples Student T Test, whereas non-normally distributed the Mann-Whitney-U test (Wilcoxon signed- rank). The significance level was set to a *P*-value of <0.05.

Results: The mean age of the study group was 51.2 (±10.17) years, with a minimum of 27 and a maximum of 63 years, and a gender distribution of 24 women and 6 men. Only the data for heart rate followed a normal distribution, all others were non-normally distributed. The statistical pre-post analysis revealed non- significant changes, neither in the HRV-parameters heart rate (*P*=0.124), stress index (*P*=0.8), high frequency (*P*=0.116), low frequency (*P*=0.136), HF/LF ratio (*P*=0.715), NN50 (*P*=0596), pNN50 (*P*=0.811) nor in the serum cortisol levels (*P*=0.093).

Conclusions: This study came to the result that the hypothesis that the HRV parameters would improve with a 4-week course of multimodal pain therapy must be rejected due to the lack of significant changes. However, the statistical limitations such as small sample size, short duration between measurements, and the subjective nature of pain perception, have to be mentioned. Although non-significant, positive tendencies were observed for SI and cortisol. There is a need for more studies on this topic with improved study design.

9 CROATIAN SUMMARY

Naslov: Retrospektivna pre-post analiza promjena parametara varijabilnosti srčanog ritma kod pacijenata s kroničnom boli koji su proveli četverotjednu multimodalnu terapiju boli.

Ciljevi: Prethodna istraživanja su pokazala da je varijabilnost srčanog ritma smanjena kod pacijenata s kroničnom boli. Cilj ovog istraživanja bio je ispitati učinke četverotjedne multimodalne terapije boli na parametre varijabilnosti srčanog ritma kod pacijenata s kroničnom boli i provjeriti hoće li se poboljšati.

Materijali i metode: Izvršena je retrospektivna pre-post analiza analizirajući zapise HRV-a 30 pacijenata koji su sudjelovali u četverotjednoj multimodalnoj terapiji boli u Centru za bol u bolnici Regiomed Coburg, Bavarska, Njemačka, u razdoblju od kolovoza 2022. do veljače 2023. HRV parametri prikupljeni na početku i kraju terapije koji su uzeti u obzir u ovom istraživanju su sljedeći: srčani ritam, indeks stresa, visoka frekvencija, niska frekvencija, HF/LF omjer, NN50, pNN50. Osim toga, razine kortizola također su uzete u obzir za opći profil stresa. Prikupljeni podaci analizirani su pomoću JASP-a (Verzija 0.17.2.0), a normalno distribuirani podaci uspoređivani su uparenim uzorcima t-testom, dok su neregularno distribuirani podaci testirani Mann-Whitney-U testom (Wilcoxonov potpisani rang). Razina značajnosti postavljena je na vrijednost $P < 0.05$.

Rezultati: Srednja dob studijske skupine bila je 51,2 (±10,17) godina, s minimalnom dobi od 27 godina i maksimalnom dobi od 63 godine, uz rodnu raspodjelu od 24 žene i 6 muškaraca. Samo podaci o srčanom ritmu imali su normalnu distribuciju, dok su svi ostali bili neregularno distribuirani. Statistička pre-post analiza otkrila je neznačajne promjene, ni u jednom od parametara varijabilnosti srčanog ritma - srčani ritam (P=0,124), indeks stresa (P=0,8), visoka frekvencija (P=0,116), niska frekvencija (P=0,136), HF/LF omjer (P=0,715), NN50 (P=0,596), pNN50 (P=0,811) niti u razinama kortizola u serumu (P=0,093).

Zaključak: Ovo istraživanje je došlo do rezultata da se hipoteza da će se parametri varijabilnosti srčanog ritma poboljšati četverotjednim tečajem multimodalne terapije boli mora odbaciti zbog nedostatka značajnih promjena. Međutim, treba napomenuti statistička ograničenja kao što su mali uzorak, kratko vrijeme između mjerenja i subjektivna priroda percepcije boli. Iako nisu značajni, primijećene su pozitivne tendencije za indeks stresa (SI) i kortizol. Potrebno je provesti više studija na ovu temu s poboljšanim dizajnom istraživanja.