Method of Electrical Stimulation Triggered by Cardiac Cycle to Facilitate the Treatment of Fibromyalgia and other Chronic Diseases - Systolic Extinction Training (SET) Protocol

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Abstract

**Background:** Recent studies by our group have shown that a specific cardiac cycle triggered electrical stimulation in conjunction with operant-behavioral pain treatment (OBT) can reset the abnormal relationship between blood pressure (BP) and pain in fibromyalgia and chronic pain patients. The process called "systolic extinction training" (SET) promotes a learning process that increases baroreflex sensitivity (BRS), which reestablishes the normal inverse correlation between BP and pain (BP↑pain↓) by activating nucleus tractus solitarius (NTS) reflex arcs. Herein, we present the SET electrical stimulation design, which is administered during the systolic or diastolic phases of the cardiac cycle.

**Method:** The complex trigger for the SET stimulation processes the ECG signal and predicts when the maximum and minimum BP pulse wave at the arterial baroreceptor using a 3-lead derivation by Einthoven. The stimulation routine is:
1. Capture and filter the ECG signal.
2. Calculate the Inter-beat Interval (IBI) for the last 4 beats and predict the next systolic and diastolic trigger points.
3. Deliver a randomized amplitude electrical pulse sequence to avoid adaptation.

**Results:** By delivering electrical stimuli to the arterial baroreceptor when the pressure wave from the systolic peak is the highest, maximizes the efferent signal to the brain. This type and timing of stimulation is theoretically maximizes the impact in the brain for a given stimulus level and increases the brain’s receptivity to the operant therapy, which then follows.

**Conclusion:** The described electrical stimulation design is used to activate NTS reflex arcs. Preliminary results suggest that SET provides long lasting treatment effects in diseases such as chronic pain, essential hypertension, sleep apnea and hyperglycemia.

Keywords: Electrical-stimulation; R-wave trigger; Baroreflexsensitivity; Fibromyalgia; Chronic pain; SET

Introduction

Pain regulatory systems are modulated by cardiovascular dynamics. The inverse correlation between blood pressure (BP) and pain (BP↑pain↓) is disturbed in patients with chronic pain. Fibromyalgia patients, in particular, show a positive correlation (BP↑pain↑) and reduced baroreflex sensitivity (BRS) [1]. BRS is a marker for the responsiveness of the body to regulate BP changes in response to changes in heart rate and defined as (∆heart rate/∆BP) [2]. "Systolic extinction training" (SET) provides a learning process that increases BRS, that reestablishes the normal inverse correlation between BP and pain (BP↑pain↓). The restored modulation of the cardiovascular dynamics allows naturally inhibition of pain sensation.

The purpose of the stimulation is to influence the link between triggered pain-stimuli and BP. BP sensitive cells, baroreceptors located in the carotid sinus, mediate BP, heart frequency, and venous tone, and interact with pain perception [3,4]. Increased arterial BP in healthy individuals activates afferents in the carotid sinus that terminate in NTS in the brain stem. Activated NTS neurons project to regions in the brain stem that regulate sympathetic and parasympathetic tone. Stimulation of the baroreceptors (via increased arterial BP or cardiopulmonary baroreceptors (via increased venous BP or lung expansion) decreases sympathetic tone and increases parasympathetic activity. This sympathico-vagal balance along with heart rate, arterial and venous BP, and vascular resistance create a continuously adjusting chaotic regulatory system. Activation of baroreceptors also modulates sensory functions and pain sensitivity through activity in NTS neurons and modulates network areas involved in pain perception (for example insula, ACC, SI, and SII). Additionally, considerable evidence suggests that quick phase changes in arterial BP during the cardiac cycle influences pain perception. The activation of baroreceptors in the carotid sinus during the systolic phase of the cardiac cycle reduces experimental pain perception, which can be identified by differences in electro-cortical activity [5,6]. To summarize, an increase in tonal or phasic activation of arterial BP in healthy individuals leads to decreased pain perception. The electrical stimuli have two effects, elevating blood pressure through the reaction of the autonomic nervous system that stimulate the baroreceptors and activating the limbic system for pain processing.

Adaptation in healthy subjects, essentially a learning process,
reduces the brain’s activation level and there is a reduced need to inhibit pain. Fibromyalgia patients, in contrast, do not inhibit their pain, but rather increase activity in pain-related brain regions and perceive increased pain [7,8]. Our assumption is that reduced BRS, which occurs in fibromyalgia patients and with other types of persistent pain, prevents the normal pain inhibition process that is implemented through the NTS reflex arc. SET, the stimulation, along with the associated operant-behavioral pain therapy (OBT), builds new associations in the brain to inhibition and reduce pain-related brain activity. This effect is most commonly found with the increasing failure over time of pain medication and the increased pain experience of long-term opiate use.

Device description and preliminary considerations

Some pre-considerations are required to administer an accurately timed electrical stimulus synchronized to the cardiac cycle. Independently of the hardware (data acquisition unit, PC...), it is necessary to examine time and the flow of events in terms of the heartbeat cycles and the beat-to-beat changes. Heart rate is individual and depends on age, physical fitness, and stress factors. The normal resting rate is between 60 bpm and 100 bpm, which correspond to inter-beat-intervals (IBI) of 1000 ms and 600 ms. Figure 1 shows a simplified ECG of the relevant times on an IBI of about 1000 ms.

The cardiac cycle can be divided into two main phases, the systolic and diastolic phases. A more detailed description of the time and pressure changes, reflecting the changes of the left ventricular and atrial pressure is shown in Figure 2.

In order to trigger a stimulus at the peak of the pressure wave at the arterial baroreceptor, we need to determine how the arterial pressure varies over time. The systolic phase begins with the rise of the left ventricular pressure. When the ventricular and the arterial pressure, both rise up to its maximum, this point is marked as the T-wave. The end of the T-wave is also the end of the systolic phase and the beginning of the early-diastolic phase. The diastole ends with the next P-wave, which also initiates the next cycle.

The resulting arterial pulse wave (APV) arrives at different times. The arrival delay is called pulse transit time (PTT). Variations in PTT are caused by pulse wave velocity (PWV) which depends on changes in blood vessel geometry (eg. changes in vessel transitions, superpositions with reflected waves) and is strongly influenced by the “stiffness” of the blood vessels [9,10]. The goal is to deliver an electrical stimulus triggered by the R-wave after compensating for the PTT and intrinsic system delays (calculation time and electrical pulse transit time).

The design cannot adjust for instant IBI variation or PTT variation, which are minor, but does adjust for hardware related latencies. The specific design of acquisition and stimulation setup is presented in Figure 3. 1) The first step is to capture the ECG Signal. 2) The detection of the R-wave in the ECG-Signal can be done with software (analyzing and detection in hardware is also possible). 3) The generated trigger pulse is transmitted to the stimulation-control-unit. This unit is controlled by a microprocessor that controls stimulation time and pulse design pursuant to an event table – see below in Table 1. This information is send to the stimulation-unit, which generates and administers the electrical stimulus.

Material and Methods

ECG-Derivation

The used data-acquisition main-unit MP150 is branded by BIOPAC Systems, Inc. To record the ECG, the amplifier module ECG100C also branded by BIOPAC was used in Einthoven’s 3-limb-lead configuration. The ECG100C provides a R-wave detector, but this function was not used because of the loss of the ECG-waveform. For visualization, calculation, and storage, the software AcqKnowledge was employed.

R-Wave-Detection

For the determination of the loss of time caused by analyzing the ECG signal, it is necessary to understand the R-wave detection process. One of the simplest methods to detect the R-wave is to define amplitude thresholds. Figure 4 illustrates the general procedure. In most cases, it is useful to filter the ECG-signal before R-wave detection to eliminate trends and disruptive frequencies. For this we use a band pass filter is used that eliminate signals below 0.05 and above 35 Hz. The detection formally follows the simple threshold function (eq. 1).

\[
y(t)_{\text{thr}} = \begin{cases} 1, & \text{if } L_y(t) \leq y(t) \text{ and } L_y(t) \leq y(t) \\ 0, & \text{any other} \end{cases}
\]

If the R-wave amplitude reaches the first threshold \( L_y(t) \), the analysis begins and the start time of the trigger pulses is set. When the R-wave amplitude achieves the second level \( L_y(t) \), the R-wave detection of this wave is completed and the end time of the trigger pulse is defined.

To identify the intrinsic delays that might be generated by the R-wave detection, an ECG simulation was done. A well-defined signal (eq. 2) was generated by a function-generator and recorded simultaneously by the acquisition unit and oscilloscope. A second channel at the oscilloscope was used to record the generated output trigger signal.

\[
f(x) = \sin(x) / x
\]

Figure 5a shows the recorded signal at the acquisition unit and the corresponding trigger-pulse. For evaluation of the intrinsic delay, it is valuable to look at the differences between \( t_{\text{end}} \) and \( t_{\text{start}} \). The time of the maximum of the simulated R-wave on both the acquisition unit and oscilloscope was used as the reference point to identify the time shift between input R-wave signal and output trigger pulse. At the site of the acquisition unit we registered a time difference of:

\[ t_{\text{end}} - t_{\text{start}} \]
Given our assumptions, it is nearly half of the length of the trigger-pulse. In figure 5b you can see that there is a slight lag between the output trigger-pulse and the input sin(x)/x signal. Also striking is a slightly reduced pulse width on the output trigger signal. This could be caused by the generation processes of the output signal in the hardware of the acquisition unit. This was not investigated further because only the trigger start time was in focus of interest. To verify the delay we also calculate the difference of:

$$\Delta t = t_{max}^{acq} - t_{max}^{acq} = 708.1 \text{ms} - 665.5 \text{ms} = 42.6 \text{ms}$$

This results in a delay as follows:

$$T_{delay} = \Delta t_{acq} = 31.4 \text{ms}$$

Considering the lengths of the systole and diastole phases, an intrinsic delay of this magnitude can be easily taken into account by increasing the delay calculation of the stimulation time point. Relative to the exact time point of the R-peak there is no delay because the first detection threshold is achieved in time before the R-peak occurs. But as already mentioned this is strongly dependent on selection of threshold values and modulated by the variation of the width of the R-wave curve. As the first threshold value increases with a narrow curve is, the probability of getting a real delay increases.

**Calculating Stimulus-Time**

For the calculation of the stimulus onset for the next cardiac cycle it is necessary to estimate the duration of the next IBI. In the device design, we assume a constant heart rate and a constant IBI over the last four beats. This is realistic since the subject is in a relaxed state, sitting in a chair and is accustomed to the process.

<table>
<thead>
<tr>
<th>StimTime (%) of IBI</th>
<th>StimOn (ms)</th>
<th>StimOff (ms)</th>
<th>Duration (count)</th>
<th>Amplitude (mA)</th>
<th>Pause (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>7</td>
<td>12</td>
<td>5</td>
<td>DT</td>
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</tr>
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<td>80</td>
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</tbody>
</table>

Table 1: Stimulation protocol.

**Figure 3:** Acquisition and stimulation setup.

**Figure 4:** Schema: a) ECG waveform, b) Level L2 first detection threshold and L1 second threshold c) Output, generated trigger-pulse.
The stimulation control unit registers every trigger pulse from the acquisition unit. With every incoming pulse a calculation of the actual IBI and an estimation of the next occurring IBI over an averaging of the last three IBIs is performed (eq. 4).

\[ \tilde{T}_{IBI}^{\text{actual}} = \frac{1}{N} \sum_{i=1}^{N} T_{IBI}^{i} \]  

(4)

In our treatment design, two stimulation times are scheduled: One at 20% of the estimated IBI for stimulation in the systolic phase, and one at 80% for the diastolic phase. If the IBI is divided into about 40% systolic phase and about 60% diastolic phase, it is easier to see differences between the estimated and actual IBI. The transition between systolic and diastolic phase in one cycle is about at \( 0.4 \Delta T_{IBI}^{\text{actual}} \), stimulation at 20% of estimated IBI would occur in this transition region by differences as follows:

\[ 0.2 \tilde{T}_{IBI}^{\text{estim}} = 0.4 T_{IBI}^{\text{actual}} \rightarrow 0.5 \tilde{T}_{IBI}^{\text{estim}} = T_{IBI}^{\text{actual}} \]  

(5)

Sensitivity: If the estimated IBI is 800 ms and the actual IBI is 400 ms, this would result in fast beat-change from 75 bpm up to 150 bpm, which is very unlikely within a few heartbeats. The other limits are also improbable:

\[ 0.8 \tilde{T}_{IBI}^{\text{estim}} = 0.4 T_{IBI}^{\text{actual}} \rightarrow 2 \tilde{T}_{IBI}^{\text{estim}} = T_{IBI}^{\text{actual}} \]  

(6)

\[ 0.8 \tilde{T}_{IBI}^{\text{estim}} = T_{IBI}^{\text{actual}} \]  

(7)

The definition of the stimulation times (20% to 80%) has another advantage. The pulse transit time (PTT) is the transit time of the outgoing pulse wave from the heart to the baroreceptors, which are located in the carotid sinus. Our first experimental investigation of the time between the maximum of the R-wave in the ECG and the pulse wave maximum in the carotid sinus is about 100 ms (Figure 6). This includes both the PTT and the time for the rising left ventricular pressure. Thus stimulus onset is only slightly delayed at the baroreceptor activation point. This does not include the transmission time from the baroreceptor to the NTS.

**Stimulus-Design**

The Table 1 describes the sequence of events for the stimulation routine. Every row represents a discrete stimulation event. \( \text{StimTime} \) is the delay for the stimulation in percentage of IBI. \( \text{StimOn} \) is the stimulation onset time in milliseconds (biphasic square wave at 1KHz which equals a 500 µs pulse width). \( \text{StimOff} \) is a delay, which immediately follows the \( \text{StimOn} \). \( \text{Duration} \) is the number of repeats of the \( \text{StimOn} \) and \( \text{StimOff} \) cycle. \( \text{Amplitude} \) is the patient-specific intensity of the stimulation in milliampere that is input immediately prior to the stimulation by determining the patient’s actual thresholds. \( \text{Pause} \) in seconds is the delay before the next discrete event in the table. The events in the Table 1 occur in a pseudo randomized order to minimize adaptation, but each table event occurs each time the table is run. This results in a treatment time of about 8 minutes. Our own recent experiments [11] showed that healthy individuals begin adaptation after about 8 minutes of stimulation, hence the 8-minute treatment time. A design goal is to avoid adaptation.

We use 3 different stimuli adjusted to the individual sensory and pain tolerances, which as stated previously are captured immediately before the stimulation. We capture detection threshold (DT), pain threshold, and tolerance threshold. The stimulation then consists of 1 pain-free (DT) stimulus and 2 pain stimuli that are defined by:

\[ \text{HTT} = \text{PainThresh} + 50\% \cdot (\text{ToleranceThresh} - \text{PainThresh}) \]  

(8)

\[ \text{TT} = \text{PainThresh} + 75\% \cdot (\text{ToleranceThresh} - \text{PainThresh}) \]  

(9)

**Figure 5:** Measured Signals on both sites: acquisition-unit and oscilloscope. (a) Recorded Signal and corresponding output trigger pulse (Acquisition-unit). (b) Input Signal and output trigger-pulse (Oscilloscope).

**Figure 6:** Synchronized measurement of ECG and pulse-wave. Pulse wave was measured by an inductive motion sensor.
These 3 different stimuli provoke different BP levels that follow different pressure intensities in the carotid sinus. Dworkin et al. showed that the variation of the pressure intensities in the carotid sinus activates the baroreceptors, which change their rate of firing based upon the local pressure [3]. The speed/intensity of the response to baroreceptor activation is captured by BRS, which is the slope of the change in heart rate divided by the change in BP. An elevation of BRS corresponds to a higher activation of the NTS. To the extent that BRS is changed in response to the stimulation, it can be thought of as a new-structuring of CNS response to peripheral and experienced pain. The response triggers the efferent and afferent pathways that result in normal inhibition of pain. Experimentation with the devices with Fibromyalgia patients shows that this actually occurs in the short run and, more importantly, with the proper OBT therapy, that this change can be maintained at least over 12 months [12].

The current stimulus is administered in the form of a biphasic square wave to avoid net potential charges. The stimulus has a phase change frequency of 1 kHz.

The negative edge of the cathodal pulse activates the axons of primary afferents directly, bypassing the receptor and receptor processes such as sensitization and fatigue. The sensitivity of axons to the electrical stimulus is related to directly to axon diameter. As stimulating current is increased from zero, the first sensory axons activated are the large diameter, thickly myelinated A-beta afferents that mediate fine touch. As stimulating current is further increased the stimulus activates the thinly myelinated A-delta afferents, a subset of which mediate localized pain sensation, usually of a sharp pricking or buzzing quality. This is the mechanism of pain activation used here. Increasing stimulus current further activates the unmyelinated C-fiber afferents, a subset of which evokes pain that is usually perceived as burning. C-fiber stimulation is used in methods that evoked the nociceptive reflex. The sensations are quite unpleasant and not necessary for the method described here.

Conclusion

The device delivers randomized pain and pain-free stimuli in conjunction with the cardiac cycle at the point that they are most useful. This procedure – the method of peripheral electrical stimulation dependent on cardiac cycle - is designed to have the greatest impact upon the pain regulatory systems of the brain and the heart, which influences both the sympathetic and parasympathetic excitatory and inhibitory pain systems. In essence, the stimulation creates a situation in which the brain can relearn how to react to pain. SET uses this pain pattern disruption in conjunction with OBT that addresses pain behaviors, pain cognitions, and pain adaptations and lead to a new programming of the brain. This paper describes the technical details of the stimulation protocol.

This electrical stimulation design may activate NTS reflex arcs. The NTS, at the head of the nervus vagus, inhibits pain, improving sleep and decreasing blood pressure.

In pilot studies with fibromyalgia and low back pain patients, we applied the electrical stimulation design as a treatment with 10 repetitive sessions applied within 5 weeks that were combined with the highly effective operant-behavioral pain therapy (SET). This initial approach resulted in remission of the chronic pain for more than 6 months in 100% of the patients and for 12 months in 82% of the patients. An own RCT-study has found that either of treatment protocols alone are only marginally effective, however when combined the treatment is highly effective. Comorbid symptoms such as hypertension, unrefreshed sleep, diabetes mellitus were significant clinically improved. Thus, diseases such as chronic pain, essential hypertension, sleep apnea and hyperglycemia might profit, with long-lasting effects, from treatment that combines OBT and electrical stimulation dependent on the cardiac cycle.

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Author Contributions

Thieme K.: Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data as well as drafting the article or revising it critically for important intellectual content and final approval of the version to be published;

Malinowski R.: Substantial contributions to conception, acquisition of data and analysis as well as drafting the article or revising it critically for important intellectual content and final approval of the version to be published;

Monbureau O.: Substantial contributions to conception and design, acquisition of data as well as drafting the article and final approval of the version to be published;

Gracey RH.: Substantial contributions to conception and design, or analysis and interpretation of data as well as drafting the article or revising it critically for important intellectual content and final approval of the version to be published.

All authors are agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Disclosure

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