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Original Article

A double-blind placebo-controlled heart rate variability investigation to evaluate the quantitative effects of the organic nanoscale aeon patch on the autonomic nervous system

Homer Nazeran

Department of Electrical and Computer Engineering and Biomedical Engineering Graduate Programs University of Texas at El Paso, USA

ABSTRACT

In this first double-blind-placebo-controlled investigation of the Aeon Patch, electrocardiographic data were acquired from 50 well-hydrated volunteers [21 females and 29 males, age: 19-79, weight: 117 - 334 lbs, height: 5'-6",3"], under 3 different conditions for a total duration of 15 min (5 min/condition). Condition 1: Control (C) - while wearing no Patch, Condition 2: Placebo (P) or Active (A) - after wearing either the Placebo or the Aeon Patch for 20 min, and Condition 3: Active (A) or Placebo (P) - after wearing either the Aeon or the Placebo Patch for 20 min. There was a washout period of 15 min between Conditions 2 and 3. All involved in the investigation were blind to the (A) and (P) Patches as they looked exactly the same and were assigned in a random fashion. The hypothesis to be tested was: Wearing the Aeon Patch for 20 min reduces stress. Data were first quality assured and those subjects who showed a parasympathetic response after wearing the Patch within 20 min were identified as early responders. Thirty subjects (60%) achieved a relaxed state after wearing the Aeon Patch as early as 20 min. Statistical analysis (one-sample inference) was used to compare the spectral features of the responders. The normalized LF/HF decreased significantly ($24\% \pm 9\%$ after 20 min) in condition (A) compared to condition (P) with a p -value < 0.047 ($n = 30$) in responders. Therefore, the hypothesis that wearing the Aeon Patch for 20 min reduces stress was accepted as true.

Keywords acupuncture, aeon nanoscale organic patch, heart rate variability signal analysis, lifewave, stress reduction, CV6 acupuncture point

INTRODUCTION

The Aeon Patch is designed by its manufacturer as a unique and novel organic nanoscale patch that mildly stimulates a specific acupuncture point (CV6) to reduce “stress and inflammation.” [For a general description of LifeWave patented non-transdermal patch technology, please refer to Nazeran et al., 2012]. Preliminary clinical research has shown that this Patch starts exerting a balancing effect on the autonomic nervous system (ANS) within as early as 10 min of its application as a consequence of eliciting a *relaxation response* (creating a calm and stress-free body state). Infrared thermal imaging has illustrated that this Patch reduces inflammation by lowering the C-reactive protein that can damage healthy tissue and even DNA [manufacturer’s unpublished data].

Heart Rate Variability (HRV) signal refers to beat-to-beat variation of heart rate (HR) and represents the cyclical changes in HR. As HR is modulated by both parasympathetic and sympathetic inputs of the ANS, HRV can be utilized as an indirect and non-invasive marker of autonomic regulation and control under different physiological conditions (McMillan,

2002). High HRV reflects an ANS that is adaptable and dynamically responsive to change whereas reduced HRV is indicative of an abnormal or restricted ability of the ANS in maintaining homeostasis (McMillan, 2002; Pumprla et al., 2002). Pharmacological studies and spectral analysis of the HRV signal have revealed two clear peaks in its power spectrum: a High Frequency (HF) and a Low Frequency (LF) component. The HF peak which is typically centered on 0.25 Hz (0.15 – 0.4 Hz) arises from the coupling of the respiratory and cardiac cycle and is termed Respiratory Sinus Arrhythmia (RSA). Vagal blockade abolishes this HF peak suggesting that it is parasympathetically mediated. The LF peak, which is typically centered around 0.1 Hz (0.05 – 0.15), arises from blood pressure changes (Mayer-waves) and can be modified by both vagal and sympathetic blockade and therefore reflects both sympathetic and parasympathetic influences (Pumprla et al., 2002). The spectral band 0.003 - 0.05 Hz, known as Very Low Frequency (VLF), is possibly related to the long-term regulatory mechanisms. A better measure of sympathetic modulation is the LF/HF, which is indicative of the balance between sympathetic and parasympathetic activity (sympathovagal balance) with a low frequency bias suggesting sympathetic dominance. The LF/HF is an index that relates the *balance* between sympathetic and parasympathetic parts of the autonomic nervous system and hence shows the level of sympathetic or parasympathetic dominance (stress or deep relaxation) in a subject.

A number of research studies in recent years have

*Correspondence: Homer Nazeran

E-mail: hnazeran@utep.edu

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confirmed that higher variability in HR is indicative of a healthy ANS, while reduced variations in the HR is a sign of diseased or pathological state. Hundreds of research articles have been published on applications of HRV signal analysis. These articles have explored the relationships between HRV signal and blood pressure, myocardial infarction, nervous system, cardiac arrhythmia, diabetes, respiration, renal failure, gender, age, drugs, smoking, alcohol consumption, to name a few (Malik, 1996). HRV signal analysis seems to become even more popular in quantitative patient data analysis in the future. In short, HRV signal analysis provides a quantitative marker of the autonomic nervous system as the regulation mechanisms of beat-to-beat variations in the HR originate from the sympathetic and parasympathetic arms of the ANS.

Previous double-blind-placebo-controlled clinical studies in humans have shown that LifeWave patches produce a thermoregulating effect by mild stimulation of the acupuncture points on the body, promoting the parasympathetic nervous system activity. This parasympathetic dominance has a relaxing, stress reducing, or skin cooling effect (Nazeran, 2007; Nazeran et al., 2012). This in turn elicits targeted physiological responses.

To provide quantitative evidence and substantiate the claims that Aeon Patch reduces *stress*, it was necessary to acquire physiological data in a comfortable and noninvasive fashion to assess and quantify the level of *stress* and its reduction by using well-proven and established analytical research tools in a double-blind-placebo-controlled investigation. Therefore, a small wearable wireless electrocardiographic (ECG) data acquisition system was used to capture ECG data from 50 volunteers under 3 different conditions: *Control* (C) – while wearing no Patch, *Placebo* (P) – while wearing a Placebo Patch for 20 min, and *Active* (A) – while wearing the Aeon Patch for 20 min. After quality assurance and processing the ECG data, HRV signals were derived and analyzed to provide their spectral features (LF, HF, and LF/HF) among other parameters, which are quantitative measures of sympathetic and parasympathetic activities of the ANS. Statistical means were then deployed to test the hypothesis and evaluate the effects of the Aeon A Patch with reference to C and P conditions.

MATERIALS AND METHODS

The study protocol was reviewed and approved by the National Foundation for Energy Healing (project#10-05-11-17). Participants were asked to keep well-hydrated and avoid taking any medications one day before data collection or drinking any stimulants (i.e. coffee) in the morning before participating in data collection. To assure adequate hydration, water bottles were provided to the subjects prior to the intervention and data collection. The study excluded subjects with cardiovascular disorders, those on 4 or more medications, those who were terminally ill, or had received chemotherapy in the last 12 months, those who had surgery in the previous 12 months, and those with HIV, and pregnant women. Both the investigator and the volunteers were blind to the A and P Patches as they looked exactly the same, were marked as Set 1 and Set 2 by the manufacturer (LifeWave LLC, San Diego, California, USA), and were assigned to subjects in a random fashion by the investigator through the research assistant responsible for data collection. So each subject could have been assigned to wear from either Set 1 or Set 2 first followed by wearing a patch from the other set next. ECG data collection involved using a CleveMed BioRadio 150 (Cleveland Medical Devices Inc,

Cleveland, OH, USA) device, and a Dell XPS laptop computer (Dell Inc, Austin, TX, USA). Three disposable Ag/AgCl electrodes were applied to the right wrist (RA), left wrist (LA), and right ankle (RL as reference) after proper cleaning and preparation of the skin at the bioelectrode application sites.

After giving informed consent and filling out a demographic form, 50 well-hydrated volunteers [21 females and 29 males, age: 19 - 79 (33.1 ± 14.5) years, weight: 117 - 334 (177.5 ± 51.5) lbs, height: 5'-6",3" ($5',7" \pm 4"$)], participated in ECG data collection under 3 different conditions for a total duration of 15 min (5 min/condition). Condition 1: C - while wearing no Patch, Condition 2: P or A - after wearing either the Placebo or the Aeon Patch for 20 min, and Condition 3: A or P - after wearing either the Aeon or the P Patch for 20 min. There was a washout period of 15 min between Conditions 2 and 3. The investigator, research assistant, and volunteers were blind to the A and P Patches as they looked exactly the same, were marked as Set 1 and Set 2 by the manufacturer, and were assigned in a random fashion by the investigator. The subjects were instructed to apply the A or P Patch about 2 inches inferior to the navel (below belly button) on the *CV6 acupuncture point* (based upon instructions from the manufacture). Fig. 1. shows the anatomical position for applying the P or the A Patch. The hypothesis to be tested was: Wearing the Aeon Patch for 20 min reduces stress (elicits a deep relaxation response or produces a parasympathetic effect).

ECG data acquired (during 2011 and 2012) from the volunteers were quality assured offline and were recorded in a digital data base. These stored data were then processed to derive the HRV signals by deploying advanced digital signal processing/analysis algorithms, codes, and instructions developed at the Massachusetts Institute of Technology (MIT) and Harvard Medical School, which are available from PhysioNet or PhysioBank website [<http://www.physionet.org/physiobank/>]. To perform short-term HRV signal analysis, ECG signals from each volunteer were recorded for three 5 min intervals during each condition, while wearing no patch C or wearing either a P or an A Patch for 20 min.

Power spectral analysis of HRV signals provides the basic information on how power within the signal is distributed as a function of frequency. Variations in the HR, occurring at the spectral frequency band of 0.15 - 0.4 Hz, known as HF band, are indicative of parasympathetic (vagal) activity. Variations in the spectral band 0.05 - 0.15 Hz, known as LF band, are linked to the sympathetic modulation, but this component includes

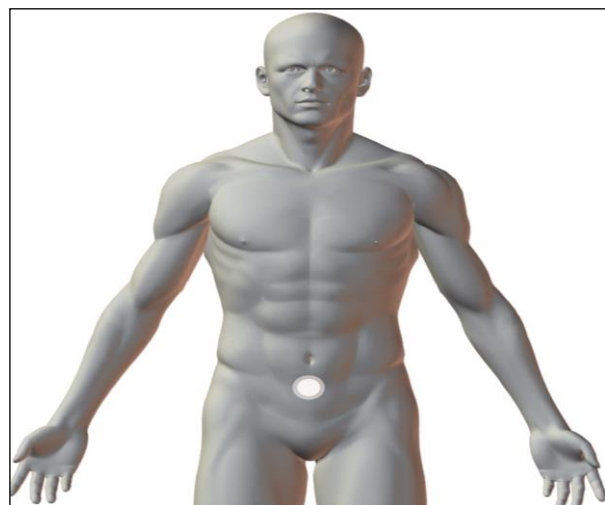


Fig. 1 Anatomical position for wearing the Placebo or the Y-Age Aeon Patch on CV6 acupuncture point

Table 1a. HRV spectral analysis results for *C* condition (healthy 27 years old female subject)

Frequency Band	Peak (Hz)	Power (ms ²)	Power (%)	Power (n.u.)%
VLF (0 - 0.04 Hz)	0.0039	6039	35.1	
LF (0.04 - 0.15 Hz)	0.0430	5690	33.1	51.0
HF (0.15 - 0.4 Hz)	0.1523	5468	31.8	49.0
Total		17197		
LF/HF		1.041		

Table 1b. HRV spectral analysis results for *P* condition (healthy 27 years old female subject)

Frequency Band	Peak (Hz)	Power (ms ²)	Power (%)	Power (n.u.)%
VLF (0-0.04 Hz)	0.0039	51074	69.4	
LF (0.04 - 0.15 Hz)	0.0430	16263	22.1	72.1
HF (0.15 - 0.4 Hz)	0.1523	6285	8.5	27.9
Total		73622		
LF/HF		2.588		

Table 1c. HRV spectral analysis results for *A* condition (healthy 27 years old female subject)

Frequency Band	Peak (Hz)	Power (ms ²)	Power (%)	Power (n.u.)%
VLF (0 - 0.04 Hz)	0.0039	16167	47.7	
LF (0.04 - 0.15 Hz)	0.0430	7406	36.5	69.8
HF (0.15 - 0.4 Hz)	0.1680	6625	15.8	30.2
Total		30198		
LF/HF		1.118		

some parasympathetic influence (sympathovagal influences). The spectral band 0.003 - 0.05 Hz, known as VLF, is possibly related to the long-term regulatory mechanisms. It is well established that the level of *physical activity* is clearly reflected in the HRV power spectrum. For example, when a healthy subject stands up, there is an increase of HRV in the *LF* spectral band, which is considered to be an estimate of the sympathetic influence on the heart. Consequently, the *LF/HF* is a quantitative indication of sympathovagal balance (Pumprla et al., 2002).

The spectral components, namely the VLF, LF, HF and LF/HF of the HRV signals, as well as a number of HRV time-domain, frequency-domain and nonlinear dynamics measures were calculated from 5-min ECG recordings under 3 different conditions while wearing no patch or wearing the P or A Patches for 20 min. Kubios HRV – Heart Rate Variability Software Analysis Software developed by the Biosignal and Medical Imaging Group at the University of Eastern Finland was used to calculate the time-domain, frequency-domain (spectral), and nonlinear dynamics features of the HRV signals [http://kubios.uku.fi/]. The power spectral components of the HRV signals were determined in normalized units (n.u.), which

represent the relative values of each power component in proportion to the total power minus the *VLF* component. The representation of *LF* and *HF* in *n.u.* emphasizes the controlled and balanced behavior of the two branches of the ANS (McMillan, 2002). It has been shown that *LF* and *HF* can increase under different physical and physiological conditions. An increase in normalized LF is observed during 90° tilt, standing, *mental stress* and *moderate exercise* in healthy subjects. Conversely, an increase in normalized HF is induced by controlled respiration, cold stimulation of the face and rotational stimuli (Malik, 1996).

RESULTS

Tables 1a, 1b, and 1c show the results of frequency-domain analysis of 5 min long datasets acquired from a healthy female subject (Age: 27 years old, Weight: 150 lb, Height: 5', 8") under 3 different conditions: baseline or *C*, wearing the P Patch for 20 min, and wearing the A Patch for 20 min, respectively as an example. Comprehensive HRV analysis results and graphs for this female subject under these conditions as produced by the

Table 2a. HRV spectral analysis results for *C* condition (healthy 25 years old male subject)

Frequency Band	Peak (Hz)	Power (ms ²)	Power (%)	Power (n.u.)%
VLF (0 - 0.04 Hz)	0.0391	1318	17.3	
LF (0.04 - 0.15 Hz)	0.1133	4498	59.1	71.5
HF (0.15 - 0.4 Hz)	0.1523	1797	23.6	28.5
Total		7613		
LF/HF		2.503		

Table 2b. HRV spectral analysis results for *P* condition (healthy 25 years old male subject)

Frequency Band	Peak (Hz)	Power (ms ²)	Power (%)	Power (n.u.)%
VLF (0 - 0.04 Hz)	0.0039	3404	50.0	
LF (0.04 - 0.15 Hz)	0.0430	2616	38.4	76.9
HF (0.15 - 0.4 Hz)	0.1523	786	11.5	23.1
Total		6806		
LF/HF		3.329		

Table 2c. HRV spectral analysis results for *A* condition (healthy 25 years old male subject)

Frequency Band	Peak (Hz)	Power (ms ²)	Power (%)	Power (n.u.)%
VLF (0 - 0.04 Hz)	0.0039	4469	47.7	
LF (0.04 - 0.15 Hz)	0.0430	3423	36.5	69.8
HF (0.15 - 0.4 Hz)	0.1523	1481	15.8	30.2
Total		9374		
LF/HF		2.311		

Table 3. Statistical measures for LF/HF for P and A conditions and % reduction of LF/HF Active: Placebo (n = 30).

Statistical Measure	LF/HF Placebo Patch	LF/HF Aeon Patch	% reduction in LF/HF compared to Placebo
Mean	1.960	1.500	24
Standard Deviation	1.100	1.000	9
<i>p</i> -value = 0.047			

Kubios-HRV Analysis Software are available electronically from the author upon making an email request.

Tables 2a, 2b, and 2c show the results of frequency-domain analysis of 5 min long datasets acquired from a healthy male subject (Age: 25 years old, Weight: 250 lb, Height: 5', 10") under 3 different conditions: baseline or C, wearing the P Patch for 20 min, and wearing the A Patch for 20 min, respectively as a second example. Comprehensive HRV analysis results and graphs for this male subject under these conditions are available electronically from the author upon making an email request.

Spectral features of the derived HRV signals were used to assess the parasympathetic effect or the deep relaxation response elicited by the Y-Age Aeon Patch for the study population. Data from the 3 conditions: C, A, and P were first quality assured after data collection and those subjects who achieved a parasympathetic response after wearing the Active patches within 20 min were identified as *responders*. Out of the 50 subjects, 30 (60%) could achieve a relaxed state after wearing the Aeon Patch as early as 20 min. Table 3 shows the statistical summary of the LF/HF for the responders under P and A conditions. The % reductions in LF/HF ranged from 2% to 56% in responders.

Statistical analysis (one-sample inference) was used to compare the LF/HF of the responders under these 3 different conditions. The normalized LF/HF indicative of sympathovagal balance decreased significantly ($24\% \pm 9\%$ after 20 min) in condition A compared to condition P with a *p*-value < 0.047 (n = 30) in responders. There was also a statistically significant difference (% reduction in LF/HF due to wearing the Aeon Patch compared to when no patch was worn) between LF/HF spectral features between conditions A and C with a *p*-value < 0.05. There was also a nearly statistically significant difference between spectral features in condition P to condition C. Such differences in spectral parameters are indicative of the Placebo Effect. This is an indication of how the subjects responded to the feeling of wearing a patch.

To evaluate the effectiveness of the Aeon Patch in eliciting a deep relaxation response *with time*, a single subject pilot investigation was carried out (in early 2011) before initiation of the double-blind-placebo-controlled (DBPC) study. This was a critical preliminary step to inform the data collection and study protocol design in the DBPC. The results of the pilot investigation enabled the principal investigator to arrive at a reasonable time estimate (about 20 min) to elicit a relaxation response in the majority of population by using the Aeon Patch. This time factor was very important in the data collection protocol as it was essential to limit the amount of time commitment from each subject (to about 1 h) for ECG data collection and consequently reduce the subject inconvenience. Tables 4a, 4b, and 4c show the results of frequency-domain analysis of 5 min long datasets acquired from a healthy male subject (age: 28 years old, weight: 175 lb, height: 6') at 3 different times: baseline or C, after wearing the Aeon Patch for

1 h and after wearing the Aeon Patch for 2 h. Comprehensive HRV analysis results and graphs for this male subject under these conditions as produced by the Kubios-HRV Analysis Software are available electronically from the author upon making an email request.

DISCUSSION

From the spectral analysis of the HRV signals of 5 min recordings of ECG datasets acquired in this study population and the statistical analysis of the results for 50 subjects, the following observations could be made:

1. There was a nearly significant difference ($p = 0.071$) between spectral parameters indicative of the relaxation response or stress reduction effect (as measured by normalized LF/HF power) when the subjects wore the P Patch compared with when the subjects wore *no* Patch (C condition). Such differences (a reduction of $25\% \pm 60\%$) in spectral parameters (LF/HF) are indicative of the P Effect.

Table 4a. HRV spectral analysis results for C condition (healthy 28 years old male subject)

Frequency Band	Peak (Hz)	Power (ms ²)	Power (%)	Power (n.u.)%
VLF (0 - 0.04 Hz)	0.0039	4736	61.4	
LF (0.04 - 0.15 Hz)	0.0430	2502	32.5	84.2
HF (0.15 - 0.4 Hz)	0.1523	471	6.1	15.8
Total		7709		
LF/HF		5.317		

Table 4b. HRV spectral analysis results after wearing the Aeon Patch for 1 h (healthy 28 years old male subject)

Frequency Band	Peak (Hz)	Power (ms ²)	Power (%)	Power (n.u.)%
VLF (0 - 0.04 Hz)	0.0039	10061	76.2	
LF (0.04 - 0.15 Hz)	0.0430	2112	16.0	67.2
HF (0.15 - 0.4 Hz)	0.2813	1031	7.8	32.8
Total		13205		
LF/HF		2.049		

Table 4c. HRV spectral analysis results after wearing the Aeon Patch for 2 h (healthy 28 years old male subject)

Frequency Band	Peak (Hz)	Power (ms ²)	Power (%)	Power (n.u.)%
VLF (0 - 0.04 Hz)	0.0039	878	60.4	
LF (0.04 - 0.15 Hz)	0.0430	300	20.6	52.1
HF (0.15 - 0.4 Hz)	0.3164	276	19.0	47.9
Total		1454		
LF/HF		1.087		

This is an indication of how the subjects responded to the feeling of wearing a patch.

2. After wearing the Aeon Patch, the majority of the participants (60%) called the responders could achieve stress relief within as early as 20 min. The degree of stress relief or relaxation response in responders due to wearing the Aeon Patch ranged from 2% to 56%. This is indicative of the fact that different individuals relax at different rates under the influence of these patches.
3. There was a consistent *decrease* in the normalized % of LF Power (indicative of the Sympathetic dominance) when the subjects wore the Aeon Patch compared with the condition when the subjects wore the P Patch. In the female subject (Table 1), LF Power (n.u.)% *decreased* from 72.1% to 69.8%. For the male subject (Table 2), LF Power (n.u.)% *decreased* from 76.9% to 69.8%. There was also a consistent *decrease* in LF Power (n.u.)% with *time* (Table 4). This value *decreased* from 84.2% to 67.2% after 1 h with a further *reduction* to 52.1% after 2 h, due to wearing the Aeon Patch compared to condition C.
4. There was an *increase* in the normalized % of HF Power (indicative of the Parasympathetic dominance) when the subjects wore the Aeon Patch compared with the condition when the subjects wore the P Patch. In the female subject (Table 1), HF Power (n.u.)% *increased* from 27.9% to 30.2%. For the male subject (Table 2), HF Power (n.u.)% *increased* from 23.1% to 30.2%. There was also a consistent *increase* of HF Power (n.u.)% with *time* (Table 4). This value *increased* from 15.8% to 32.8% after 1 h with a further elevation to 47.9% after 2 h, due to wearing the Aeon Patch.
5. There was a *statistically significant* ($p < 0.047$) *decrease* in the normalized LF/HF power when the subjects wore the Aeon Patch for 20 min compared with the condition when the subjects wore the P Patch for 20 min.
6. There was a large *decrease* in the normalized LF/HF power when the subject wore the Aeon Patch for 1 h compared with the baseline (C) condition. The effectiveness of the Aeon Patch in eliciting a deeper relaxation response with time was clearly demonstrated in the single subject investigation that caused a reduction of normalized LF/HF power from 5.317 at baseline to 2.049 (more than 2.5 times reduction) after 1 h and to 1.087 (with a further two-fold decrease) after 2 h.
7. A statistical comparison was performed between the average male and female LF/HF values in all the responders. No statistically significant differences ($p = 0.7$) were found between these two groups.

Based on these observations it could be concluded that wearing the Aeon Patch for 20 min elicited an enhanced parasympathetic response and could enable the majority of the participants to achieve a reduced stress state with varying degrees. This response could be quantified by a reduction in normalized LF/HF power. The single subject investigation revealed that the effectiveness of Aeon Patch in causing a stress relief increases with time. The statistical results revealed that the Aeon Patch showed a significant effect ($p < 0.047$) compared to the Placebo Patch in reducing the normalized LF/HF power after 20 min, there was a large reduction in LF/HF with time. The data also showed the Placebo Effect, which is an indication of how the subjects responded to the feeling of wearing a patch. Based upon these results, it is reasonable to expect that wearing the Aeon Patch may cause a significant relaxation effect after 30 min in the majority of the population.

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CONFLICT OF INTEREST

The author does not have any conflict of interest in the present study.

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