RESONANCES IN THE CARDIOVASCULAR SYSTEM
Investigation and Clinical Applications

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Abstract: The baroreflex, as a control system with negative feedback, is a mechanism that buffers changes in blood pressure (BP), thereby precluding strong, abrupt shifts in arterial pressure. As a closed-loop control system with delays, the baroreflex possesses resonance features at frequencies of about 0.1 and 0.03 Hz. These resonance frequencies correspond to a ~5-s delay in the BP response to changes in heart rate (HR) (HR baroreflex closed-loop) and a ~15-s delay in the vascular tone (VT) response to changes in BP (VT baroreflex closed-loop). Thus, whereas a single impact on the cardiovascular system (CVS) elicits a HR, BP, and VT oscillatory response that fades over time, 0.1 or 0.03 Hz rhythmical stimulation of the CVS produces steady HR, BP, and VT oscillations with significantly higher amplitudes comparing to stimulation at other frequencies. Resonances in the baroreflex system are essential for the maintenance of optimal health by keeping autonomic regulation active via HR, BP, and VT variability, providing adaptive responses to internal and external stimuli, and buffering stress and emotional reactivity via inhibitory effect in the brain. This study investigates the phenomenon of resonances in the CVS and the ability to employ these resonances for clinical applications.

1 INTRODUCTION

The arterial baroreflex is a mechanism that participates in blood pressure (BP) control. A shift in BP triggers the baroreflex, which changes heart rate (HR) and vascular tone (VT) to counteract the BP shift. Most often, these HR and VT baroreflex systems are modelled using the classic "control system theory" approach, which conceptualizes the baroreflex as a closed-loop control system with negative feedback. These models are consistent with the premise that a critical function of the baroreflex system is to buffer BP oscillation (Just et al., 1994; Jones, Christou, Jordan, & Seals, 2003; Jordan et al., 2002). Control system models of the baroreflex, however, often identify resonance properties at certain frequencies (Magosso, Biavati, & Ursino, 2001; Julien, 2006; van de Vooren et al., 2007), which, at first glance, seems inconsistent for a system that is defined by its ability to buffer BP variability. By definition, though, a closed-loop control system with a delay possesses resonance features and thus the classic control system theory is consistent with both the baroreflex's buffering functions and its resonance properties.

The baroreflex system in humans demonstrates resonance properties at frequencies of about 0.1 Hz and 0.03 Hz (van de Vooren et al., 2007; Vaschillo et al., 2002). In the HR baroreflex closed-loop, a shift in BP causes a compensatory HR response that is delayed for approximately 5 seconds. In the VT baroreflex closed-loop, the compensatory response of the vasculature is delayed for approximately 10-15 seconds (Vaschillo et al., 2002; Magosso, Biavati, & Ursino, 2001). These delays of 5 and 15 seconds coincide with resonance oscillations at 0.1 and 0.03 Hz because the periods of these oscillations are equal to twice the value of the delay.

A closed-loop system always possesses resonance properties because all biological or technical control systems have delays associated with inertia. When creating a stabilizing technical system with a closed-loop, the delay is manipulated so that the resonance frequency falls far outside of the operating frequency range. In the case of the baroreflex system, there are two resonance frequencies within its very narrow (~0.01-0.5 Hz)

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operating range.

Despite the current view that the main role of the baroreflex is to buffer BP oscillations and "that resonance is the price to be paid for effective buffering at other frequencies" (van de Vooren et al., 2007), we consider resonance properties of the baroreflex as essential elements for the regulation of autonomic and central nervous system functions. We posit that the resonances in the baroreflex systems are integral for the vast autonomic variability that underlies efficient and effective homeostatic reflexes. This is supported by evidence that baroreflex resonance properties can act to amplify adaptive responses to internal and external stimuli and buffer stress and emotional reactivity through the initiation of a cascade of neurobiological events that produces a generalized inhibitory effect on the brain (Dworkin et al., 1994; Nyklicek et al., 2005; Yasumasu et al., 2006).

This paper presents the results of our investigations of baroreflex resonance features using a classic engineering approach. Based on the importance of autonomic variability as well as of the frequency dependence of autonomic reactions to external and internal influences, our goal is to develop therapeutic methods based on the resonance properties of the baroreflex.

2 0.1 HZ RESONANCE IN THE CVS

Gatchel & Lang (1973) and Lang et al. (1993) found that HR responses to a single stimulus tended to last approximately 10 seconds and have a triphasic waveform, consisting of a small initial HR deceleration, a larger mid-interval acceleration, and a final deceleration. Onset of any stimulus - visual (Lang, Greenwald, & Bradley, 1993) or acoustical (Bradley & Lang, 2000), long (few second) (Bradley & Lang, 2000) or brief (few tens ms) (Codispoti, Bradley, & Lang, 2001) - caused the same HR waveform response. We suggest that the triphasic waveform of the instantaneous HR response results directly from the inherent resonance properties of the HR baroreflex closed-loop. Further, we hypothesize that this basic feature of the HR baroreflex closed-loop can serve as the foundation for eliciting stable resonance oscillations in HR, BP, and VT using rhythmical 0.1 Hz stimulation.

2.1 0.1 Hz Resonance in the CVS Caused by Respiration

Respiratory activity continually perturbs the cardiovascular system. It is well known that breathing modulates HR with respiratory periodicities, a phenomenon known as respiratory sinus arrhythmia. Clynes (1960) showed that a single inhalation or exhalation elicits nearly identical triphasic HR waveform responses. In addition, he reported that 0.1 Hz breathing caused high amplitude oscillations in HR. Angelone & Coulter (1964) then calculated amplitude and phase transfer functions with respiration as the input and HR as the output for one subject who performed paced breathing exercises at different frequencies (0.01 – 0.5 Hz range). They found that the 0.1 Hz breathing produced the highest HR oscillation and defined this phenomenon as resonance in the CVS. These early studies guided the development of a heart rate variability (HRV) biofeedback procedure based on paced resonance frequency breathing as a novel approach for correcting abnormal autonomic regulation (Lehrer, Vaschillo, & Vaschillo, 2000).

HRV biofeedback has significant clinical potential because respiration is a physiological

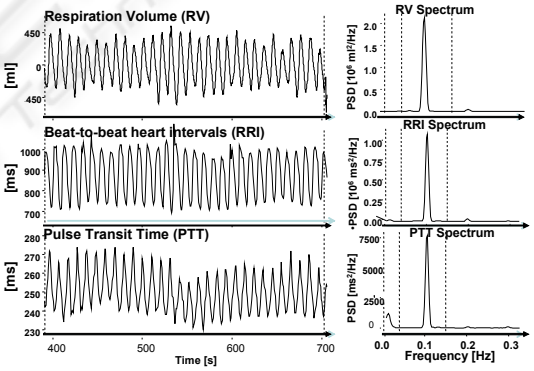

Figure 1: 0.1 Hz paced breathing triggers resonance oscillations in cardiovascular functions.

function that is under voluntary control and breathing at one's resonance frequency produces high-amplitude oscillations in HR, which, through the baroreflex, spreads to other functions, such as BP and VT (Fig. 1).

Further, we recently calculated the amplitude and phase transfer functions of the HR control system for eight participants and observed that each participant demonstrated a unique resonance frequency between 0.075 – 0.107 Hz, and that the 0º phase shift between respiration and HR curves

occurred precisely at the resonance frequency (Vaschillo & Vaschillo, 2009). Thus, paced breathing represents an easily manipulated trigger for inducing maximal oscillations in HR and other interrelated cardiovascular functions.

In contrast to the usual respiratory rate of 12-18 breaths per minute (0.2-0.3 Hz), HRV biofeedback teaches participants to breathe easily and naturally (i.e., slowly but not too deeply, to support normal minute ventilation) at a rate of ~6 times per minute. As part of this procedure, participants are instructed to breathe at their resonance frequency for ~ 40 minutes per day over a 10-week period.

HRV biofeedback successfully normalized autonomic regulation, as measured by increased baroreflex gain and peak expiratory flow (Lehrer et al., 2003). It demonstrated efficacy in the treatment of asthma (Lehrer et al., 2004), major depression (Karavidas et al., 2007), fibromyalgia (Hassett et al., 2007), neurosis (Chernigovskaya et al., 1990), and hypertension (McCraty et al., 2003). The therapeutic effects in these studies were achieved through systematic, everyday use of the HRV biofeedback procedure and the elicited high amplitude oscillation in HR, BP, VT, and other autonomic functions retrained and toned homeostatic reflexes. Activation of the baroreceptors by these oscillations also activated inhibitory processes in the brain, thereby dampening stress. Taken together, these data suggest that daily "exercise" of autonomic functions associated with normalized autonomic regulation can restore sympathetic-vagal balance (Lehrer et al., 2004) and buffer patients from the negative influences of stress.

2.2 0.1 Hz Resonance in the CVS Caused by Rhythmical Muscle Tension

The respiration is natural rhythmical stimulator of the CVS; however, there are other effective methods to stimulate the CVS at its resonance frequency. For example, the CVS functions adaptively to react to physical load. This suggests that rhythmical paced muscle tension (muscle tense-release cycles) at a frequency of 0.1 Hz may also trigger resonance in the CVS.

Method: Sixteen young healthy participants (9 female, 7 male) performed four 3.5-minute tasks (30 second inter-task interval), including a paced, 6 breaths/minute (~0.1 Hz) task as well as three paced muscle tension tasks at frequencies of 0.05, 0.1, and 0.2 Hz in random order. Participants were seated in a comfortable armchair in front of a computer screen with their legs extended and supported parallel to the floor. During the paced muscle tension tasks participant tensed their skeletal muscles when the computer screen turned red and relaxed their muscles when the screen color changed to green. ECG and finger pulse were recorded during all tasks. Beat-to-beat HR and pulse transit time (PTT) and their Fourier spectra were calculated for each task. PTT was considered as estimation of the vascular tone (shorter PTT corresponds to higher VT). The power of the spectra at tested frequencies was used to estimate HR and VT reactions in each task.

Results: The 0.05, 0.1, and 0.2 Hz muscle tension manipulations produced HR and VT oscillations at corresponding frequencies in all participants; however, only rhythmical 0.1 Hz muscle tension caused high amplitude HR oscillations like those observed with 0.1 Hz breathing. Averaged across all participants, HR and VT reactions to muscle tension at 0.1 Hz were 4-6 times higher than at 0.2 Hz or 0.05 Hz (see Fig. 2). Nonetheless, average HR reaction to the 0.1 Hz muscle tension task was significantly lower than to 0.1 Hz breathing. In contrast, average VT reaction to the 0.1 Hz muscle tension task was significantly higher than to 0.1 Hz breathing.

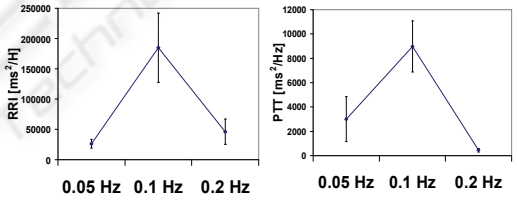

Figure 2: Heart rate (RRI) and vascular tone (PTT) reactions to rhythmical muscle tension at 0.05, 0.1, and 0.2 Hz. Y-Axis: power of the spectra at tested frequencies. Data are presented as the mean ± 2 standard error bars.

Discussion: Rhythmically stimulating the CVS at its resonance frequency with muscle tension and breathing elicited significantly higher oscillations than at other frequencies. These oscillations were robust in both the HR and VT spectra. The efficacy of the muscle tension task to stimulate HR oscillations was lower than the efficacy of the breathing task, but higher for VT oscillations. This may be related to the physical load of muscle tension, which increased mean HR and consequently depressed HRV. These findings parallel those reported by Lehrer et al. (2009), who noted that the amplitude of oscillations in BP and VT caused by 0.1 Hz muscle tension stimulation was relatively higher than those in HR. This suggests that increased BP and VT oscillatory activity acts as a

compensatory reaction to dampened HRV.

Conclusion: Results confirmed that rhythmical 0.1 Hz muscle tension tasks can trigger resonance in the CVS. The ability to produce high amplitude oscillations at this resonance frequency makes the rhythmical muscle tension techniques potentially valuable for developing clinical applications. In fact, France, France, & Patterson (2006) have developed the Rhythmical Skeletal Muscle Tension (RSMT) technique to lower risk of a vasovagal reaction (fainting). RMST has been successfully employed to avert fainting episodes that often occur during blood collection procedures and may discourage people from donating blood. It has also been successfully used to treat patients with blood and injury phobias. In their study, healthy young adults performed the RSMT task at frequency of 0.1 Hz and demonstrated significant increases in HR, systolic and diastolic BP, and cerebral oxygen. High amplitude 0.1 Hz oscillation in HR, BP, and VT were also observed.

The mechanisms by which the 0.1 Hz RSMT procedures prevent vasovagal reactions have not been examined. It may be due to resonance in the CVS or simply to the increased sympathetic arousal caused by the muscle tension. We propose that the effect is due to the high amplitude oscillations that activate the regulatory processes that balance autonomic functioning and modulate the inhibitory processes in the brain that buffer the body from stress. Accordingly, we speculate that other kinds of 0.1 Hz RSMT procedures can be exploited by researchers and clinicians for the development of novel approaches to correct abnormal autonomic regulation. France's RSMT technique was originally intended to be a single session performed immediately prior to an event that could induce a negative physiological reaction. Systematic, every day use of this technique, however, may produce a cumulative and longer lasting effect and, in this way, be practical in the same way as the HRV biofeedback procedure. In fact, such procedures may prove especially useful in the rehabilitation process of patients following a cerebral stroke or myocardial infarction, in treatments where physical exercises are prescribed (Buch, Coote, & Townend, 2002), or in sport medicine.

2.3 0.1 Hz Resonance in the CVS Caused by Emotional Pictures Cues

The CVS actively participates in emotional regulation, and emotions strongly affect cardiovascular function. Picture cues that elicit emotional reactions have been reported to produce the common triphasic HR response. Moreover, the magnitude of this triphasic response, particularly the accelerative leg, appears to accurately discriminate picture valence (Gatchel & Lang, 1973; Lang et al., 1993). In accordance with our model, instigating rhythmical emotional reactions at 0.1 Hz should produce resonance oscillation in HR, and the oscillation amplitude should discriminate the degree of emotional arousal. To test this, emotionally arousing picture cues were presented at frequency of 0.1 Hz to trigger CVS resonance. In addition, the ability of the resonance amplitude to discriminate the degree of emotional arousal caused by block of picture cues was assessed.

Method: Seventy-six healthy participants, between 21 and 24 years old, were individually tested. Each participant viewed six categories of picture blocks (negative emotional, positive emotional, and neutral, as well as alcohol, marijuana, and ecstasy) with 30 pictures in each. Pictures were presented for 5 seconds with a 5-second inter-picture interval, resulting in a 0.1-Hz picture presentation frequency. The interval between each picture block was 30 seconds. Pictures were presented on a 75-cm LCD TV (View Sonic N3000W). ECG and finger pulse were recorded during all tasks. Beat-to-beat RRI and pulse transit time (PTT) and their Fourier spectra were calculated for each picture cue exposure task. Reaction of the CVS to the picture cue block was estimated by the power of RRI and VT spectra at frequency of 0.1 Hz (i.e., the 0.1-Hz HR index and the 0.1-Hz VT index, respectively). To evaluate the sensitivity of the 0.1-Hz HR index for estimating emotion valence, common HRV indices (total HRV, high frequency (HF) HRV, and low frequency (LF) HRV) were also calculated.

Results: In most cases, pictures presentation at a frequency of 0.1 Hz caused high amplitude HR and VT oscillations at the resonance frequency of the CVS. The resonance in VT, however, was less prominent than in HR. Participant's average 0.1-Hz HR index response to neutral picture cues was significantly less than for any other cue block. Conversely, the average 0.1-Hz HR index response to negative picture cues was significantly higher than for other picture cue blocks. Averaged 0.1-Hz HR index responses to positive, alcohol, marijuana, and ecstasy picture cues did not differ significantly from one another, but there were individual differences in the response patterns of 0.1-Hz HR indices across picture cue blocks. For example, one participant strongly reacted to negative and alcohol stimuli but weakly reacted to positive and marijuana cues; another participant showed high 0.1-Hz HR

index responses to ecstasy cues, a moderate response to negative and positive cues, and a weak response to all other cue blocks (see Fig. 3).

The 0.1-Hz HR index detected individuals' reactions to the picture cue blocks differently than other, more commonly used HRV indices (total HRV, HF HRV, LF HRV). For example, the 0.1-Hz HRV index more sensitively differentiated reactions to negative versus neutral picture cue blocks than common HRV indices. Further, there was no significant variability in individual reactions to different cue blocks detected with the common HRV indices.

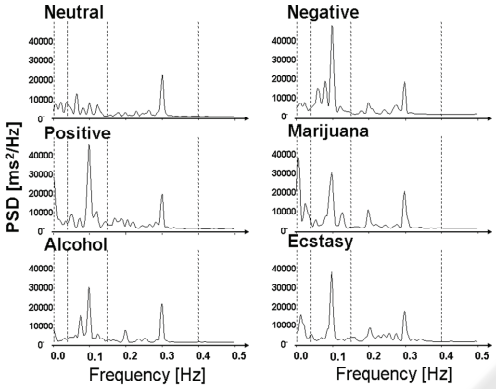

Figure 3: One participant's RRI spectra for all 0.1 Hz picture cue tasks. The power of spectra at 0.1 Hz reflects the strength of emotions caused by picture cue blocks.

Discussion: Emotions modulated by rhythmical picture cue exposure at frequency of 0.1 Hz imposed high amplitude resonance oscillation on HR and other cardiovascular functions. We hypothesize that the amplitude of the oscillations depends on the degree of emotional arousal elicited by the paced visual stimulation, but were not able to directly assess this hypothesis. Nevertheless, the fact that some individuals reacted more strongly to emotional picture cues whereas others reacted more strongly to drug-related picture cues suggests that the salience of the stimuli has a significant impact on the amplitude of resonance oscillations.

It is unlikely that picture cues presented at the resonance frequency caused greater emotional arousal than picture cues presented at others frequencies; rather, we hypothesize that the amplified reactivity we observe is directly related to the presentation of emotional cues at the CVS resonance frequency.

Our approach of using the CVS' 0.1 Hz resonance frequency to assess degree of emotional arousal in response to stimuli is similar to the engineering approach of measuring weak oscillatory signals. An engineer tunes a measurement device to the main frequency of the weak signal. Tuning to the resonance frequency does not change the value of the signal, but rather enhances the sensitivity of the measurement device.

Conclusion: The method we have developed for estimating emotional arousal may be useful in psychophysiological research, particularly, for the diagnosis of psycho-emotional disorders. In addition, the use of paced visual stimulation may prove useful for the treatment and rehabilitation of a variety of disorders because visual cues may cause high-amplitude HR oscillation similar to those caused by paced breathing or paced muscle tension. An advantage of picture cue stimulation is that the content of the stimuli can be easily manipulated; thus, it is conceivable that rhythmical visual stimulation using cues with specific cognitive content (e.g., emotional cues to induce altered mood states or drug-related cues to induce craving) may open new doors to treatment applications in the mental health and addictions field.

3 0.03 HZ RESONANCE IN THE CVS

The VT baroreflex is one of two interconnected branches of the baroreflex, but is much less studied than its counterpart, the HR baroreflex. Like the HR baroreflex, the VT baroreflex controls BP and participates in modulating the coordinated actions of the central and autonomic nervous systems; however, it does so by modulating the stretch of blood vessel walls and operates in a lower frequency range (Aljuri, Marini, & Cohen, 2004). Based on prior research (Vaschillo et al., 2002; Vaschillo et al., 1983), we hypothesized that a resonance frequency of ~0.03 Hz would be found for the VT baroreflex.

Based on the utility of the 0.1 Hz resonance in developing novel medical applications for treating various physical and mental disorders, we expected that exploration of the 0.03 Hz resonance could prove valuable in much the same way. However, little is known about this resonance frequency and thus additional basic experimental investigations are necessary prior to the assessment of its clinical value. Accordingly, we performed two studies to define whether external stimuli can elicit a 0.03-Hz oscillatory HR response (the 30 second triphasic

waveform response) in addition to a 0.1 Hz response. Very strong stimuli were used to effectively induce a 30 second triphasic response.

The first study investigated the HR response to highly unpleasant sounds.

Method: Seventeen adult participants were exposed to 8 synthetic sounds which were chosen as the most unpleasant from 362 sounds created in the lab. Participants sat in a room and listened to each sound at 82 dB (A) or 92 dB (A) for 2 minutes (with a 30 second inter-stimulus interval) from four equidistant speakers. ECG was collected and beat-to-beat HR curves were calculated (see Fig. 4).

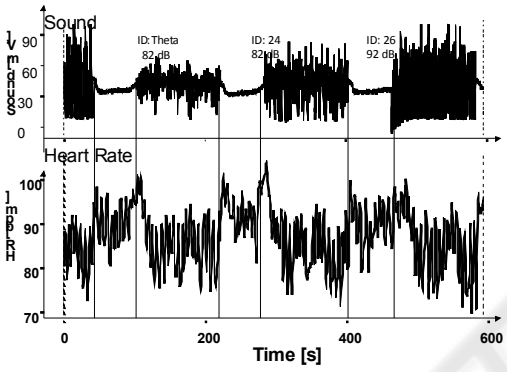

Figure 4: Heart Rate during aversive sound exposure.

Results: Onset of unpleasant sounds usually caused a long-duration triphasic HR response, which appeared to contain overlapping 10-second triphasic waveforms that lasted for about 30 seconds (see Fig. 5) Sound offset occasionally caused the same response. Two types (Tab. 1) of 30-second triphasic responses were found: one with an initial HR deceleration and one with an initial HR acceleration.

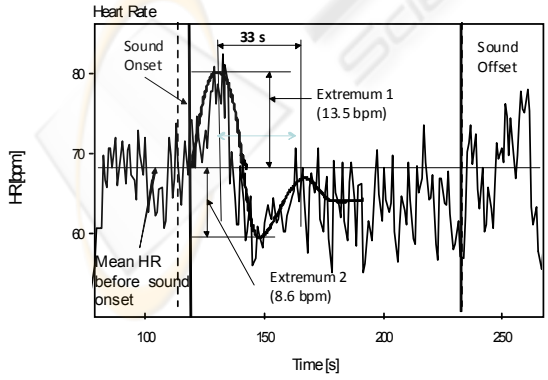

Figure 5: An example of ~0.03 Hz oscillatory HR reaction to aversive sound (30-s triphasic waveform HR response).

Table 1: The two types of 30-s triphasic waveform HR responses averaged across all participants and sounds characteristics.

HEART RATE RESPONSE	EXTREMUM 1 (M ± STD ERR)	EXTREMUM 2 (M ± STD ERR)	OSCILLATORY PERIOD (M ± STD ERR)	OSCILLATORY FREQUENCY (M ± STD ERR)
UNITE	[BPM]	[BPM]	[S]	[HZ]
TYPE 2	7.86±0.58	-5.03±0.79	28.62 ±1.23	0.035±0.006
TYPE 2	- 8.34±0.78	4.14±1.1	26.74 ±1.86	0.037±0.007

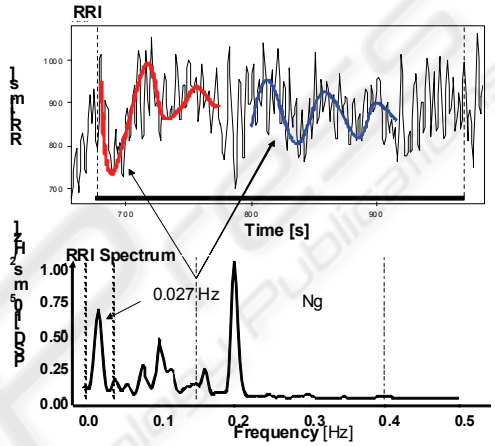

Figure 6: An example of ~0.03 Hz oscillatory HR reaction to aversive picture cues.

The second study investigated the HR response to highly negative pictures.

Method: See section 2.3.

Results: We found that very negative pictures (e.g., plane crashes, blood, violence) sometimes caused a strong ~0.03 Hz oscillatory HR response. This HR response usually demonstrated a significantly higher amplitude than the 0.1 HR response (see Fig 6).

Discussion: Strong stimuli from various modalities elicited oscillatory HR responses at a frequency of about 0.03 Hz, which overlapped with the 0.1 Hz response. This effect may be the result of resonance in the VT baroreflex closed-loop. In these studies, we employed very strong stimuli and clearly observed 0.03 Hz oscillatory responses. Less aversive stimuli should also be capable of eliciting these slower oscillations; however, these oscillations may be masked by those associated with HRV. Future studies are needed to assess the malleability of the 0.03 Hz resonance and its utility in clinical applications.

Conclusion: To be value for clinical application, it is necessary to develop experimental methods that

can reliably and easily produce stable high amplitude oscillation in the CVS. The use of very strong negative stimuli, while capable of producing such oscillations, may not prove clinically useful because of the possibility of negative psychological side effects. Exploration of paced breathing or rhythmical muscle tension techniques at ~0.03 Hz warrants further study as these procedures may also be capable of triggering therapeutic oscillation in the same way as 0.1 Hz stimulation triggers them. Elements of such stimulation can be found in eastern health procedures (e.g., Yoga, Tai Chi).

4 DISCUSSION

Two resonance frequencies, at 0.1 and 0.03 Hz, have been identified in the CVS. These resonances are thought to reflect two interdependent closed-loop systems with delays, namely the HR and VT baroreflex systems and contribute independently to the overall resonance properties for the CVS. Typically, the baroreflex system is touted for its ability to buffer perturbations in BP (Just et al., 1994; Jones, Christou, Jordan, & Seals, 2003; Jordan et al., 2002; Magosso, Biavati, and Ursino, 2001; van de Vooren et al., 2007); however, because it has a very narrow operating frequency range (~0.01-0.5 Hz) with 2 resonance frequencies inside this range, the ability of the baroreflex system to stabilize the CVS is limited. The high frequency boundary is defined by inertia of blood mass and slow changes in vessel tone, while the low frequency boundary is defined by differentiative property of the baroreceptors (i.e., they react only to the speed of BP changes).

The long term aim of investigating the dynamic properties of the HR and VT baroreflexes is to develop new therapeutic methods for treating diseases associated with the dysregulation of the autonomic and central nervous systems. HRV biofeedback is capable of harnessing the resonances within the CVS and promoting health benefits. These therapeutic effects have been linked to the generation of generalized high-amplitude oscillations in autonomic functions that are elicited by the biofeedback procedure (Chernigovskaya et al., 1990; Lehrer et al., 2003, 2004) and act to retrain autonomic reflexes. The systematic retraining of autonomic reflexes normalizes and improves autonomic regulation. Our studies show that breathing, visual cues, and muscle tension management of the 0.1 Hz resonance is useful for the treatment of various unhealthy physical and mental conditions. We believe that novel therapeutic interventions involving the VT baroreflex and its resonance at 0.03 Hz through passive or active tasks may also be beneficial, but additional investigations are needed.

5 CONCLUSIONS

Classical control system theory applied to the investigation of physiological systems can be a useful tool for the medical practice. An engineering approach offers the opportunity to create simple, clinically-useful stimulation procedures which may be used to enhance an individual's regulatory capacity and thus open new doors to treatment applications in the mental health and addictions field.

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